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Review Article

Stem cell treatment for the spinal cord injury – A concise review

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ARTICLE INFO

Article history:
Received 19 May 2014
Accepted 28 May 2014
Available online 12 June 2014

Keywords:
Spinal cord injury
Stem cells
Bone marrow
Bone marrow derived stem cells
Mesenchymal stem cells

ABSTRACT

A spinal cord injury (SCI) is any injury of the spinal cord caused due to trauma and mostly comprise of damage to the nerves associated with the spinal cord and they can be classified as being complete or incomplete. Spinal cord injuries account for a majority of lower body disabilities due to accidents and trauma. Cell transplantation, as a therapeutic intervention for spinal cord injury (SCI), has been extensively studied by scientists and researchers in recent years using stem cell that has shown considerable promise in treating patients with SCI and thus restores lost functions by replacing lost or damaged cell populations. Spinal cord injuries account for a majority of lower body disabilities due to accidents and trauma. SCI also paves way for a lot of other disabilities associated with blood vessels as well and bone deformities. The global burden of SCI, economically, runs into millions as complete cure is not possible. The number of clinical trials that have been conducted for phase 1 studies of spinal cord injury is a staggering number and currently 246 trials are being conducted in their initial phases. However, many questions remain unanswered and more continue to emerge. This review will comprehensively cover publications in the field from the last years and examine the biological effects of SCI.

1. Introduction

Spinal cord injury (SCI) is a devastating condition associated with significant functional and sensory deficits, emotional, social, and financial burdens, and an increased risk of cardiovascular complications, deep vein thrombosis, osteoporosis, pressure ulcers, autonomic dysreflexia, and neuropathic pain.[1] The estimated annual global incidence of SCI is 15–40 cases per million. Despite much work having been done, the only treatment to date known to ameliorate neurologic dysfunction that occurs at or below the level of neurologic injury has been intravenous methyl prednisolone therapy. The most common causes of traumatic SCI are road traffic accidents, falls, occupational and sports-related injuries that result in contusion and compression of the spinal cord. In studies conducted in India, the majority of the causes for SCI were due to falls from height (58.9%), while motor vehicle

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http://dx.doi.org/10.1016/j.ijnt.2014.05.008

accidents come second (21.3%); fall of weight (7.2%) and other traumatic cases (12.6%) account for the other reasons for Spinal Cord injury. Approximately 55% of SCIs occur at the cervical level (C1 to C7-T1) with a mortality of 10% in the first year following injury and an expected lifespan of only 10–15 years post-injury, and thoracic (T1–T11), thoracolumbar (T11–T12 to L1–L2) and lumbosacral (L2–S5) injuries each account for approximately 15% of SCI.

Much research over the past 30–40 years has focused on elucidating the mechanisms of spinal cord injury, with the complex pathophysiologic processes slowly being unraveled. With a greater understanding of both primary and secondary mechanisms of injury, the roles of calcium, free radicals, sodium, excitatory amino acids, vascular mediators, and apoptosis have been elucidated.[2] Depending on the age of the patient, severity, and levels of SCI, the lifetime cost of health care and other injury-related expenses can reach dollar 25 million.[3] Despite recent technological advancements in the field of neurophysiology and the management of spinal cord injuries related pain, most patients are not healed even though cutting edge pain management systems are used to ameliorate their pain.

The acute phase of spinal cord injury refers to the immediate post-injury period when there is continuing tissue damage. In subacute spinal cord injury, the spinal cord starts the reparative process shortly after the injury. This is apparent from the massive collections of inflammatory cells that appear at the injury site by 12–24 h. The first inflammatory cells that appear are neutrophils, followed by lymphocytes, and then macrophages. The first two types of cells come from the blood. Within 48 h, a majority of the cells at the injury site may be macrophages, with myelin and other cell fragments inside them. These cells start cleaning up the dead cells and debris. Complete or prolonged suppression of the inflammatory response to injury can impair recovery. In the chronic injury phase, several weeks after injury, the lesion or injury site usually contains a thin rim of surviving white matter close to the pial surface. In contused rat spinal cords, the injury site has a cystic cavity filled with loose cellular matrix. In severely injured spinal cords, evidence of Schwann cells has been found at the injury site. These cells myelinate peripheral nerves and are usually not seen in the spinal cord. It has been hypothesized that they may have migrated into the injury site from spinal roots. This only occurs in severe injuries that have damaged most of the astrocytes since astrocytes usually respond to Schwann cells by walling them off. However, when Schwann cells are present at the injury site, they thickly myelinate every axon present at the site. Many of the axons in the preserved white matter rim may be thinly remyelinated by oligodendroglial cells which normally myelinate spinal axons. Macrophages can be seen around the edges of the contusion but typically cluster around degenerating or degenerated spinal tracts. Growing axons can be often seen in these degenerated tracts with growth cones, as long as 3 months or longer after injury. This suggests that there may be continued pressure for regrowth of axons in the spinal cord that continues for long periods after spinal cord injury.[4]

