**Neuroimmunology
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Review

Mesenchymal stromal cells as a choice for spinal cord injury treatment

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Abstract

Spinal cord injury (SCI) is a serious clinical problem that affects approximately 17,500 new patients per year in the United States. The main causes of SCI are vehicle collisions, falls, violence (mainly gunshot wounds), and sports/recreational activities. The final severity of the damage results from primary and secondary mechanisms that begin at the time of injury and last for months after trauma. To reduce the extent of damage, several treatments have been proposed. This review summarizes results from several studies that have pointed to cell therapy as the main form of neuroregenerative treatment. Mesenchymal stromal cells (MSCs) are important candidates for tissue regeneration due to the release of bioactive factors, as well as antiapoptotic effects, scar inhibitors, and angiogenic effects. Studies have shown that MSCs act in various ways on injured tissue, such as immunomodulation of the inflamed environment, release of bioactive factors, restoration of axon myelin, prevention of neuronal apoptosis, and neuroregeneration. Current research using MSCs aims to prevent secondary injury, promote regeneration, and replace destroyed spinal cord tissue. This review presents information about the damage from primary and secondary events after SCI, treatments usually used, and pre-clinical and clinical results aiming at the cell therapy using MSCs as a tissue regeneration strategy.

Keywords: Tissue regeneration, immunomodulation, neuroregeneration
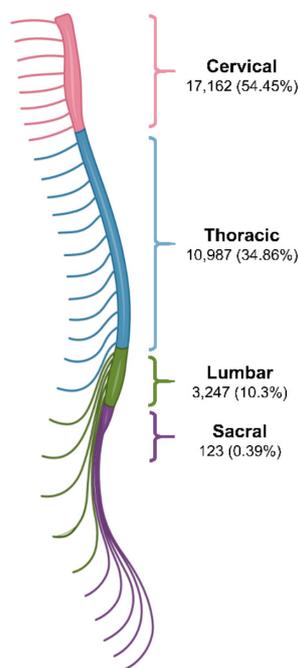
SPINAL CORD INJURY

Spinal cord injury (SCI) is a very serious health problem, and available treatments are not capable of spinal cord regeneration[1]. SCI can lead to permanent neurological deficits, including motor and sensory disabilities, with high rates of physical disability and mortality. It can lead to serious damage to the physical and mental health of patients, which can cause serious socioeconomic issues[2,3]. According to the National
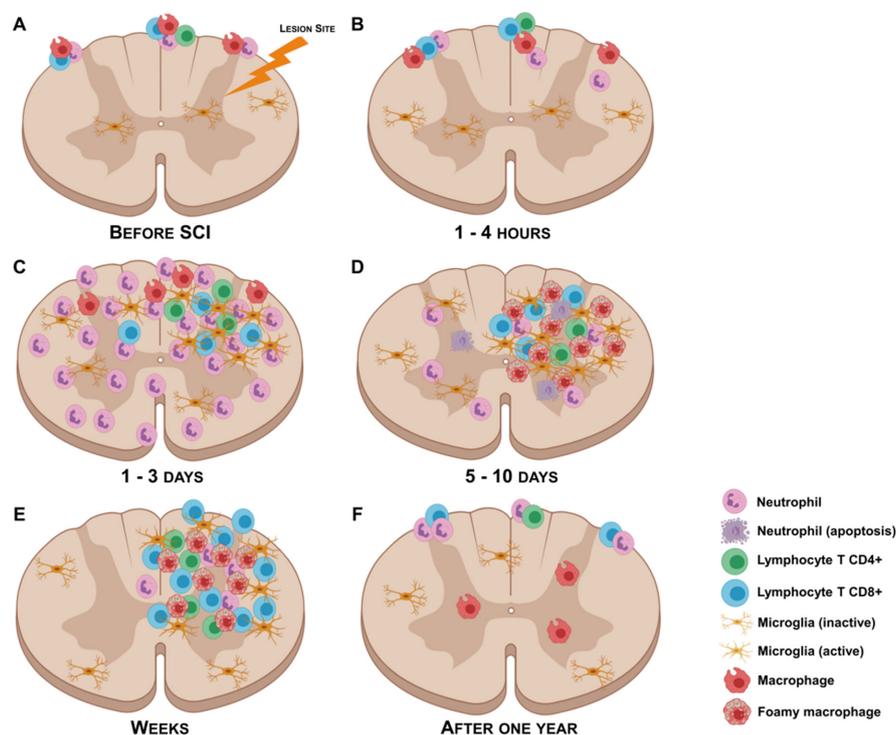
Figure 1. Number of cases of spinal cord injury according to trauma level. According to the National Spinal Cord Injury Statistical Center in the United States. The first region of the spine, the cervical region, is the most affected, accounting for more than half (54.45%) of the total number of cases, followed by the thoracic (34.86%) and lumbar (10.3%) regions. The sacral region is the least injured, accounting for 0.39% of cases

