Cell and Tissue Research (2019) 377:125–151
https://doi.org/10.1007/s00441-019-03039-1

REVIEW

Spinal cord injury: pathophysiology, treatment strategies, associated challenges, and future implications

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Received: 11 June 2018 / Accepted: 1 April 2019 / Published online: 7 May 2019

Abstract

Axonal regeneration and formation of tripartite (axo-glial) junctions at damaged sites is a prerequisite for early repair of injured spinal cord. Transplantation of stem cells at such sites of damage which can generate both neuronal and glial population has gained impact in terms of recuperation upon infliction with spinal cord injury. In spite of the fact that a copious number of pre-clinical studies using different stem/progenitor cells have shown promising results at acute and subacute stages, at the chronic stages of injury their recovery rates have shown a drastic decline. Therefore, developing novel therapeutic strategies are the need of the hour in order to assuage secondary morbidity and effectuate improvement of the spinal cord injury (SCI)-afflicted patients' quality of life. The present review aims at providing an overview of the current treatment strategies and also gives an insight into the potential cell-based therapies for the treatment of SCI.

Keywords Spinal cord injury · Neural stem cells · Biomaterial channels · Cell-matrix hybrids · Neuroregeneration · Remyelination

Introduction

Spinal cord injury (SCI) is a serious damage to the spinal cord that can lead to severe dysfunction of the spinal cord. The injury can be a result of either a physical trauma or any other non-traumatic causes. The traumatic causes includes fractures, road accidents, work-related falls, acts of violence, and sports/recreation activities, whereas the non-traumatic causes are insufficient blood supply, infection, cancer, osteoarthritis, etc. Spinal cord damage has a high burden of impairment and devastating outcomes in either ways (Kennedy and Chessell 2013).

As per the recent reports from the National Spinal Cord Injury Statistical Center (NSCISC) at the University of Alabama, Birmingham, the diversity of causes for SCI has changed drastically since 2010 and has been documented as follows: 38% due to road accidents, 30.5% due to falls, 13.5% due to violence, 9% for sport activities, and 9% for various other reasons. The annual incidence of SCI is around 54 cases/million population/year in the USA. The average age at which a person is afflicted with SCI is increased from 29 to 42 years during the 1970s to 2016 out of these cases males accounted for 80%. The average annual expenses for all groups (high or low tetraplegia and paraplegia) of SCI patients were reported to be $676,000 in the USA. Thereby, SCI poses to be a serious financial burden on any individual patient along with their family and the society as well (NSCSC 2016). In India, the scenario of SCI remains more challenging because of the low global gross domestic product (GDP) (~$4000) as compared to the global economy (~$13,100). In India, the accessing of all components of SCI management at a comprehensive spinal injury center is even more difficult not only due to lack of proper infrastructure but also because of monetary constraints (Chhabra and Bhalla 2015). Hence, it is very important to have

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a gold-standard economic medical technology for SCI, which regenerates the damaged tissue and helps in faster recovery.

The current status of occurrence of SCI, both regionally and worldwide necessitates the development and implementation of novel treatment strategies to reap the maximum therapeutic benefit for effective regeneration of the damaged part of spinal cord in a cost-effective manner. The prevalent SCI treatment methods involve the usage of anti-inflammatory medications (ketorolac, minocycline, riluzole, magnesium, etc.); decompression surgery (decompression and instrumentation) to stabilize the spinal column; and good supportive management for preventing secondary injury.

Acute management of SCI is very important immediately after the injury for quick recovery of neurological functions. Early surgical decompression has been shown to decrease the odds of SCI by two-grades in ASIA impairment scale. Treatments with anti-inflammatory drugs, blood pressure augmentation, and stabilizing the respiratory and cardiac complications are crucial in the rehabilitation process to prevent the secondary complications after the injury (Hachem et al. 2017). The rehabilitation treatment for SCI patients requires a multidisciplinary approach involving a team consisting of a physiotherapist, psychiatrist, occupational therapist, dietician, social worker, speech therapist, and one of the patient's family members. Even though the rehabilitation process is time consuming and expensive, the results from this approach are promising. A study by Berlowitz and Tamplin demonstrated the positive implication of respiratory muscle training (RMT) for cervical SCI. RMT is effective to increase the strength of respiratory muscles and also lung volumes for people with cervical SCI. Further long-term studies are required on functional outcomes following RMT (such as cough efficacy, dyspnea, and quality of life) (Berlowitz and Tamplin 2013). The randomized controlled trials (RCTs) performed with SCI patients to compare locomotor training and exercise with the controls (no treatment) witnessed inconclusive results with locomotor training on walking function compared with any other physical rehabilitation. Locomotor training for people after SCI did not show a significant increase neither in the walking velocity nor in the walking capacity (Mehrholz et al. 2012).

Although neural stem cell transplantation (NSCT) therapies have shown potential therapeutic effects, their clinical use is hindered due to the lack of their long-term survivability. Various researchers have tried embedding stem cells within different matrix materials like, collagen, laminin, and fibronectin and have shown significant enhancement in terms of their growth, differentiation, and survival rate (Somaiah et al. 2015; Yang et al. 2004). This systematic review therefore addresses the successful pre-clinical approaches that are used currently and gives an assessment of the challenges involved in the evolvement of novel three-dimensional neural stem cell (NSC) cultures with the prospect of their relevant clinical translation.

Spinal cord injury

Spinal cord injury may result from a direct impact of a fast-moving object hitting the spine or by indirect force caused by movements of the spine, which are beyond the physiological range. These injuries are usually related to compression, flexion, extension, or rotation. The common mechanisms of SCI in the lower cervical spine include distractive hyperflexion, compressive hyperflexion, distractive hyperextension, compressive hyperextension, and axial compression. According to Denis (1983), the injuries to the thoracic and lumbar spine can be classified as wedge compression fracture, burst fracture, fracture dislocation, and seat belt injury. Such injuries usually result in breakage of the vertebral ring and obstruction of the spinal canal. The individual commonly suffers from a spinal shock, described as a period of transient inexcitability or hypoexcitability of the isolated spinal cord, situated below the level of transaction of the cord (Braakman 1991). Spinal cord lesions can also be caused due to non-traumatic events such as congenital and developmental disorders, degenerative CNS disorders, genetic and metabolic disorders, infections, inflammations, ischemia, toxicity, and tumors (McDonald and Sadowsky 2002).

Spinal cord injuries are usually graded on the ASIA (American Spinal Cord Injury Association) impairment scale (Table 1):

Certain clinical syndromes associated with SCI

Based on the clinical presentation, SCI has been grouped into various SCI syndromes. The incidence of these SCI syndromes varies with their etiologies. Central cord syndrome (CSS) is the most common of the SCI syndromes, accounting for approximately 9% of all traumatic SCIs and others accounted as anterior cord syndrome (ACS) is 2.7% and Brown-Sequard syndrome (BSS) is 1–4%. Conus medullaris syndrome (CMS) and cauda equina syndrome (CES) are accounted less than 1% (McKinley et al. 2007).

Central cord syndrome A lesion occurs almost exclusively in the cervical region, resulting in the development of a sacral sensory sparing along with a greater weakness in the upper limbs than in the lower limbs (Epstein and Hollingsworth 2015).

Brown-Sequard syndrome A lesion that produces relatively greater ipsilateral proprioceptive, motor loss and contralateral loss of sensitivity to pain and temperature (Tseng et al. 2015).

Table 1 The American Spinal Injury Association (ASIA) impairment scale (modified Frankel classification)

ASIA grade	Description	
A	Complete	No sensory or motor function persists in the sacral segments S4–S5
B	Incomplete	Sensory and not motor function remains below the neurological level, including the sacral segments S4–S5
C	Incomplete	Motor function is pertained below the neurological level. More than half of the key muscles below the neurological level possess a muscle grade less than 3
D	Incomplete	Motor function is restored below the neurological level, and at least half of the key muscles below the neurological level have muscle grade greater than or equal to 3
E	Normal	Sensory and motor functions remain normal

Anterior cord syndrome A lesion that produces variable loss of motor function and sensitivity to pain and temperature, while maintaining proprioception (Diaz and Morales 2016).