Following spinal cord injury (SCI), the blood–brain barrier is disrupted and an influx of inflammatory cells occurs, which is facilitated by their expression of matrix metalloproteinases (MMPs).[5] MMPs, other proteolytic and oxidative enzymes, and proinflammatory cytokines that are produced by infiltrating neutrophils and macrophages, along with resident microglia, induce a reactive process of secondary cell death in the tissue that surrounds the original injury site. Evidence suggests that inflammation may be a beneficial response to SCI. Macrophages phagocytoses the myelin debris present in the injured spinal cord, which is known to inhibit axonal regeneration, and increase in the number of macrophages in a CNS injury can promote nerve regrowth.[6] In addition, macrophages may also release protective cytokines such as basic fibroblast growth factor, nerve growth factor (NGF), and neurotrophin 3, which promote neuronal regeneration and tissue repair.[6,7]

1.1. *Primary injury*

There are four characteristic mechanisms that occur in primary injury: a. impact plus persistent compression; b. impact alone with transient compression; c. distraction; and d. laceration/transection. The first and most common mechanism involves impact plus persistent compression. This is evident in burst fractures with retropulsed bone fragment(s) compressing the cord, fracture-dislocations, and acute disc ruptures.

1.2. *Secondary injury*

The primary mechanical injury serves as the nest from which additional secondary mechanisms of injury extend. These secondary mechanisms include neurogenic shock, vascular insults such as hemorrhage and ischemia–reperfusion, excitotoxicity, calcium-mediated secondary injury and fluid-electrolyte disturbances, immunologic injury, apoptosis, disturbances in mitochondrion function, and other miscellaneous processes.

1.3. *Pathophysiology of spinal cord injury*

Pathophysiological events occurring after SCI include acute (e.g., edema and hemorrhage), subacute (e.g., inflammation), and chronic (e.g., cavitation) phases. The primary and secondary injury mechanisms involve many anomalies like edema, hemorrhage, inflammation, apoptosis, necrosis, excitotoxicity, lipid peroxidation, electrolyte imbalance, ischemia/vasospasm, and blood vessel occlusion. Endogenous repair and regenerative mechanisms that occur during the secondary phase of injury minimize the extent of the lesion (through astrogliosis), reorganize blood supply through angiogenesis, clear cellular debris, and reunite and remodel damaged neural circuits. The spatial and temporal dynamics of these secondary mediators are fundamental to SCI pathophysiology and as such offer exploitable targets for therapeutic intervention.[8,9] Mechanical damage to the spinal cord cause neuronal cell death and disruption of the blood–spinal cord barrier. This primary damage that occurs in the spinal cord triggers a potent inflammatory response and initiates complement activation.