Spinal Cord Injury Statistical Center, in the United States, there are approximately 17,500 new cases per year, of which 81% are male. The average age of new cases has changed since the 1970s, from 29 to 43 years old. The main causes are vehicle collisions, falls, violence (mainly gunshot wounds), and sports or recreational activities[4]. In 2018, a survey conducted by the same institution about the frequency of SCI cases according to the level of the spinal cord showed that, of the total of 31,519 cases, 17,162 (54.45%) are lesions in the cervical region, 10,987 (34.86%) in the thoracic region, 3247 (10.3%) in the lumbar region, and 123 (0.39%) in the sacral region[4] [Figure 1].

According to the National Spinal Cord Injury Statistical Center, in the United States, the first region of the spine, the cervical region, is the most affected, accounting for more than half (54.45%) of the total number of cases, followed by the thoracic (34.86%) and lumbar (10.3%) regions, while the sacral region is the least injured, accounting for 0.39% of cases.

SCI results in disruption of the connection between the central nervous system and the rest of the body. Trauma, disease, and even spinal cord degeneration can compromise the sensory, motor, autonomic, and reflex functions of affected individuals, and only 0.4% of cases show complete recovery from their deteriorated functions[5]. The pathology of SCI results from two stages: (1) primary injury, which triggers damage to the spinal cord; and (2) secondary injury, characterized by events arising after the initial injury. Primary injury is usually the determining factor of the severity of the damage and the effects vary according to the affected site, which may be the cervical, thoracic, thoracolumbar, or sacral lumbar region[6].

After trauma, secondary events such as ischemia, anoxia, and inflammation further compromise the injured tissue. There is the migration of inflammatory cells to the lesion site, which release inflammatory cytokines; formation of reactive oxygen species (ROS), which lead to DNA damage and protein oxidation; and mitochondrial malfunction due to ionic imbalance[6,7].

Figure 2. Immune cell migration in response to spinal cord injury (humans) (A-C): neutrophils migrate from vessels and perivascular region immediately after trauma, while lymphocytes, macrophages, and microglia migrate later. (D-F): the production of proinflammatory factors in response to the injured tissue results in tissue deterioration and damage spreading (secondary injury), which may compromise and determine the patient's grade of spinal cord injury recovery

Prior to the occurrence of SCI [Figure 2A], inflammatory cells, except for microglia, are found in the blood vessels and perivascular regions of the spinal cord. The microglia are distributed by gray and white matter. Mechanical damage to the injury (or trauma) results in immediate neuronal and glial death at the injury site. After the injury, an inflammatory process mediated by neutrophils, macrophages, lymphocytes, and microglia present in the vascular and medullary region develops. This secondary process leads to late deterioration of the spinal cord, resulting in worsening of the lesion condition. Immediately after injury, there is immediate neutrophil extravasation [Figure 2B] to the medulla, followed by late migration [Figure 2C] of lymphocytes and macrophages to the lesion site[8,9]. The microglia are activated [Figure 2C] and shorten and thicken their branches and migrate to the site of injury. Inactivated microglia remain in uninjured regions. During this period, there is production and release of proinflammatory factors (mainly activated microglia and macrophages), such as TNF-α and IL-6β, as well as proteases and lysosomal enzymes. The inflammatory environment promotes the spread of damage, inducing cell death and preventing any spontaneous spinal cord regeneration[10,11]. Within 5-10 days [Figure 2D], neutrophils enter apoptosis, while macrophages and microglia proliferate in the lesion region. After a few weeks [Figure 2E], the number of CD8+, CD4+, and T lymphocytes increases in the vessels of the injured region and the macrophage/microglial population remains in large numbers. The few remaining neutrophils accumulate in the necrotic region. One year after the injury [Figure 2F], neutrophils and lymphocytes are found in the intravascular region. The microglia remain in the region of white matter in their inactivated form, while macrophages are found in the gray matter[8-11] [Figure 2].