Conus medullaris syndrome Injury of the sacral cord (conus) and lumbar nerve roots within the spinal canal, usually resulting in an areflexic bladder and bowel and lesions in the lower limbs. Sacral segments may occasionally show preserved reflexes, e.g., bulbocavernosus and micturition reflexes (Diaz and Morales 2016).

Cauda equina syndrome Injury to the lubosacral nerve roots within the neural canal which results in areflexic bladder and bowel and lesions in the lower limbs (Kirshblum et al. 2011).

A potent indicator of the extent of SCI is muscle-strength and it is scored after certain tests that are listed as follows:

0 = Total paralysis
1 = Palpable or viable contraction
2 = Active movement, gravity eliminated
3 = Active movement, against gravity
4 = Active movement against some resistance
5 = Active movement against full resistance (Kirshblum et al. 2011; Maynard Jr et al. 1997)

Pathophysiology

The pathophysiology of SCI has two phases, a primary phase and a secondary phase. The primary phase involves the initial mechanical injury during which force is directly imparted to the spinal cord, disrupting axons, blood vessels, and cell membranes. This is followed by a delayed period of tissue destruction, which involves vascular dysfunction, edema, ischemia, excitotoxicity, electrolyte shifts, free radical production, inflammation, and restrained apoptotic cell death (Rowland et al. 2008). This period of secondary injury phase is a critical therapeutic target for the prevention of injury progression (Kim et al. 2017). Primary injury leads to direct cell death and bleeding (Hausmann 2003) but it rarely transects or fully disrupts the anatomical continuity of the spinal cord (Rowland et al. 2008). It has relevant significance as the spared axon acts as the neural substrate for emerging therapeutic strategies. Animal studies have shown 5% of the original number of axons is optimal for sustenance of neurological functions (Fehlings and Tator 1995; Kakulas 2004; Rowland et al. 2008). The secondary phase can be further subdivided into acute, subacute, intermediate, and chronic phases. The most immediate phenomenon of the secondary phase is inflammation and hemorrhage within the gray matter leading to necrotic cell death or ischemia (Ahuja et al. 2017a; Rowland et al. 2008). This phenomenon is concomitant with the activation of microglia, T-cells, and astrocytes and an upregulation of pro-inflammatory cytokines like the tumor necrosis factor alpha (TNFα) and interleukin 1 beta (IL-β) which disrupts endothelial cells, thereby increasing permeability of the blood-brain barrier (Donnelly and Popovich 2008; Kim et al. 2017; Pineau and Lacroix 2007). Other biochemical events of the secondary injury include Ca^{2+}-dependant glutamate-associated cell death (Hausmann 2003; Jancso et al. 1984; Mills et al. 2001) and production of free radicals and nitric oxide causing damage to proteins, nucleic acids, lipids, and extracellular matrix proteins such as glycosaminoglycans leading to neuronal cell death and loss in function (Bao and Liu 2002; Hausmann 2003; Schmidley 1990). This stage is also marked by excitotoxicity, a condition in which excitatory neurotransmitters such as glutamate and aspartate are overproduced causing apoptosis of glial cells and neurons (Li and Stys 2000; Park et al. 2004). SCI also results in vascular damage, which in turn causes energy loss, hypoxia, and subsequent dysfunction of mitochondria (Saikumar et al. 1998; Tator and Koyanagi 1997). The onset of apoptosis of oligodendrocytes leads to chronic demyelination, causing anterograde neurodegeneration, which results in fibers with disrupted myelin sheath called Wallerian degeneration (Hausmann 2003).

Factors that affects neural regeneration

Glial scar

Neural regeneration occurs in order to reconnect the damaged neuronal tissue at the site of injury. However, reinnervation of nerve fibers is hindered due to the formation of scar tissue (Kawano et al. 2012). Astrocytes that respond to the inflicted injury are known as reactive astrocytes and the process is referred to as reactive gliosis. Glial scar has been shown to possess both advantageous and harmful effects (Karimi-Abdolrezaee and Billakanti 2012). Hypertrophic astrocytes (with increased production of GFAP and vimentin) with very long processes over the tips of non-regenerating fibers form a barrier known as glial barrier or glial wall (Bignami and Dahl 1976; Sofroniew and Vinters 2010). With time, the glial scars tend to develop into tenacious, rubbery, and growth-blocking membranes. Additionally, in order to prevent nerve regeneration, it provides remarkable beneficial functions for stabilizing the damaged CNS tissue. After injury, the components of glial scar repair the blood-brain barrier (BBB) via amelioration of inflammatory response and reduction of cellular degeneration (Gesteira et al. 2016). Faulkner et al. demonstrated the beneficial effect of glial scar by using avian herpes simplex virus infected to mammalian astrocytes, followed by ganciclovir (GCV) delivery to deplete the subpopulation of reactive astrocytes that surrounds the core of lesion in a spinal cord injury model (Faulkner et al. 2004). GCV could successfully ablate the reactive astrocytes population resulting in the failure of BBB repair, leukocyte infiltration, severe demyelination, local tissue disruption, and neuronal and oligodendrocytes death with pronounced motor deficits (Faulkner et al. 2004). Hence, one of the functions of glial scar is to demarcate the injury site from healthy tissue in order to prevent further uncontrolled tissue damage. However, glial scarring also prevents subsequent growth of neurons. Therefore, identification of new interventions that would modulate scar development, leading to translation into a restorative purpose in the field of spinal cord injury is of utmost significance.

Chondroitin sulfate proteoglycans

Chondroitin sulfate proteoglycans (CSPGs) are a combination of proteoglycans (protein core) and glycosaminoglycan (GAG) side chains. During central nervous system (CNS) development, these CSPGs function as control cues and are essential for cell migration and axonal growth (Siebert et al. 2014). Expression of these molecules are drastically upregulated after spinal cord injury, resulting in deposition of CSPGs post-injury. This phenomenon contributes to the formation of a glial scar, which then acts as mechanical barrier. The presence of CSPGs creates an inhibitory environment for axonal regeneration, which leads to failure of axonal growth cones at the injured site of CNS. CSPG also inhibits the migration and differentiation of oligodendrocyte progenitor cells (OPCs) (Siebert and Osterhout 2011). A study by Siebert and Osterhout described the role of CSPG using OPC culture in vitro. In the presence of CSPG, OPCs did not show any instances of migration and differentiation. However, this effect was abolished by an enzyme chondroitinase ABC (ChABC), which neutralizes the CSPG function by removing the GAG chains from the core protein (Siebert and Osterhout 2011). ChABC is a bacterial enzyme that trims the carbohydrate side chains of large extracellular proteins that helps in regeneration of damaged nerve fibers at the site of spinal cord injury. Intrathecal treatment of ChABC to the spinal cord lesioned rats showed potent regeneration of both ascending sensory projections and descending corticospinal tract axonal fibers (Bradbury et al. 2002; Olson 2002). Taken together, these results suggest that axon outgrowth capacity of ChABC might prove to be useful in the regeneration of damaged neurons of SCI.