1.4. *Cellular therapy*

The regenerative capacity of neurons in the central nervous system (CNS) is severely limited compared to the neurons in the peripheral nervous system, largely because of the production of inhibitory molecules that inhibit axonal growth, preventing regeneration of injured nerve tracts. In contrast to neuroprotective therapies, which limit the extent of acute neural injury, neuroregenerative therapies facilitate neuronal regrowth by several mechanisms, such as those including blockade of these inhibitory pathways. A multitude of characteristics of cells that have been tested pre-clinically and clinically make them potentially attractive to address the multifactorial nature of the pathophysiology of secondary SCI which include anti-inflammatory, immunomodulatory,[10] anti-gliotic,[11] pro-oligodendrogliogenic,[12] pro-neurogenic,[13] and secrete various anti-apoptotic and pro-angiogenic neurotrophic factors. Given the pathophysiological targets of SCI, transplanted cells should be able to: a. enables regenerating axons to cross barriers; b. functionally replace lost cells; and/or c. create an environment supportive of neural repair. Different cell sources and types are being tested in clinical trials for SCI, including embryonic stem cells (ESCs), neural progenitor cells (NPCs), bone marrow mesenchymal cells (BMSCs), bone marrow mononuclear cells (BMMNC's) and non-stem cells such as olfactory ensheathing cells and Schwann cells.[14] Other cell types are also being developed for clinical use, including other sources from fetal mesenchymal cells,[15] adipose tissue, umbilical cord, adult and immortalized neural progenitors,[16] skin-derived progenitors, induced pluripotent stem cells[17] and endogenous spinal cord progenitors.

There are two types of bone marrow stem cell, hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), which are known to differentiate into hematopoietic and mesenchymal cell lineages, respectively. For clinical transplantation, HSCs and MSCs represent attractive cell sources as they can be easily and reproducibly isolated from bone marrow aspirates and reintroduced into patients as autografts. In rodent models of SCI, cellular transplantation has promoted remyelination, axonal sparing, and functional recovery.[18–20] Several studies have shown successful engraftment of HSCs and MSCs into the injured spinal cord. HSCs are defined by their lifelong ability to reconstitute all of the hematopoietic lineages in transplanted hosts.[21,22] Although HSCs have shown to proliferate *in vivo*, there are as yet no definitive *in vitro* assays to detect and expand purified HSCs, as HSCs in long-term culture form progenitor populations that can differentiate along the hematopoietic lineages. Researchers have yet to find a single molecular marker that is only exclusively expressed by HSCs. However, HSCs can be distinguished and isolated from mature blood cells by their lack of lineage-specific markers and presence of other cell surface antigens such as CD34 and CD133.[23] CD34 has been routinely used to enrich freshly isolated hematopoietic cell populations, which include the HSC population, for clinical transplantation in patients. MSCs are a population of cells that differentiate along various mesenchymal lineages, for example, to form osteoblasts, adipocytes, and chondrocytes.[24] These multipotent cells have received considerable interest as possible donor cells for cell therapies as they can be isolated from the bone marrow with relative ease. Adherent stromal cells (MSCs) will outgrow any fully differentiated and nonproliferating cells, which might also adhere to bone marrow mononuclear cell seeded-culture plates. Unlike HSCs, MSCs can be culture expanded to generate large numbers.

The therapeutic potential of human umbilical cord blood cells for intractable neurological disorders has been demonstrated using *in vitro* and vivo models. The umbilical cord blood cells are immune naïve and are able to differentiate into other phenotypes, including the neural lineage. Cord blood has shown its ability to produce several neurotropic factors and to modulate immune and inflammatory reactions has also been noted. Recent evidence has emerged suggesting alternative pathways of graft-mediated neural repair which involve neurotrophic effects[25] and they are caused by the release of various growth factors that promote cell survival, angiogenesis and anti-inflammation. These multifaceted protective and restorative effects from umbilical cord blood cell grafts may be interdependent and they act in harmony to promote therapeutic benefits for SCI. Nevertheless, clinical studies with umbilical cord blood cells have their own concerns related to safety and efficacy and a major concern being the major histocompatibility in allogeneic transplantation is an important issue that needs to be addressed in future clinical.

1.4.1. *Mechanistic action of cellular therapy*

A large population of neurons and glia located in the lesion site undergo cell death due to the disruption of cell membranes or as a consequence of the ischemia caused by vascular disruption, which in turn results in hemorrhage that extends rostrally and caudally from the lesion site. The massive cell death extended in the secondary phase occurs by apoptosis and necrosis, and affects all functional neurons and glial cell population, including oligodendrocytes. Although the mechanism of oligodendrocyte apoptosis is not clearly known, it has been reported that Fas receptors located on the surface of oligodendrocytes can be activated by Fas ligands expressed by activated microglia, which in turn could trigger the caspase cascade and initiate apoptotic cell death. In addition, a few serum proteins like thrombin have shown to have a neurotoxic effect that could promote additional neural death by themselves or by activating the protease-activated receptors on the microglia.