Secondary events mainly lead to neuron necrosis and apoptosis, which occur in the first hours after trauma[6,7]. At the same time, the body tries to prevent the injury from becoming more serious. In this

sense, repair cells act and try to reverse the damage caused, expressing factors responsible for the formation of new vessels, eliminating cell debris, and remodeling damaged neurons[5].

Treatment of the injury is limited by the low regenerative potential of the central nervous system, but spinal cord plasticity may support the recovery of some lost mechanisms after the injury. Spinal cord plasticity is related to factors such as synaptic reorganization, axonal sprouting, and neurogenesis[12]. There is little evidence of spontaneous axon regeneration after SCI but there is evidence for axonal sprouting as synaptic compensation. Regeneration is the growth of new axons, while sprouting involves the growth of collateral branches of the fibers. Due to the formation of a glial scar, which is a physical and chemical barrier to axonal regeneration, axonal sprouting is an alternative found because it can occur around a glial scar. To support SCI repair, studies have shown that functional exercise, neurotrophic factors, and cell therapy can effectively improve spinal cord neural plasticity response[12,13].

TREATMENTS

After SCI, mammals are unable to regenerate nervous tissue, which can lead to lifelong disability[14]. Some treatments may be used after SCI to try to reduce side effects and protect injured nerve tissue. Decompression surgery is one of the treatments used to relieve pressure, reducing hypoxia and ischemia caused by edema and hemorrhage[15,16]. Studies have shown that patients who underwent decompression surgery before 24 h after SCI showed an improvement compared to patients who underwent surgery more than 24 h after SCI[16-18]. Fehlings *et al.*[17] showed that more than half of the patients who underwent surgery (before or after 24 h) had at least one grade of improvement on the American Spinal Injury Association Impairment Scale (AIS) without statistical difference between the groups. However, a higher percentage of patients had two or three grade improvement on the AIS scale in the group who underwent surgery before 24 h after 6 months of follow-up. Sewell *et al.*[18] observed that patients with spinal cord injury (cervical level) who underwent surgery before and after 24 h showed no neurological improvement on the AIS scale with significant difference after 6 months of follow-up. However, there is a tendency for improvement in patients with early surgery, particularly in patients experiencing > 2-grade AIS improvement.

Another commonly used treatment after SCI is the intravenous application of methylprednisolone sodium succinate (MPSS). The central MPSS effect on SCI is the inhibition of posttraumatic lipid peroxidation occurring in neurons and blood vessels, directly compromising the function and integrity of neuronal and axonal membranes, causing microvascular damage and secondary ischemia that indirectly contribute to secondary neuronal injury. In addition to inhibiting lipid peroxidation, MPSS inhibits post-traumatic spinal cord ischemia, supports aerobic energy metabolism, and attenuates the neurofilaments loss[19,20]. However, the use of MPSS is not a consensus among professionals, because, even with improvement when applied up to eight hours after injury, this drug can cause gastrointestinal bleeding and infection[16,21]. Due to these associated complications, MPSS should be used with caution.

Neuroprotective agents are also a treatment option for spinal cord injury. These agents aim to prevent neuronal cell death by reducing side events that result in cell dysfunction and death[16,22]. Many of these neuroprotective agents have been studied, but without positive results for thoracic spinal cord injury patients[23,24]. Riluzole, a sodium channel blocker, and hypothermia, which decreases central nervous system metabolism, have been shown to be effective neuroprotective agents for the treatment of spinal cord injury[16,25-27]. Mu *et al.*[28] associated riluzole and MPSS in rats with spinal cord injury. The combined treatment preserved the tissue at the epicenter of the lesion but did not have a clear effect on the myelination index. The results of this study clearly demonstrate the potential beneficial effects of a combined approach in treating spinal cord injury.