Microglia or macrophages

The macrophage populations of the CNS include the microglia and macrophages of perivascular, meninges, circumventricular organs, and choroid plexus. Microglia, known as resident macrophages of the central nervous system, are inactive under normal physiological conditions with small cell body and highly extended branching process (Fu et al. 2014). In response to damage/injury, these microglial cells transform into active phagocytic microglia and exhibit chemotaxis (migrates and accumulates at the site of injury) (Fan et al. 2017; Fernandes et al. 2014; Fu et al. 2014; Park et al. 2008). Microglial cells function via secretion of pro- and anti-inflammatory cytokines, growth factors, chemokines and neurotrophins and are responsible for clearing cellular debris and toxic substances by phagocytosis (Fu et al. 2014). Therefore, they aid in maintenance of normal cellular homeostasis at the local injury site. For demarcation of the deleterious insults, microglia express a set of pattern recognition receptors for various factors that are released by injured neurons such as glutamate (Liu et al. 2009), cytokines, ATP, and growth factors. The activated microglial cells transform into ameboid morphology similar to that of blood-borne macrophages, followed by proliferation and migration toward the site of tissue damage. Once they reach there, microglia act as the physical barrier between injured and healthy tissues (Davalos et al. 2005). Ohsawa et al. demonstrated P2Y12 receptor-mediated activation of microglial processes in response to the release of ATP from damaged neurons. This chemotactic response with respect to ATP levels proved vital for proper functioning of microglia at injured sites of CNS (Honda et al. 2001; Ohsawa et al. 2007; Ohsawa et al. 2010). Microglia-induced neuronal death is triggered due to the release of numerous pro-inflammatory cytokines in

response to a specific stimulus. For example, exposure of microglia to myelin-induced neuronal culture causes release of glutamate, nitric oxide (NO), and TNFα which leads to death of neuronal cells (Pinteaux-Jones et al. 2008). At certain conditions, microglia also activates a NADPH oxidase-related reactive oxygen species (ROS) pathway, which in turn leads to surplus accumulation of zinc (Zn^{2+}), calcium (Ca^{2+}), and potassium. This might contribute to neuronal cell death (Bossy-Wetzel et al. 2004; Knoch et al. 2008; Redman et al. 2009; Schulien et al. 2016). On the other hand, microglia also demonstrates beneficial responses upon short-term activation via phagocytosis. It has been documented that the level of the microglial response is regulated in correspondence to the level of inflammatory stimulus (Kraft and Harry 2011). Li et al. illustrated that a dose of 1 μg/ml and above of liposaccharides (LPS) induced pro-inflammatory cytokine release, followed by neurotoxicity. At concentrations less than 500 ng/ml, the neuronal culture showed increased viability and enhanced neurite outgrowth (Li et al. 2007). The M2-activated subset of microglia is considered to be less inflammatory than M1 microglia (Kigerl et al. 2009). These M2 microglial cells are known to produce low levels of NO and increased levels of anti-inflammatory cytokines. Neuronal cultures upon exposure with M2 microglia exhibited extensive neurite outgrowth even at inhibitory surfaces (Colton 2009; Colton et al. 2006).

Degraded myelin

Injury to the neural tissue results in death of neuronal as well as glial cells (astrocytes and oligodendrocytes). Myelin is a fatty pad, which serves as an insulation sheath for axonal nerve fibers in the nervous system. Myelin sheaths facilitate proper impulse transmission through enabling "saltatory conduction" and maintains axonal functions (Barres et al. 1993). Any disturbance (injury or damage) can cause various CNS disorders ranging from congenital to autoimmune diseases. Progressive demyelination results in degeneration of axonal fibers that leads to disruption of axo-glial signaling. During this process, release of high amounts of myelin (demyelination) at the site of injury is also one of the inhibitory factors for axon outgrowth (Alizadeh et al. 2015). The components of myelin such as myelin-associated glycoprotein (MAG), oligodendrocyte myelin glycoprotein (OMgp), ephrin B3, and the transmembrane semaphoring 4D (Sema4D/CD100) act as bi-functional cues based on the microenvironment (inhibition upon injury and recuperation during CNS development). For example, ephrinB3 can function as inhibitors of axon repair in adults and has beneficial roles during postnatal stages of myelinating oligodendrocytes (Kullander et al. 2001). Similarly, CD100 is expressed in mature oligodendrocytes during injury and triggers growth cone collapse (Moreau-Fauvarque et al. 2003). In a study by Keirstead et al., the role of galactocerebroside with monoclonal antibodies in an embryonic model of SCI delineated the complete neuroanatomical repair and improved functional recovery was demonstrated (Keirstead et al. 1992). McKerracher et al. (1994). also described the role of MAG as a critical inhibitor of neurite growth. Immunodepletion of MAG from injured mammalian CNS resulted in restoration of neurite outgrowth by 63%. Altogether, many of the myelin proteins, functionally active during the initial development of nervous system, portrayed an inhibitory effect on axonal growth after the onset of the injury (Keirstead et al. 1992; Kullander et al. 2001; McKerracher et al. 1994; Moreau-Fauvarque et al. 2003; Mukhopadhyay et al. 1994).

Current treatment strategies

Treatment strategies vary in accordance with the progressive stage of SCI. If SCI is in acute stage, pharmacological-based treatment is advised and if it is in secondary stage, various combinations of therapeutic treatment involving the usage of neural tissues and neurotrophic factors are suggested (Fig. 1).

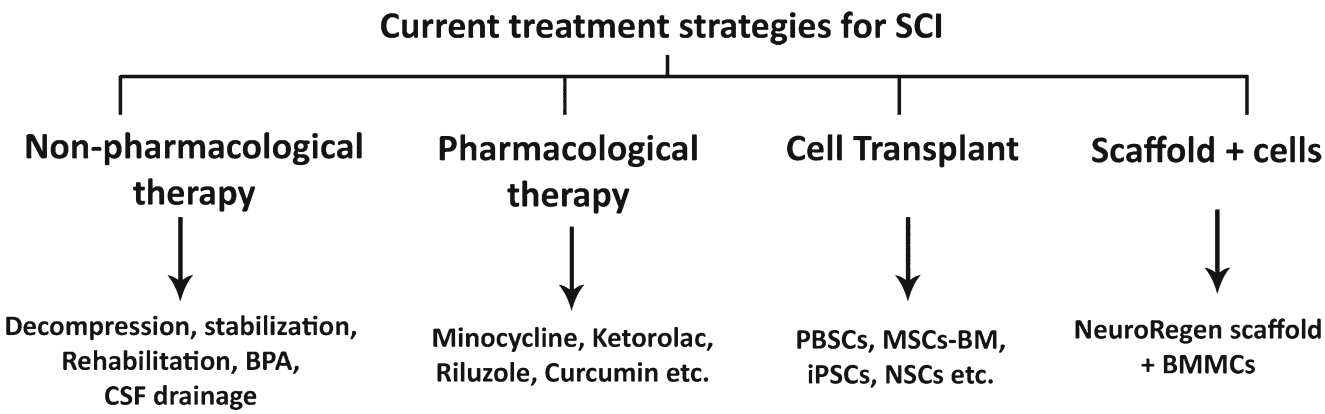

Fig. 1 Current treatment options for spinal cord injury. Current methods which are available for spinal cord injury such as non-pharmacological and pharmacological therapies, cell transplantation, and cells with scaffold transplantation therapies. In particular, injections of stem cells with scaffolds into the damaged part of spine are reported with recovery of motor and sensory functions of spinal cord injured rodent models

Pharmacological-based neuroprotection

Riluzole

Riluzole is a neuroprotective drug that prevents stimulation of glutamate receptors by sodium channel blockade. Although the Food and drugs administration (FDA) has approved riluzole for treatment of amyotrophic lateral sclerosis (ALS), the same is not approved for spinal cord injuries. However, few clinical trials (NCT01597518, NCT00876889, and NCT02859792) have been registered for SCI treatment using riluzole. Currently, a multicenter clinical trial (NCT01597518) is in progress at 11 centers from the year 2014 (Nagoshi et al. 2015). In a pre-clinical trial, riluzole has provided the evidence on sustained functional improvements of damaged neuronal cells after 1 h of injury and every 12 h thereafter for 7 days at 6 mg/kg compared with vehicle group (Satkunendrarajah et al. 2015). This drug has been shown to reduce excitotoxicity and confer neuroprotection which can lead to enhanced functional recovery at the site of injury.