The exact mechanism of action by which HSCs and MSC transplantation promote functional recovery after SCI is still not clear. HSCs secrete some neurotrophic growth factors, such as angiopoietin-1 and have been suggested to encourage vascularization[26] and thereby encourage wound healing in SCI. Transplanted MSCs might bring about CNS functional recovery by modifying the SCI milieu directly. MSCs may promote axonal regeneration or encourage functional plasticity by establishing an environment, which supports axonal growth, for example, by abrogating the inhibitory influence of the glial scar. MSCs synthesize a number of neurotrophic cytokines that stimulate nerve growth, including brain-derived

neurotrophic factor, NGF (Neural growth factor), and vascular endothelial growth factor (VEGF),[27] and others, have shown that MSC conditioned media stimulates neurite outgrowth *in vitro*, that in turn proved to promote nerve growth over inhibitory molecules which are present in the glial scar. An important interpretation of this finding is that the neurotrophic factors secreted by MSCs may have limited effect in the context of the SCI milieu. MSCs have been proposed to act as guiding strands for regenerating axons across the lesion site in the injured cord and along spinal cord tracts *in vivo*.[28] Human MSCs express various cell adhesion molecules and receptors that may function in MSC: neuronal interactions and hence axonal regeneration. These include ninjurin 1 and 2, Netrin 4, neuronal cell adhesion molecule, Robo1, and Robo4, that are known to regulate neuronal cell migration and axon guidance in development.[29] Alternatively, MSCs may also degrade nerve-inhibitory molecules present in the SCI milieu. Human MSCs express membrane type I matrix metalloproteinase and MMP2, which degrade chondroitin sulphate proteoglycans (CSPGs). The acute or subacute milieu of the damaged spinal cord may influence the mechanism by which HSC or MSC graft may induce tissue protection/repair in a manner that differs to the chronic setting. BMSCs from the stromal compartment of bone marrow and fractioned from hematopoietic stem cells by virtue of either their adherence to tissue culture plastic or their expression of distinct cell surface antigenic markers. BMSCs are non-teratogenic with anti-inflammatory and immunomodulatory effects and secrete neurotrophic factors, making them attractive candidates in central nervous system cell rescue and as autologous transplanted cellular sources of trophic support for endogenous and co-implanted cells.[30] Despite several claims of their neurogenic differentiation potential both *in vitro* and/or *in vivo*; there is no conclusive evidence to support this fact.[31]

2. Embryonic cell therapy vs. adult stem cell therapy

The advantage of embryonic stem cell therapy over adult neural stem cell therapy is that these cell lines can be cultivated *in vitro* for further use; but the disadvantage is that it is not autologous. There are risks that are involved of immunological rejection, tumor or teratoma formation. There has also been evidence that supports the fact that there have been tumorous proliferations owing to this unproliferated growth. Also there is an ever present risk of mutations, dedifferentiation and transdifferentiation and infections. The risk of infection is related to the direct injection of the cell lines into the meninges. The mechanism of differentiation is unknown, and there are major ethical issues regarding the use of live human embryos.

The greatest challenge in stem cell research is the inability to uncover the extracellular and intracellular mechanisms that determine and control the self-renewal and differentiation properties of stem cell in physiological and host environment. There is no means by which cell differentiation and the rate of cell renewal can be controlled. In the process, it has been shown that most of them rather become scar cells and this is perhaps one of the reasons for the very high incidence of increased pain in these patients.[32,33] On the other hand, adult stem cell therapy has the advantage of having an autologous or allogeneic source, with a low risk of immune rejection, and thus the need for immunosuppression can be avoided. Also, there is no risk of tumor or teratoma formation and no major ethical issues.

