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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All authors declared that there are no conflicts of interest.

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Consent for publication

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