Ketorolac

Ketorolac is well-known potent analgesic and non-steroidal anti-inflammatory drug (NSAID) which acts by inhibiting the cyclooxygenases (COX1 and COX2). Ketorolac has been shown to exert neuroprotective effects by reducing the neuronal death at the site of ischemic insult which leads to improvement in the hindlimb motor function comparable with the control group (Bagriyanik et al. 2008; Hsieh et al. 2005). This drug could also reduce post-operative joint pain. Intra-articular injection of ketorolac significantly reduced the spinal activation of astrocytes at day 1 animal group, whereas the group which received ketorolac injection immediately after injury did not have any effect (Dong et al. 2013). Protease activated receptor-1 (PAR1) expression was also significantly downregulated by ketorolac treatment which was independent of time of administration (Dong et al. 2013). Although, neuroprotective properties of ketorolac were beneficial at shorter time points but long-term studies are required for clinical translation.

Minocycline

Minocycline has been proven as a neuroprotective agent in various neurodegenerative diseases including multiple sclerosis, spinal cord injury, amyotropic lateral sclerosis, and Huntington's disease (Kwon et al. 2011; Stirling et al. 2005). Minocycline exerts its anti-inflammatory action by modulating CNS immune cells (microglia, neutrophils and macrophages) and their secreted pro-inflammatory cytokines such as IL-6, IL-1β, and TNFα. Minocycline also regulates the levels of anti-inflammatory cytokines and prevents neuroinflammation and cell death through inhibition of the p38 mitogen-activated protein kinase pathway (Nikodemova et al. 2006). Three clinical trials have also been registered (NCT00559494, NCT01828203, and NCT01813240) with this drug for spinal cord injury treatment. Only one study result is published so far (NCT00559494) where the usage of minocycline in the treatment of acute SCI patients demonstrated the feasibility and safety of the procedure. In addition, motor improvement was significantly observed in the cervical acute SCI patients. However, no significant difference was seen in the thoracic SCI patients (Arnold and Hagg 2011; Casha et al. 2012). These neuroprotective effects of minocycline have the potential to be translated into clinical practice for treatment of spinal cord injury and other neurodegenerative diseases.

Fingolimod

Fingolimod (FTY720) is a specific agonist for the sphingosine receptor modulator which induces lymphopenia and has been shown to be effective in the treatment of a variety of experimental immune disorders. Norimastu et al. demonstrated the therapeutic efficacy of FTY720 in spinal cord injury models. Oral administration of this drug at acute SCI injury has been shown to significantly improve motor function. T cell infiltration, vascular permeability, and astrocyte accumulation were also significantly decreased by FTY720 in the spinal cord injury models. However, FTY720 did not attenuate early filtration of neutrophils and inflammatory cytokines in the injured spinal cord (Norimatsu et al. 2012).

Magnesium

Neuroprotective properties of magnesium have been reported in various neurodegenerative or central nervous system injury models. Magnesium is an antagonist for N-methyl-D-aspartate (NMDA) receptor, which plays physiological role in neuronal cells by competing with calcium ions and acts as endogenous calcium channel blocker (Suzer et al. 1999). Magnesium is essential for neuronal cells to maintain their cellular respiration, membrane integrity, mRNA transcription, and energy metabolism (Ebel and Gunther 1980; Garfinkel and Garfinkel 1985). Kaptanoglu et al. (2003) reported the neuroprotective property and improved motor functional scores of magnesium sulfate treatment on contusive injured spinal cord rodent models. Clinical study of 107 patients with acute ischemic stroke demonstrated that the use of magnesium sulfate as a safe neuroprotective agent. Significant recovery was also observed when compared with the control group (Afshari et al. 2013).

Methylprednisolone

Methylprednisolone (MPSS) is an anti-inflammatory corticosteroid and the most commonly used drug that acts as an antioxidant. MPSS enhances the blood flow of spinal cord by reducing calcium influx and attenuating lipid peroxidation. However, this drug failed in reversing the problem of neuronal death and has a plethora of adverse effects, which include pulmonary and gastrointestinal complications (Lee et al. 2008).

Gacyclidine (GK-11)

A non-competitive N-methyl-d-aspartate receptor antagonist proved promising as a neuroprotective agent in rodent models as evidenced by the efficient motor and sensory performance, attenuation of spinal cord damage, and reduction in apoptosis of oligodendrocytes via inhibition of microglial-production of pro-NGF (Feldblum et al. 2000; Gaviria et al. 2000; Xue et al. 2010; Yune et al. 2007). Hence, its translation into clinical trials necessitates further studies.

GM-1

A ganglioside found in the neuronal cell membrane promotes recovery in a number of animal models. In clinical trials, it has shown statistically significant improvement in ASIA motor score but has failed to depict a significant difference in its primary outcome measure as depicted by a 2-point improvement on the modified Benzel walking scale (Geisler et al. 1991; Landi and Ciccone 1992; Schonhofer 1992).

Altogether many other anti-inflammatory drugs have been shown to be neuroprotective at acute stage (immediate or day 1), but same drugs failed at chronic stage (> 3 months). Many other growth factors such as granulocyte colony-stimulating factor (G-CSF) (Chung et al. 2014), fibroblast growth factor (Sugiyama et al. 2018; Zhou et al. 2018), and tryptophan-releasing hormone (Arias 1987; Pitts et al. 1995) have been shown to decrease lesion size, attenuate cell death, promote angiogenesis, and downregulate pro-inflammatory cytokines (Hachem et al. 2017). However, strong randomized trials are required to confirm their efficacy.

Natural anti-inflammatory compounds

Natural polyphenols are known to have neuroprotective effects against various neurodegenerative diseases and or spinal cord injuries. Polyphenols are plant metabolites and are proven to have various biological functions such as being antioxidant, anti-inflammatory, and anti-apoptotic. Turmeric, olive oil, green tea, grape, etc., are considered as the best resources for the polyphenol compounds (both flavonoids and non-flavonoids). Therapeutic importance of these polyphenols have been reported by various studies. MSCs pre-conditioned with curcumin have shown enhanced improvements in locomotory functions of pre-clinical rat SCI models compared with untreated group (Ormond et al. 2014; Ruzicka et al. 2018a). Curcumin also showed superior functional improvements when in combination with other factors such as epigallocatechin gallate (Ruzicka et al. 2018b) and electroacupuncture (Alvarado-Sanchez et al. 2019). Various studies demonstrated that intraperitoneal administration of curcumin can significantly reduce inflammatory cytokine levels, attenuate lipid peroxidation and oxidative stress, and further prevent apoptotic death which can help in reduction of glial scar (lesion cavity) at the site of injury (Gokce et al. 2016; Machova Urdzikova et al. 2015; Ormond et al. 2012). Curcumin also could enhance survival and proliferative effects of BMSCs in a dose-dependent manner and had no effect on NSCs proliferation (Attari et al. 2015). Olive oil phenolic compound called oleuropein is also shown to have antioxidant and neuroprotective effects in pre-clinical SCI animal models (Khalatbary and Ahmadvand 2012). A green tea polyphenol, epigallocatechin-3-gallate (EGCG), has been proven to have strong neuroprotective functions by attenuating the canonical NF-κB pathway. In addition to axonal sprouting, EGCG also showed better behavioral performance of SCI rat models (Machova Urdzikova et al. 2017). Ayurveda drugs and panchakarma procedures have also proven to improve the neurological deficits in spinal cord injured patients (Singh and Rajoria 2015). All together, these natural polyphenolic compounds could be used as an adjunctive therapeutic remedy to enhance the levels of neuroregenerative growth factors and locomotory functions (Khalatbary 2014).