The objective of regenerative cell therapy is axonal elongation restoring myelin and complete integration into the host environment. The other ways in which cell therapy works on the injury site include peripheral nerve regeneration, using highly enriched Schwann cell suspension, activated macrophages, olfactory ensheathing cells or oligodendrocyte precursor cells. The majority of HSC and MSC transplantations in animal models of SCI occur in the acute injury phase. However, there are a number of studies using chronic models of SCI in animals that have reported increased functional recovery following MSC transplantation 6–12 weeks after injuries were induced, which is considered chronic in these model systems. Literature indicates that both the acute, subacute, and chronic injury may well be a therapeutic target for MSC grafting. It will be important to study these effects in future studies using HSCs and MSCs, as locomotor training activity when combined with other types of cell transplant has previously been reported to improve functional recovery in animal models of SCI.[34]

2.1. *Preclinical studies*

There is an impressive number of promising approaches for inducing regeneration or limiting neuronal damage by neuroprotective treatments based on rodent spinal cord injury models.[35–37]

Olfactory ensheathing cells transplanted into the injured spinal cord in animals promote regeneration and remyelination of descending motor pathways through the site of injury and the return of motor functions. Olfactory ensheathing cells are specialised glial cells that surround the olfactory sensory axons in the nose. They have properties of Schwann cells in promoting and assisting growth of axons. These properties have led to an increasing use of olfactory ensheathing cells in preclinical models of transplantation for spinal cord repair including complete transection, hemisection, tract lesion, and contusion with over 50 studies published in the last 10 years.[38–40] Transplantation of olfactory ensheathing cells into the lesioned corticospinal tract led to recovery of paw usage,[41] transplantation after complete transaction of the spinal cord led to recovery of coordinated walking and transplantation after spinal cord hemisection led to recovery of paw use and climbing.[42] Nasal olfactory ensheathing cell transplants assist recovery after spinal cord injury, including complete transection and there is evidence that adult olfactory tissue is effective when transplanted 1 month after spinal cord transection in the rat.[43]

Numerous electrophysiological and histological preclinical studies have revealed that the implantation of stem cells from bone marrow in animal models of SCI results in spared white and gray matter, neuronal and axonal regeneration, astrocyte proliferation, myelination, neovascularization, and functional improvement.[27,44,45] Several scientists have tried to generate neural progenitor/stem cells, motor neurons, oligodendrocyte

Table 1 – Tabulated information showing major clinical trials in SCI using stem cell therapy.

Reference	Lesion	Transplant	Source	Route of administration	Functional outcome
Lu et al, 2005[55]	Cervical: microwire dorsal column lesion.	2×10^5 cultured MSCs, neurally induced MSCs were injected at site after SCI.	BM-MSC	Intra thecal	No change in BBB score.
Neuhuber et al, 2005[26]	Cervical:2 mm hemisection.	5×10^5 MSC's seeded into gel foam and transplanted; 2×10^5 was injected directly after SCI.	BM-MSC	Intra thecal	Significant improvement on BBB scores was donor dependent.
Sigurjonsson et al, 2005[56]	Lumbar: 1–3 segment stretch of neural tube excised.	2×10^5 CD34 + HSCs were injected directly into lesion.	BM-MNC	Intra thecal	Transplanted MSCs exhibited indicative neuronal active membrane potentials.
Čízková et al, 2006[57]	Thoracic: balloon compression.	1×10^6 MSCs were injected intravenously 7 days after SCI.	BM-MSC	Intravenous	Significant improvement in BBB scores.
Himes et al, 2008[58]	Thoracic: 10 g weight dropped from a height of 12.5 mm (mild), 50 mm (severe), or 25 mm (moderate).	5×10^5 cultured MSCs injected directly into mild/severe lesions, 1×10^6 injected directly at the rostral and caudal edge of moderate lesions 7 days after SCI.	BM-MSC	Intra thecal	Significant improvement in BBB scores.
Courtney et al, 2009[59]	Cervical: hemisection.	1×10^6cultured MSCs injected via LP or intravenously. In other cases, 4.5×10^5 MSCs were injected directly into lesion. All immediately after SCI.	BM-MSC	Intra thecal/intra venous	No functional assessment.
Samdani et al, 2009[60]	Cervical: dorsolateral funiculotomy.	1.5×10^5 cultured MSCs were injected directly into the lesion immediately after SCI.	BM-MSC	Intra thecal	No functional assessment.
Yoon et al, 2007[61]	48 patients; 30 cervical, 18 thoracic.	17 acute (<14 days of SCI), 6 subacute (between 14 days and 8 weeks after SCI) and 12 chronic (>8 weeks after SCI) patients transplanted with 2×10^8 autologous MCPs injected directly into lesion. Post surgery, 5 cycles of GM-CSF injected subcutaneously (250 mg/m^2body surface area).	BM-MNC	Intra thecal/subcutaneous	29.5% of acute, 33.3% subacute 0% chronic, and 7.7% of control patients showed improved neurological function.
Pal et al, 2009[62]	20 patients; 3 cervical, 22 thoracic.	15 acute (<6 months after SCI) 10 chronic (>6 months after SCI) patients transplanted with 2 doses of 1×10^6 autologous cultured MSCs per kg body weight at 1-week interval via LP.	BM-MSC	Intra thecal	Follow up duration: 1–3 years, no significant improvement in ASIA scores. QoL improvement.
Deda et al, 2008[63]	9 patients; 6 cervical, 3 thoracic.	Between 20×10^6 and 67×10^6 autologous MCPs injected at multiple sites into lesion, in a carrier gel foam and intravenously.	BM-MNC	Intra thecal/intravenous	1 year follow up, all patients with considerable improvement. No adverse events.