Electroacupuncture/electrostimulation is another treatment that has long been used in spinal cord injury therapy and has been shown to inhibit inflammation, promote the secretion of neurotrophic factors, and reduce secondary injuries[29,30]. Chen *et al.*[31] performed electroacupuncture on rats with spinal cord injury and found that this treatment is effective to prevent oligodendrocyte apoptosis and to improve functional recovery after spinal cord injury. Krueger *et al.*[32] performed the association of electrostimulation with mesenchymal stromal cells derived from adipose tissue in dogs with SCI and observed improvement, but without statistical difference between the associated treatments (electrostimulation and MSCs) and isolated.

There are many studies developing different techniques to assist the recovery of spinal cord injury patients. These studies aim to combat the primary or secondary events of the injury, aiming at patient improvement, but without regenerating the nervous tissue. Cell-based therapy is the only promising treatment aimed at regeneration. Many cell types from different sources and infusion pathways have been studied or are being evaluated in ongoing studies.
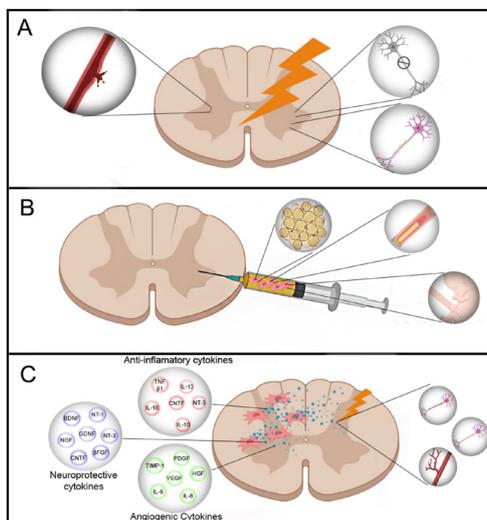
STROMAL CELLS THERAPY

Cell therapy brought the promise of regenerating tissue after SCI, although the mechanism by which this type of cell therapy achieves neurological recovery have not yet been fully explained. Adult stem cells, such as MSCs, are stromal cells with potential self-renovation, multiple lineage differentiation, and immunomodulatory potential[33]. MSCs are major candidates for tissue regeneration due to release of bioactive factors, as well as anti-apoptotic, scar inhibitor, and angiogenic effects[34]. These cells also have the potential for differentiation into various adult cell types, including neurons[35,36]. The main source of MSCs is bone marrow, but other sources such as adipose tissue and umbilical cord, which are easily collected tissues, are also being used in preclinical and clinical studies. Following MSC transplantation, several repair processes occur, including: (1) the release of neurotrophic factors that may prevent nerve degeneration and apoptosis, as well as support neurogenesis, axonal growth, remyelination, and cellular metabolism; (2) reduction of neuroinflammation because MSCs can secrete a variety of soluble molecules, such as anti-inflammatory cytokines; (3) induction of angiogenesis, an important process by which new vasculature sprouts from pre-existing blood vessels; and (4) activation of endogenous spinal cord mechanisms capable of restoring some previously lost neurological functions[37-39] [Figure 3].

Although the precise mechanism by which MSCs transplantation promotes functional recovery after SCI is still unclear, it is widely accepted that most benefits of MSCs transplanted rely on the secretion of different factors and biomolecules[40]. MSCs release cytokines that may be neuroprotective and neuroregenerative. Some cytokines, e.g., neurotrophic factor, monocyte chemoattractant protein-1, and granulocyte-macrophage colony stimulating factor, play a role in neuroprotection; induce monocyte recruitment during inflammation, enhancing myelin debris clearance in central nervous system injuries; and inhibit apoptosis of neuronal cells and gliosis after SCI[41]. Other neurotrophic factors expressed by bone marrow derived mesenchymal stromal cell (BM-MSC) such as brain derived neurotrophic factor, glial-derived neurotrophic factor, and nerve growth factor can assist nervous tissue neuroregeneration including the formation of new synapses and myelination and promote axonal regeneration and functional recovery after SCI[42,43].

MSCs also reduce inflammation, which is a secondary event after trauma. These cells change the inflammatory profile to the anti-inflammatory one, which could have a beneficial effect on functional recovery after SCI[42]. Transplantation of MSCs also reduces the expression of glial scar marker (GFAP), a characteristic compatible with a resolutive inflammatory reaction[42], and increases the expression of Treg-gene[44].