Decompression surgery

Decompression of compressed discs followed by surgical stabilization of spinal fractures has shown little improvement in decompression surgery. However, this approach is limited to primary injury. It involves removal of broken down bone/disc pieces and ligament fragments to decompress the injured cord. This kind of surgery is commonly used for the treatment of lumbar spinal stenosis. In a study by Anjarwalla et al. (2007), decompression surgery was performed in order to ascertain the long-term outcome with respect to pain and physical function. The study was performed in 77 patients with follow-up assessments for 5 years. A significant progress was observed in back and leg pain, which was sustained for a period of 1 year only with improved physical function. Although there was a significant improvement of physical function, the effect was not pertained beyond 5 years (Anjarwalla et al. 2007). Kim et al. demonstrated the bone turnover rate before and after decompression surgery in 23 lumbar spinal stenosis patients. After 3 months of follow-up, the bone resorption marker N-terminal telopeptide (NTX) exhibited a significant

downregulation along with an increased expression of the bone formation marker, alkaline phosphatase (ALP). This suggested that decompression surgery has a beneficial role on bone metabolism. However, the results of this study were effective until a period of 3 months; long-term effect (> 5 years) of these studies is required to elaborate on the consistency of bone turnover markers expression (Kim et al. 2009). Even though decompression followed by spinal stabilization is pivotal for the prevention of tenderness and progression of further neurologic shortfalls (e.g., tingling, weakness, and bowel problems), this may not revert the complete damage of spinal cord.

Tendon transfer surgery

Severe injury to spinal cord leads to loss of voluntary control of all muscles and sensory functions that originates from below the level of injury. An individual afflicted with completely or partially paralyzed limbs (quadriplegia or tetraplegia) are incapable of performing their own physical activities. Tetraplegic patients are unable to control their arm in air, their hand grip, and pinch strength (Johanson et al. 2016; Wangdell et al. 2016). Under such situations, tendon transfer surgery is the only treatment of choice. Tendons are very strong cords that join muscles to bones and transfer muscle action into joint-movement, wherein they are grafted. The benefits of tendon transfer have been documented in juvenile SCI patients. The assessment of hand functions after the surgery revealed significant improvements in terms of pinch force, which improved considerably during the first year of treatment. Functional Independence Measure (FIM) and the Common Object Test (COT) analyses revealed that unilateral and bilateral functions facilitated the patient's independence in hand functions with respect to eating, brushing teeth, writing, and applying tooth paste (Dunn et al. 2016; Mulcahey et al. 1995).

Blood pressure augmentation

After the primary injury period, series of secondary mechanisms include reduction in blood flow, neuronal cell death, hemorrhage, vasospasm, and thrombosis. Strategies that prevent secondary injury immediately after acute SCI are considered as hopeful therapy to protect neuronal cells from further damage. Increase in flow of blood in the spinal cord (penumbra) by elevating the systemic mean arterial pressure (MAP) is becoming an emerging neuroprotective strategy for SCI. Recommendations from the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) to avoid hypotension and prevent further secondary complications patients can be managed clinically by maintaining mean arterial blood pressure (MAP) at > 85 mmHg for 7 days (Ahuja et al. 2017b; Resnick 2013). Several studies have been reported to examine the MAP elevation in SCI condition (Hawryluk et al. 2015; Levi et al. 1993; Martin et al. 2015; Vale et al. 1997). Although these results showed negligible morbidity with enhanced neurological outcome, there were controversial debates on the therapy (Ahuja et al. 2017b; Resnick 2013). So far, only one clinical trial have been registered with Identifier # NCT02232165 to compare normotension (MAP ≥ 65 mmHg) versus induced hypertension (MAP ≥ 85 mmHg) for 7 days following acute SCI. Estimated study completion date is June 2019 (clinicaltrials.gov 2014).

Cell transplantation therapies

Cell transplantation therapies are considered to be the most promising therapeutic strategy for SCI treatment. Different cells including stem cells (neural stem cell, embryonic/pluripotent stem cells, mesenchymal/hematopoietic stem cells) and mature somatic cells (neural cells, oligodendrocytes, astrocytes, Schwann cells, and olfactory ensheathing cells) have been used for the transplantation therapies (Tetzlaff et al. 2011) to treat various stages of SCI (Table 3).

Stem/progenitor cells

Neural stem/progenitor cells

Neural stem cells (NSCs) are the only cells that have tripotential capability (neurons, astrocytes, and oligodendrocytes). These cells are located in a specialized neurogenic niche in the brain, i.e., in the subventricular zone (SVZ) and subgranular zone (SGZ). Since they are insufficient in terms of their numbers, they are not clinically used for neurodegenerative defects or for treatment of SCI disorders. The stem cells from CNS are capable enough in order to differentiate into cells based on their need in the injured spine. Therefore, researchers aim at the production of unlimited number of NSCs in vitro from other stem cells sources such as embryonic stem cells (ESCs) (Elkabetz et al. 2008; Shin et al. 2006), pluripotent stem cells (PSCs) (Choi et al. 2014) and mesenchymal stem cells (MSCs) (Fu et al. 2008; Hermann et al. 2004). Iwai et al. demonstrated allogenic transplantation of ESC-derived neural stem/progenitor cells (ESC-NS/PCs) in non-human primates to study their functional recovery in SCI model. The transplanted ESC-NS/PCs differentiated into neurons, which formed synaptic connections and myelination with the host neurons. The grafted cells did not exhibit any tumorigenicity. Additionally, the motor functions lasted beyond 70 days post-transplantation (Iwai et al. 2015). In another recent study, transplantation of NPCs derived from human spinal cord

into the sites of cervical spinal cord injured primate models (*Macaca mulatta*) depicted survivability of the grafts for at least 9 months from the time of injury. Expression of both glial and neuronal markers help in formation of synapses with the host tissue, resulting in the improvement of forelimb function (Rosenzweig et al. 2018). Nori et al. reported about the formation of new synaptic connections between the graft (hiPSC-derived neurospheres)-derived neurons and host neurons, but the functional recovery was remained undetected in at the later phase (Nori et al. 2011). The number of cells per dose also dictated the fate of NSCs differentiation during transplantation at the site of injury. High dose (~ 500,000) of graft requiring high rate of engraftment, enhanced neuronal differentiation with increased migration ability. However, the cell dose had no effect on the sensory and locomotory functions (Piltti et al. 2015; Piltti et al. 2017). Transplantation timing of any stem cells post-injury is crucial for the assessment of recovery of the injured spinal cord. A study compared the recovery results of the acute (immediate after introduction of SCI), subacute (7 days after SCI), and chronic (28 days after SCI) post-transplantation of hNSCs in female rodent animal models (T-10 level). The results of Basso, Beattie, and Bresnahan (BBB) locomotor rating scores for hNSCs groups did not show any significant difference between the various groups. However, maximum improvement was observed in the subacute group, as compared to the chronic group when determined from the time of cell injection (Cheng et al. 2017).

Chondroitin sulfate proteoglycans (CPSG) restricts the NSCs integration and migration and hinders the neuroregeneration process at the injured site (Nishimura et al. 2013). LAR/RPTPσ and Rho/ROCK signaling pathways are vital mechanisms through which CSPGs are known to show its inhibitory effects. CSPG receptor knockouts have shown to increase differentiation of NPCs to myelin forming cells (oligodendrocytes) (Dyck et al. 2015). ChABC treatment demonstrates greater differentiation toward oligodendrocytes lineage than astroglial formation when compared with non-ChABC-treated rodent groups (Nori et al. 2018; Suzuki et al. 2017). This combinatorial therapy helps in long-term survival of NPCs at the lesion epicenter and shows greater differentiation potential of oligodendrocytes with enhanced synaptic connectivity and neurobehavioral recovery. However, the thermal instability of chABC is encountered by cross-linked enzyme to SH2-methylcellulose (SH2-XMC) hydrogel and helps in sustained release at the site of injury which reduces CSPG levels for 2 weeks in in vivo SCI rodent models and promotes functional repair (Pakulska et al. 2017; Pakulska et al. 2013). Suzuki et al. (2017) demonstrated that the delivery of ChABC by intrathecal osmotic pump for 1 week followed by transplantation of iPS-NSCs to the injury epicenter could reduce the lesion size and promote trilineage differentiation of NSCs with improved survivability in chronic SCI injury models.