Abbreviations: BBB – Basso, Beattie, and Bresnahan Locomotor Rating Scale; GM-CSF – Granulocyte–Macrophage Colony Stimulating Factor.

progenitor cells, and olfactory ensheathing cells *in vitro*, and transplant these cells into various animal models in order to verify the ability of neurons to functionally restore *in vivo*. The derived cells that were injected into the animal models were restricted to one specific cell lineage, therefore reducing the risk of tumorigenesis when compared with directly applying ESCs or iPS cells.[46] Stem cell-derived neural stem/progenitor cells (NS/PCs) are currently considered to be a highly promising option of various cell replacement techniques that are available for the treatment of spinal cord injury. Two different kinds of neurospheres were developed using a neurosphere based culture system, primary neurospheres and passaged secondary neurospheres,[47] and both of these neurospheres exhibited neurogenic and gliogenic potentials, respectively. Following this procedure, the cells were transplanted into rodent subacute SCI model. A coculture protocol was developed with endothelial cells for treating mouse ESCs in the expansion phase with sonic hedgehog and retinoic acid to generate motor neurons.[48] The significant recovery of sensory and motor function was demonstrated in adult mouse SCI model after transplantation. Depending on this protocol, another group of scientists working on ESC/iPSC derived stem cells presented a novel protocol which could produce a pure population of long-term self-renewing ESC/iPSC-derived neural stem cells.[49] In another model of SCI in rodents, chondroitin sulphate proteoglycans (CSPGs) were transplanted in chronically injured rats with NPCs and transplanted in the spinal cord with the intrathecal infusion of a growth factor cocktail. Strong evidence has been provided that this combinatorial approach can markedly increase the long-term survival of NPCs and greatly optimize their migration and integration in the chronically injured spinal cord. Furthermore, multiple mechanisms have also been demonstrated using this combinatorial strategy.[50]

2.2. *Clinical trials*

Out of the total 246 clinical trials that are being conducted all over the world on spinal cord injury patients, 17 of the trials are making use of autologous bone marrow stem cells or mesenchymal stem cells to treat the indication. No defined demarcations have been allotted when it comes to classifying SCI as acute, subacute or chronic. In general, provided there are no life-threatening injuries or complications, the acute stage is most likely to last up to the end of the period of spinal shock during which the patient is at the highest risk of developing complications. This period lasts upto 3 weeks from the time of injury. However, the presence of life-threatening injuries or complications can prolong the acute stage until such conditions no longer pose a threat. The subacute stage can be described as the period during which all systems of the body that are affected by the SCI are managed and retrained to function as safely and as conveniently as possible. This usually lasts up to 6 months, occasionally longer. According to the International Campaign for Cures of SCI Paralysis (ICCP), the chronic state is only achieved 12 months after SCI (where the preceding 6 months have indicated no change in functional capacity, thereby providing a stable baseline).[51] In two of these clinical studies, bone marrow derived mononuclear cells (BMMNCs) have been tested in conjunction with granulocyte–macrophage colony-stimulating factor (GM-CSF) administration. GM-CSF has previously been shown to mobilize BMMNCs into the injured spinal cord and promote functional recovery from SCI in mice. For these clinical trials, it was hypothesized that GM-CSF would not only promote the migration of BMMNCs into the lesioned spinal cord but also would have a direct effect on the transplanted cells by enhancing their survival and activating them to secrete neurotrophic cytokines.