Among the molecules secreted by MSCs, pro-angiogenic factors such as vascular endothelial growth factor (VEGF) are essential for repair of damaged tissue. VEGF/PDGF (platelet-derived growth factor) stimulated

Figure 3. A: following injury, trauma and ruptured blood vessels result in ischemia, anoxia, and inflammation. This environment leads to neuronal death and degeneration; B: the infusion of MSCs can be done in different locations. There is still disagreement regarding the number of cells and infusions, but MSCs from different sources can be used for treatment (umbilical cord, adipose tissue, and bone marrow); C: after infusion, MSCs change the injured environment by releasing anti-inflammatory (TNF-β1, IL-13, IL-18, CNTF, NT-3, and IL-10), neuroprotective (BDNF, GDNF, NGF, NT-1, NT-3, CNTF, and bFGF), and angiogenic cytokines (TIMP-1, VEGF, HGF, PDGF, IL-6, and IL-8). Cell survival, remyelination, and vascular repair can also be observed. MSCs: mesenchymal stromal cells; TNF-β1: transforming growth factor β1; IL-13: interleukin 13; IL-18: interleukin 18; CNTF: ciliary neurotrophic factor; IL-10: interleukin 10; BDNF: brain-derived neurotrophic factor; GDNF: glial cell-derived neurotrophic factor; NGF: nerve growth factor; NT-1: neurotrophin 1; NT-3: neurotrophin 3; bFGF: basic fibroblast growth factor; TIMP-1: tissue inhibitor of metalloproteinase-1; VEGF: vascular endothelial growth factor; HGF: hepatocyte growth factor; PDGF: platelet-derived growth factor; IL-6: interleukin 6; IL-8: interleukin 8

angiogenesis results in a higher blood vessel density at the injured site, lesion size reduction, and white matter sparing with functional outcome after SCI[45].

Although most studies showed evidence that MSCs most likely act through their secretions (paracrine effect)[46-48] and not via their own integration/differentiation within the host tissue, some authors have reported the potential for MSCs transdifferentiation in cells of the nervous system and have shown that, after infusion into the spinal cord, these cells possibly promote regeneration of neurons because they have neuronal markers[49-52]. *In vitro* studies have shown that BM-MSC possess an intrinsic capacity to differentiate into neural-like and glial-like cells and express nestin, βIII-tubulin, neurofilaments, neuron-specific enolase, and glial fibrillary acidic protein (GFAP)[53-55].

A better understanding of the mechanisms underlying the regenerative effects of stromal/progenitor cells in the nervous system is essential for development of future cell-based therapies to treat SCI in humans.

Despite a lot of effort in recent years to develop new therapies using stromal cells to treat central nervous system trauma, there is no consensus on the cell type, source, number of cells, infusion pathways, and number of infusions suitable for achieving this goal[56].

Adult stromal cells have been used in preclinical research and clinical studies. These studies demonstrate how research uses different strategies for treating spinal cord injury using different sources of MSCs, multiple cell infusion pathways, and various models of SCI. Various types of SCI can be treated with cell therapy using MSCs, including even in patients with complete SCI[57-59]. MSCs can be transplanted intrathecally, intramedullary, intravenously, or intraarterially with different MSC sources (bone marrow, adipose tissue, umbilical cord blood, skin, and dental tissues)[5] [Tables 1 and 2].