Although ESC- and PSC-derived NSCs demonstrated better regenerative results, their clinical applications are discouraged because of the tumorigenic nature. In comparison, no tumor formation has been reported in any rodent or marmoset SCI models subjected to ESC/PSC-NSC-based cell therapy (Cummings et al. 2005; Kobayashi et al. 2012; Morizane et al. 2013; Mothe and Tator 2008). Hwang et al. developed engineered NSCs, overexpressing the Olig2 transcription factor as an effective strategy for their improved functional outcomes in terms of SCI (Hwang et al. 2009). These findings suggest that NSCs might prove to be a promising cellular therapeutic that would support functional recovery of the injured spinal cord. Alternatively, MSCs are efficient in derivation of NSCs due to their low ethical concerns, ease of availability, lack of immunogenicity, and non-tumorigenic nature. Notch signaling is essential for trans-differentiation of MSCs to NSCs and also for NSCs tri-differentiation (Venkatesh et al. 2019; Venkatesh et al. 2017). Increasing number of evidences have documented the application of MSCs in the treatment of various neurodegenerative diseases and spinal cord injuries (Dasari et al. 2014; Quertainmont et al. 2012; Venkatesh and Sen 2017). Expression of neural lineage markers such as nestin, glial fibrillary acidic protein (GFAP), β III tubulin, neurofilament medium polypeptide (NFM), microtubule associated protein 2 (MAP2), and neuron-specific enolase (NSE) also support the use of MSCs in neurological disorders (Fazeli et al. 2015; Foudah et al. 2012; Foudah et al. 2013). However, transplantation of the neural stem/progenitors is predominantly preferred because of its tri-potential differentiation capacity and hence various researchers have tried to differentiating the MSCs into NSCs for neurological treatment (Fu et al. 2008; Hermann et al. 2004; Ma et al. 2011). Li et al. transplanted the NSCs derived from placental-derived MSCs (PDMSCs) into a rodent SCI model. This resulted in significant improvement of the motor functions and BBB score were also seen to be increased from 2 points to 13 points at 3 weeks post-transplantation. The neuroelectrophysiological tests described the recovery with respect to hindlimb sensory and motor dysfunctions. All of these observations were consistent with the BBB scores. These evidences were indicative of the plausible fact that transplantation of PDMSC-iNSCs can enhance the sensory and motor functions caused by SCI (Li et al. 2014).

Hematopoietic stem/progenitor cells

Hematopoietic stem cells (HSCs) are multipotent, self-renewable cells originating from the hemangioblast cells in bone marrow. The therapeutic potential of bone marrow-derived hematopoietic progenitor cells was manifested in patients with spinal cord injury. The restoration of neurological

symptoms with autologous HSCs and hematopoietic progenitor's transplantation showed potential locomotory function improvement of about 57.4% in 202 SCI cases; however, it failed at any neurological recuperation in about 42.6% of patients (Bryukhovetskiy and Bryukhovetskiy 2015). In another study, transplantation of bone marrow stem cells in 9 patients with chronic complete SCI (ASIA-A grade) showed improvement of locomotory movements and sensory functions after 3 weeks of follow-up. These data suggest that transplantation of bone marrow-derived autologous stem cell therapy was effective and safe for the treatment of chronic SCI (Deda et al. 2008). These improvements in the patients were highlighted because of the trans-differentiation ability of HSCs into various non-hematopoietic cell lineages (Venkatesh et al. 2015; Venkatesh et al. 2013). In a clinical trial at Neurogen Brain and Spine Institute, Mumbai, 56 chronic cervical SCI patients were administered with autologous bone marrow mononuclear cells intrathecally. The results in chronic cervical SCI group showed improved functional recovery and betterment in the patients' quality of life (NCT02009124) (Kumar et al. 2009; Yoshihara et al. 2007). In a pre-clinical study, the transplantation of HSCs into animal SCI model showed significant improvement in the hind limb motor function and the grafted cells survived until a period of 5 weeks post-transplantation. These results suggest that transplantation of hematopoietic progenitors from an autologous source is an effective strategy for recuperation of damaged spinal cord (Dasari et al. 2008; Koshizuka et al. 2004). Transplantation of HSCs in the spinal cord injured rodent models portrayed significant improvements in the locomotor functions and markedly decreased the astrogliosis at the site of injury. These findings substantiated the therapeutic effects of HSCs for the treatment of SCI (Xiong et al. 2017). However, a precise delineation of HSCs is required for its successful application in regular clinical practice for the treatment of SCI.

Mesenchymal stem/stromal cells

Mesenchymal stem cells (MSCs) are a promising source for cell-based repair following CNS injury (Dasari et al. 2014; Li and Lepski 2013; Qu and Zhang 2017). MSCs, also known as bone marrow stromal cells or mesenchymal progenitor cells, possess the ability to differentiate into various distinct cell lineages (Singh et al. 2016; Venkatesh and Sen 2017). Hammadi et al. demonstrated the isolation of MSCs through cytokine (G-CSF) induction, followed by transplantation of MSCs via spinal column (intrathecally). In 88 patients, the ASIA score shifted from A to B and from A to C in 32 patients within 1 year post treatment (Hammadi et al. 2012). Transplanted MSCs significantly attenuated the chronic inflammatory response of injured spinal cord in a contusive rodent SCI model. White matter volume was also enhanced along with reduction of cyst size in the MSCs transplanted groups, upon comparison with the controls. These results suggest that the enhanced sensorimotor functions and reduced inflammatory response is mainly due to the paracrine effects of MSCs (Abrams et al. 2009). Transplantation of bone marrow stromal cells (BMSCs) was shown to promote the functional recovery of rat hind limbs after SCI (at T8–T9 levels) and the neurological deficits were significantly reduced with the combination of hyperbaric oxygen (HBO) (synergistic action). HBO therapy increased tissue oxygen and improved collagen synthesis, angiogenesis, epithelization, and attenuated focal inflammatory reaction at lesioned sites (Geng et al. 2015). The conditioned media of MSCs also showed significantly higher motor functional recovery with enhanced expression of Gap-43 and repressed the inflammatory response in comparison with the vehicle-treated rodent animal models (Cizkova et al. 2018). Watanabe et al. demonstrated the immunomodulatory effects of bone marrow-derived MSCs (BM-MSCs) on neuropathic pain in contusive SCI models. The consequential reduction of pain was mediated by suppression of protein kinase C-γ and phosphocyclic AMP response element binding protein expression in dorsal horn neurons. BM-MSCs prevented the recruitment of hematogenous macrophages via (i) restoration of the blood-spinal cord barrier (BSCB), which is associated with decreased levels of inflammatory cytokines (TNFα, IL-4, IL-1β, IL-2, IL-6, and IL-12) (Urdzikova et al. 2014); (ii) mediators of early secondary vascular pathogenesis (matrix mettallopeptidase-9); and (iii) macrophage recruiting factors (CCL2, CCL5, and CXCL10), but increased the levels of microglial stimulating factors (GM-CSF) (Vawda and Fehlings 2013; Watanabe et al. 2015). In another study, both BM-MSCs and UC-MSCs were compared to determine the therapeutic efficacy in treating SCI. Both types of cells significantly reduced the symptoms of neuropathic pain and showed improved motor recovery after SCI (at T6–T8 levels). However, survival rate of UC-MSCs was significantly higher than BM-MSC (Yousefifard et al. 2016). Additionally, the use of genetically modified HUC-MSCs overexpressed with neurotrophic factors (NTFs) can also be an attractive approach to regenerate the myelin producing cells such as Schwann cells (Galieva et al. 2018).