The first trial had made use of a combination of BMMNCs along with the administration of GM-CSF in the acute setting (within 7 days of injury) with cells injected directly into the lesion site.[52] Out of all the six patients that had been treated, five showed signs of slightly improved neurological function. This same group of researchers have now gone on to treat further approximately 17 patients with SCI at 2 weeks post injury (i.e., still acute), 6 patients between 14 days and 8 weeks post injury (subacute), and 12 patients at >8 weeks post injury (chronic).[53] A control group of 13 patients were also included in the study; these patients were treated only with standard decompression and fusion surgery. In the latter study, 29.5% of the acute, 33.3% of the subacute, 0% of the chronic, and 7.7% of the control patients demonstrated a substantial increase in their neurological function at about 10 months post-transplantation. But since very few patients have been treated at this stage, it's not clear whether the noted neurological improvements were directly attributable to the treatment provided and not due to an intrinsic repair process and inherent natural recovery.[54]

Most studies of BMSCs have found beneficial effects of the cell therapy after SCI incidents [Table 1], largely as a result of neurotrophic factor secretion and possibly also because of secretion of anti inflammatory cytokine.[64] It has been demonstrated that BMSCs can promote to a certain degree, the growth of axons and sprouting, at least in transection models, especially when treated with growth factors prior to their implantation. Neural stem/progenitor cells are somatic cells that are found in Central Nervous System which are characterized by the capacity for self-renewal and multi lineage potential.[34] Apart from these characteristics, they may also exert tropic or trophic effects that could enhance plasticity, axonal sparing, and possibly regeneration.

Karimi-Abdolrezaee et al, 2011, developed an NPC-cell-based strategy that combined NPC transplants with *in vivo* delivery of growth factors that evidently increased the long-term survival of NPCs and also directed them toward an oligodendrocyte lineage, promoted axonal remyelination, and enhanced their functional recovery in the subacute phase after SCI, very significantly. However, their findings have also shown that the time window for a successful application of a dose of NPCs after injury was narrow; as the integration of NPCs in the chronically injured spinal cord was limited.[65] Their data has suggested a strong association between the expression of CSPGs and the poor survival of NPCs that had been transplanted in the chronically injured spinal cord. CSPGs, which are upregulated after an injury is known to play a key role in preventing the regeneration and plasticity after SCI.[49,66] Moreover, the inhibition of CSPGs promotes neural plasticity and functional recovery after acute or subacute SCI. Previous clinical studies have shown a significant

improvement in the motor and sensory functions with all together an improvement in the quality of life of SCI patients after implantation of autologous bone marrow derived stem cells.[67]

3. Future prospective: induced pluripotent stem cells

A potential alternative to avoid immunological rejection after non-autologous transplantation of stem cells is the use of reprogrammed adult cell (iPSC) technology, which means derivation of patient-specific and pluripotent cells derived from adult somatic cells. These cells have been generated from mouse and human somatic cells by overexpression of several defined factors. Recently, generation of iPSCs from human NSCs with a single transcription factor, OCT4, or using direct delivery of recombinant proteins has been described. iPSCs have identical patterns in gene expression, chromatin methylation, and embryoid body and viable chimera formation as ESCs. They are capable of differentiation toward all cell types, including neurons, glia, NPCs, and motor neurons. Furthermore, the derivation of iPSCs using non viral methods or by chemicals and small molecules including protein iPSCs makes this cell replacement strategy very attractive. Nevertheless, these cell types share similar disadvantages as other cell sources: teratoma formation, aberrant reprogramming, and the presence of transgenes in iPSC populations are the most concerning obstacles.[68]

4. Conclusion

In this present day and age, the number of trials that are being conducted for treating spinal cord injury has risen tremendously. Considerable advances have also been made to use cellular therapies as a treatment mode of spinal cord injury for both acute and subacute injuries. Due to the rise in number of trials using stem cells, randomized control trials are preferred as they establish the feasibility of using stem cells as a treatment mode. Using adult stem cells becomes a safer line of treatment as autologous therapy reduces rejection in host patient.

Conflicts of interest

All authors have none to declare.

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