Table 1. Preclinical study of spinal cord injury using stromal cells

Study	SCI animal model	MSCs source	MSCs source	SCI site	MSCs infusion site	Number of transplanted MSCs	Infusion time	Results
Chen *et al.*[50] 2015	Wistar rat	BM-MSCs	Wistar Rats	T12	Tail vein and local transplantation	Tail vein: 1 × 10^6 (2 infusion) Local: 4 × 10^5 (1 infusion)	Acute (MSCs infusion after injury)	BMSC transplantation into the area of spinal cord injury can promote repair and regeneration of the SCI
Karaoz *et al.*[1] 2012	Wistar albino rats	BM-MSCs	Wistar Rats	T10-T11	Into the injured spinal cord	3 × 10^5	Acute (MSCs infusion after injury)	Cell transplantation into the contused spinal cord enhances the extent of myelination in the spared white matter and improved locomotor recovery
Quertainmont *et al.*[42] 2012	Wistar rats	BM-MSCs	Wistar Rats	T10	Caudal vein	1 × 10^6	7 days after injury	There has been an improvement in behavioral testing in mice transplanted with MSCs
Menezes *et al.*[36] 2014	Sprague-Dawley rats	ADSCs	Human fragments of subcutaneous adipose tissue and lipoaspirates	T8-T9	Cells were injected once, 1 cm rostrally to the lesion epicenter	Data not available	Acute (MSCs infusion after injury)	ADSCs are efficient in promoting regeneration after SCI and suggest laminin as a mediator of the beneficial effects of these cells
Chung *et al.*[60] 2016	Sprague-Dawley rats	UCB-MSCs	Human	T9	Injury site (in three spinal cord segments)	2 × 10^5	3 days after SCI	The therapeutic potency of transplanted UCB-MSCs occurs by increasing the levels of BDNF, NGF and NT-3 in the SCI
Melo *et al.*[53] 2017	Wistar rats	SD-MSCs	Human dermis of scalp tissue samples	T11	Intrathecal injection	10^4	One hour after SCI	Transplanted MSCs reduced the severity of tissue loss and improved functional recovery through the attenuation of immune responses and promotion of neuronal protection in the acute phase of SCI
Yang *et al.*[61] 2017	Sprague-Dawley rats	Dental stem cells	Human dental follicle, apical papilla, dental pulp	T10	Injury site (rostral and the caudal stumps) and a cell pellet was grafted into the transected gap lesion	2.5 × 10^5	Acute (MSCs infusion after injury)	Dental stem cells presented remarkable tissue regenerative capability after spinal cord injury through immunomodulation, differentiation, and protection capacities

BM-MSCs: bone marrow derived mesenchymal stromal cells; ADSCs: adipose-derived mesenchymal stromal cells; UCB-MSCs: umbilical cord blood-derived mesenchymal stromal cells; SD-MSCs: skin-derived mesenchymal stromal cells; SCI: spinal cord injury; BDNF: brain-derived neurotrophic factor; NGF: nerve growth factor; NT-3: neurotrofin-3; BMSC: bone marrow mesenchymal stem cell

As the results of preclinical trials have shown that MSCs are effective in the treatment of SCI, clinical studies have been conducted showing the safety and efficacy of MSC therapy. There are currently seven trials enrolled in the clinical trials platform that are recruiting patients for MSC therapy[62].

The results from both preclinical and clinical trials show that MSC transplantation seems to help mainly in sensory recovery. Studies demonstrated a significant enhancement in bladder compliance, bladder sensation, and bowel function, which may be an early indication of future improvements in urinary

Table 2. Clinical trials of spinal cord injury using stromal cells

Study	MSCs source	Injury type	SCI site	MSCs infusion site	SCI time	Results
Cristante et al.[63] 2009	BMSC	Complete	Cervical or thoracic	Peripheral bloodstream	Chronic	There was a positive response in 66.7% of patients for SSEP, regardless of whether the patient had paraplegia and quadriplegia
Frolov and Bryukhovetskiy[57] 2012	PHSC	Complete e incomplete	Cervical (C4-C8)	Intrathecal	Chronic	SEP and MEP improved in patients treated with MSCs
Yoon et al.[64] 2007	BMSC	Complete	Cervical or thoracic	Injury site	Acute	Neuropathic pain was observed in 20% of patients and 7.7% of control group; 20% of the treated group showed improvement from AIS A to B or C
Pal et al.[65] 2009	BMSC	Complete	Cervical or thoracic (C4-T10)	Lumbar puncture	Acute and Chronic	Two patients showed significant improvement for SSEP, MEP and NCV, being able to walk and sit with the aid of supports; three patients had improvements in bladder function
Sharma et al.[66] 2012	BMSC	-	-	Intrathecal	-	Improved muscle strength, balance, urine control, and sensation and reduced spasticity in 100% of patients
Mendonça et al.[67] 2014	BMSC	Complete	Thoracic or lumbar	Injury site	Chronic	Improvement in lower limb motor function was observed in eight patients; seven patients had sensation in the anal region, of whom six changed to AIS B and one to AIS C
Vaquero et al.[68] 2017	BMSC	Incomplete	Cervical, thoracic, or lumbar	Lumbar puncture	Chronic	There was significant motor improvement in 60% of cases; improvement in sexual function in 25% of men; 88.8% improvement in bladder function
Karamouzian et al.[69] 2012	BMSC	Complete	Thoracic or lumbar (T1-L1)	Lumbar puncture	Acute	ASIA A to C improved in 45.5% of treated patients, increasing motor and sensory score (patients were able to walk with support)
Kumar et al.[70] 2009	BMSC	Complete e incomplete	Cervical, thoracic, lumbar, or sacral	Lumbar puncture	Chronic	There was an improvement in 32.66% of the cases; ASIA A score progressed to B-D in 30.5% of patients
Shin et al.[71] 2015	hNSPC	Complete e incomplete	Cervical (C3-C8)	Injury site	Acute and Chronic	In the treated group, 26.32% of patients improved the AIS A score to B or C, compared to 6.67% in the control group; increase in recovery of motor levels was observed
Hur et al.[59] 2016	ADMSC	Complete e incomplete	Cervical, thoracic, or lumbar	Intrathecal	-	Motor ASIA score improved by 35.71%, voluntary anal contraction by 14.29%, and sensory ASIA score by 71.43% of patients
Oh et al.[72] 2016	BMSC	Incomplete	Cervical	Injury site	Chronic	There was motor improvement in the upper extremities of 12.5% of the cases
Vaquero et al.[58] 2016	BMSC	Complete	Thoracic	Injury site	Chronic	There was evolution from complete to incomplete lesion in 30% of patients; SSEP appeared in 58.3%, while MEP in 25%; voluntary contraction of muscles below the lesion was achieved in 58.3%; urinary tract functions improved in 83%