Embryonic/pluripotent stem cells

Embryonic stem cells are totipotent cells, which possess maximal capacity of differentiation. Due to their pluripotent nature, ESCs/PSCs are considered an attractive therapeutic option for various diseases (Doulames and Plant 2016). Keirstead et al. (2005) demonstrated the remyelination of neurons in injured spinal cord through the transplantation of hESC-derived oligodendrocyte progenitor cells (OPCs). Nistor et al. also showed the differentiation of hESCs into oligodendrocytes followed by transplantation into the shiverer model (myelin basic

protein mutant mice model) of dysmyelination. The results showed the formation of myelin on demyelinated neuronal cells, demonstrating the functional phenotype of transplanted cells (Nistor et al. 2005). Transplantation of induced pluripotent stem cell-derived NSCs were efficient in remyelination of the damaged axons at lesioned spinal cord sites (Salewski et al. 2015). In another study, transplanted iPSC-derived neuroepithelial stem cells (NES) were differentiated and aided functional recovery of hind limbs in a NOD-SCID mouse model (Fujimoto et al. 2012). Intraspinal administration of iPSC-derived NSCs showed extended survival than intrathecal grafting (Amemori et al. 2015) and also showed highest survivability rate than the hMSCs graft (Ruzicka et al. 2017).

In a clinical trial, the safety and efficacy of hESCs were examined with five patients who were either paraplegic or quadriplegic. The results of the treatment showed significant improvement in their locomotory and sensory functions with no adverse events such as tumor formation (Shroff 2016), graft rejection etc. (Shroff 2016; Shroff and Gupta 2015). Shroff demonstrated tracking of transplanted ESCs in SCI patients, using the magnetic resonance imaging tractography (MRIT). Improvements in the patients were clearly seen using the MRIT imaging, which paved the way for recuperation of the damaged spinal cord (Shroff 2017). Kakinohana et al. reported the survival and differentiation of hESC-derived hNPCs (up to 2 weeks to 4.5 months) following grafting into ischemia-injured lumbar spinal cord of rodent models. In a study by Kim et al., transplantation of GABAergic neurons derived from ESCs reduced neuropathic pain (hypersensitivity) in a rodent SCI model (T13 segment) (Chen et al. 2017; Kim et al. 2010). These data suggest that ESC/iPSC-derived cells such as OPCs, NPCs, and NES could represent an effective source for recuperation of damaged spinal cord (Kakinohana et al. 2012).

Primary cultures

Various researchers have reported about the transplantation of different mature cells for the repair of damaged spinal cord. Primary cells have several limitations that impede their clinical translation including their post-mitotic feature and isolation issues. However, mature cells such as Schwann cells, olfactory ensheathing glial cells, astrocytes, and oligodendrocytes have been shown in several pre-clinical studies to improve the recovery of damaged spinal cord (Table 3).

Schwann cells and olfactory ensheathing cells

Schwann cells (SCs) are myelin-forming cells for nerve fibers, located in the peripheral nervous system. Numerous studies have demonstrated transplantation of Schwann cells to be a hopeful therapeutic strategy for the repair of injured spinal cord (Dai and Hill 2018; Oudega and Xu 2006; Takami et al. 2002; Wang and Xu 2014; Yang et al. 2015). SCs provide neuroprotective effect, reduce pseudocyst formation, support axonal outgrowth, initiate remyelination process, and improve locomotory and sensory functions (Schaal et al. 2007; Wiliams and Bunge 2012). However, the repair effect of SCs is not sufficient enough to promote axonal response that can lead to complete recovery of motor functions. In a subacute contusion rodent model, Kanno et al. demonstrated accelerated axonal regeneration and improved locomotory and sensory functions following transplantation with engineered SCs that overexpressed neurotrophin (D15A/NT-3) and chondroitinase (ChABC) (Kanno et al. 2015; Kanno et al. 2014). Transplantation of SCs alone fails to regenerate supra-spinal axons which are unable to grow beyond spinal tissue. These responses are essential for restoration of voluntary motor control. Combination of SCs and olfactory ensheathing cells (OECs), however, has shown better remyelination activity and regeneration capacity than the singular transplanted groups. Interestingly, Lavdas et al. overexpressed the cell adhesion molecule L1, a protein which accelerates neurite outgrowth and helps in myelination process. Mice transplanted with L1/L1-Fc-expressing SCs exhibited better locomotor activities than the mice with just SCs and without L1 overexpression (Lavdas et al. 2010). Pearse et al. (2004) demonstrated that the combinatorial use of SCs and OECs along with methylprednisolone (MP) and interleukin-10 (IL-10) showed significant increase in the total volume of 9-mm segment after 12 weeks of spinal cord injury; however, there was no significant improvement in the behavioral functions. García-Alías et al. compared the neurological and electrophysiological outcome of transplanting OECs and SCs in a photochemically injured spinal cord (T8 segment) model. Both OEC- and SC-transplanted groups showed significant improvement in the behavioral skills that were assessed with open field-BBB scale, inclined plane, and thermal algesimetry tests. However, OEC group alone had higher motor evoked potentials and showed reduced astrocytic reactivity and proteoglycan expression in comparison with the SC-transplanted and vehicle groups. Taken together, transplantation of both OEC and SC had the potential for restoration of injured spinal cord with improved functional recovery (Garcia-Alias et al. 2004). Therefore, SC transplantation needs to be combined with other cells such as OECs or MSCs (Oraee-Yazdani et al. 2016) to improve the progressiveness of the transplant (Golden et al. 2007).

Astrocytes

Astrocytes are non-neuronal cells of neural tissue also known as astroglia. Glial cells are the most abundant cells of the CNS and provide fundamental structural and physiological functions at synaptic junctions of the neuronal

network (Venkatesh et al. 2013). Their foremost essential role includes synaptic transmission, control of cerebral blood flow, blood-brain barrier formation, regulation of extracellular ions (K^+ and Na^+ ions), antioxidant functions, secretion of a variety of neurotrophic factors, and clearance of glutamate and GABA at axo-glial junctions (Kimelberg and Nedergaard 2010). Davies et al. demonstrated the use of in vitro generated astrocytes from human glial progenitor cells (hGPCs) to treat adult SCI-induced rat (injured at C3/C4 level). Significant improvements were observed with 32–40% increase in the neuronal survival, when compared to untreated injured spinal cords (Davies et al. 2011; Kjell and Olson 2016). However, in another report, the results suggest that the therapeutic effects of transplanted astrocytes around the lesion site persisted only for a short time-period (less than 2 weeks) (Wang et al. 1995). Glial scars formed at the injured site through reactive astrogliosis are considered as the pathological hallmarks of SCI (Lukovic et al. 2015; Sofroniew 2005). This in fact becomes a major reason for not considering astrocytes as potential cells for SCI transplantation. It is remarkable that various studies now disclose the therapeutic use of astrocyte transplantation in promoting axonal regeneration and functional recovery after SCI (Davies et al. 2006; Davies et al. 2008; Nicaise et al. 2015). However, the dominance of the formation of glial scars in CNS diseases has led to the neglect of astrocytes in the use of neurological recovery (Lukovic et al. 2015; Okada et al. 2018).