hNSPC: human neural stromal/progenitor cells; PHSC: peripheral hematopoietic stromal cells; ADMSC: adipose-derived mesenchymal stromal cells; SSEP/SEP: somatosensory evoked potentials; MEP: motor evoked potentials; NCV: nerve conduction velocity; ASIA: American Spinal Injury Association; AIS: ASIA Impairment Scale; MSCs: mesenchymal stromal cells; SCI: spinal cord injury; BMSC: bone marrow mesenchymal stem cell

function [68,69]. The motor function is shown in few patients and with no significant improvement. Studies suggest that motor improvement is associated with multiple MSC applications, which may be an important factor in therapeutic effectiveness [56,58].

CHALLENGES AND PERSPECTIVES

SCI has been extensively studied and its mechanism is already known. Many preclinical and clinical studies have already been performed using drugs associated with SCI, neurotrophic factors, and stem cells. In cell therapy, several cell types and sources have already been tested. Embryonic stem cells involve ethical issues and chromosomal instability that make them difficult to use in clinical trials. MSCs have emerged as an alternative, but with a more limited differentiation capacity. Studies have already demonstrated the effectiveness of these MSCs in SCI, but the next challenges are to identify the type of cell that has the most appropriate potential to support SCI regeneration and develop an infusion methodology that can overcome the hostile microenvironment and facilitate MSCs delivery in damaged neural tissue. Understanding how the reorganization of injured neural tissues associated with MSCs is also crucial for restoring neural function but remains largely unknown and needs further clarification. While addressing these challenges, it is still necessary to maintain the safety of patients involved in the studies, as the mechanisms of action of stem cells are not yet fully described.

CONCLUSION

SCI is a serious disease which generates disability with unknown cure. Different treatments have already been developed but none of them has tissue regeneration as a result. Mesenchymal stromal cells seem to be a promising alternative because, in addition to tissue regeneration, they can act to improve the inflamed environment through immunomodulation, release of bioactive factors, and restoration of axon myelin. Preclinical and clinical research studies will enable the definition of the best source of MSCs, cell number, route of infusion, and number of infusions that may lead to clinical improvement for SCI patients.

Animal model and human clinical studies have shown the regenerative and neuroprotective potential of MSCs from different sources. In addition, it is interesting to note the absence of adverse effects after MSCs infusion. MSCs emerge as a new alternative therapy because they are not limited by the time of injury, showing promising results in patients with acute and chronic lesions, or by the type of injury, resulting in improvements in patients with complete and incomplete SCI.

DECLARATIONS

Authors' Contributions
Designed of the work, summarized the references and wrote the manuscript: Fracaro L
Summarized the references, wrote the manuscript, prepared the figures: Zoehler B
Discussed paper writing and revised the manuscript: Rebelatto CLK

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