Oligodendrocytes

Oligodendrocytes are a subpopulation of glial cells which account for 5–8% of cells in the CNS. Oligodendrocytes might be considered as a potent source for post-SCI transplantation because of their myelination function within the CNS (Li and Leung 2015). Sharp et al. demonstrated the transplantation of human ESC-derived oligodendrocyte progenitor cells (OPCs) into an injured spinal cord animal model (at C5 level) and assessed their therapeutic efficacy. hESC-derived OPCs were shown to reduce pathogenesis of the lesion and also could recover forelimb functions. Histopathological and functional outcomes of the transplants support the use of OPCs for cervical SCI models (Sharp et al. 2010). The functional phenotype of transplants (hESC-derived OPCs) was successfully demonstrated by integration and differentiation of OPCs into oligodendrocytes and exhibiting compact myelin formation in a dysmyelinated shiverer mouse model (Nistor et al. 2005). Other reports demonstrated the hESC-derived OPCs remyelination activities and locomotory functions in a contusive SCI model (T10). In contrast, these transplanted OPCs survived only for 10 months after injury and there was no improvement in remyelination or locomotor recovery after the short period (Cloutier et al. 2006; Faulkner and Keirstead 2005; Keirstead et al. 2005; Plemel et al. 2014; Priest et al. 2015). Transplanted OPCs at the injured spinal cord could also release various neurotrophic factors, hepatocyte growth factor (HGF), activin A, transforming growth factor-beta2 (TGF-beta2), and brain-derived neurotrophic factor (BDNF), which help in the survival of damaged neurons and promote axonal regeneration and contribute in the functional recovery (Kerr et al. 2010; Zhang et al. 2006). Genetically modified OPCs, overexpressing ciliary neurotrophic factor (CNTF), improved remyelination of the damaged neurons in rodent SCI models (Cao et al. 2010). Sun et al. (2013) demonstrated that transplantation of myelin forming cells such as OPCs, into the mouse SCI model (irradiated; 22 Gy radiation) could lead to engraftment of Olig2+-OPCs along with attenuation of the demyelination process resulting from irradiation. Oscillating field stimulation (OFS) also promoted the OPC differentiation and improved the remyelination process in rodent SCI models. These results suggest that OFS could efficiently repair and recover damaged cells in the spinal cord (Zhang et al. 2014). Disruption of myelin during injury causes progression of pathological feature of injured spinal cord. Hence, it is important to initiate the remyelination process by replacing the myelin forming cells (Alizadeh and Karimi-Abdolrezaee 2016).

Cell-embedded biomaterial transplantations

Repair of SCI in humans remains to be a persisting hurdle due to multiple factors, namely, extensive cell death, inflammatory molecules in the glial scar, axonal disruption, and lack of growth-promoting molecules (Silver and Miller 2004) at the site of injury. The transplanted SCs ultimately die largely during the first 3 weeks after transplantation due to the deleterious microenvironment caused mainly by low oxygen levels (hypoxic) high levels of ROS, inflammatory cytokines, and cell-mediated immune response (Hill et al. 2007). Also, the therapeutic effects of NSCT may be limited by their low survival rate after transplantation into the damaged spine (Pearse et al. 2007). Accordingly, overcoming these multi-factorial conditions requires a multi-faceted combinatorial approach (Bunge 2008). Various reports suggest that using cells and embedding them in natural/synthetic extracellular matrix (ECM) components such as collagen, chitosan, hyaluronic acid, alginate, laminin, polyethylene glycol, silicone, poly(glycolic acid) (PGA), and poly(lactic acid) (PLA) might improve their survival rate within the damaged area. Thus biomaterial scaffolds would be promising therapeutic materials to bridge the

irreversible lesions formed due to spinal cord damage. The most commonly used natural ECM components are explained below.

Alginate hydrogel-based scaffolds

Enhanced linear axonal growth was demonstrated by Günther et al. in a rodent model of SCI. Here, they used alginate-based hydrogels with linear channels that are filled with bone marrow stromal cells, overexpressing brain-derived neurotrophic factor (BMSCs-BDNF). The rodent SCI model (C5 hemisection lesion) with alginate scaffolds showed significant linear axonal growth with the axons able to cross the lesion site in comparison to the group without the scaffolds (Gunther et al. 2015). A study by Blasko et al. used MSCs for embedding into alginate hydrogels and was transplanted into injured rat spinal cord models (T8–T9 levels). Three weeks post-transplantation, axonal growth (GAP-43), expression of glial markers lba-1(microglia), and GFAP (astrocytes) were observed at lesioned area (Blasko et al. 2017). Anisotropic alginate-based capillary hydrogels also support axonal growth, which is accompanied by astroglial migration. However, the axonal density is dependent on the diameter of the capillaries of alginate-based hydrogels; with increased diameter of capillaries, the longitudinally oriented axon outgrowth gets diminished (Pawar et al. 2015). Thus, it describes the importance of scaffolds with capillary structures which are well suited for axonal guidance at the lesion/damaged site for regeneration.

Collagen tube-based scaffolds

Collagen is the natural ECM component found in most of the cellular niches. Therefore, a large volume of studies have shown interest in utilizing collagen as a backbone scaffold in various designs for tissue degenerative diseases. Collagen scaffolds have the potential to align the reparative tissue with its structural property and can accommodate the Schwann cells, which can reduce the formation of fluid-filled cysts at the lesioned site. Bozkurt et al. demonstrated the potential effects of collagen-based microstructured nerve guides with cultivated rat Schwann cells. Schwann cells were shown to align in a columnar fashion and survived for 6 weeks post implantation. These nerve guides may hold great promise for the repair of peripheral nerve defects (Bozkurt et al. 2012). Implantation of collagen tubes regulates the healing process and repairs the damaged tissue through the migration of astrocytes into the wound site as well as promotes proper alignment of the regenerating axons along the spinal cord axis (Spilker et al. 2001). After lower thoracic spinal cord injury, there is a heavy loss of peripheral nerves that lead to paralysis. Collagen tubing can also help in guiding the regrowth of neurons from spinal cord to the periphery. In an experimental group with rodent SCI model (left hemicord T12 to 5 mm below), neurons that regrew into the lumbar ventral roots were reported. These results indicated that the rostral spinal axons can reconnect the ventral roots with the help of collagen tubes (Liu et al. 2001). Nauyen et al. demonstrated the preparation of three-dimensional aligned nanofibers in collagen hydrogel scaffold for controlled delivery of neurotrphin-3 (NT-3) in order to promote axon regeneration in the SCI. Researchers observed growth of aligned axons being associated with reduced inflammatory response and scar tissue formation (Nguyen et al. 2017). Cholas et al. demonstrated the potential use of collagen scaffold-filled tubes in the treatment of SCI. These collagen tubes were shown to reduce the formation of pseudocysts and facilitated in the alignment of tri-differentiated cells from NSCs, which overexpresses GDNF, thus helping in bridging the SCI defect (Cholas et al. 2012).

Chitosan channel-based scaffolds

Chitosan is a natural polysaccharide found in the exoskeleton of insects and crustaceans. In vitro studies reported that chitosan is biodegradable and compatible for the growth of neurons and their adhesion and differentiation. Implantation of chitosan tubes filled with type 1 collagen can significantly improve axonal regeneration of damaged spinal cord and showed functional recovery after 12 months of implantation in rodent SCI models (T9 level) (Li et al. 2009). Transplantation of dental pulp stem cells (DPSCs) with chitosan scaffolds into a SCI rodent model resulted in the better recovery of hind limb locomotor functions (Zhang et al. 2016). In another study, chitosan channels filled with peripheral nerve grafts showed large number of axons in the chitosan embedded nerve graft group, when compared with the chitosan groups alone. Thus, chitosan channels containing neural tissue can prove to be a promising strategy for the repair of damaged spinal cord (Nomura et al. 2008). Neural tissue repair was effectively induced by chitosan with water as fragmented physical hydrogel suspension (chitosan-FPHS), which modulated the inflammatory response and suggested that this might be a promising new approach to treat SCI (Chedly et al. 2017). Bozkurt et al. used spinal cord-derived NS/PCs of rat and seeded on intramedullary chitosan channels that were then implanted in a subacute rodent SCI model (T8 level), followed by examining their functional improvements after 6 weeks. Chitosan channels containing NSPC showed enhanced survival of grafted cells in the lesion cavity, when compared with the NS/PCs transplantation group alone. Additionally, there was no worsening of the

functional deficit. However, there was no significant difference in the functional recovery between the control and treatment groups and it did not completely curtail the damaged spinal cord (Bozkurt et al. 2010). This suggests that additional modifications of the channels are required to enhance transplant survival and improve bridging, such as administration of associated growth factors on these channels which may help in enhanced recovery (Bozkurt et al. 2010).

Clinical trails

Various clinical trials are registered with clinical trial database maintained by the National Institutes of Health (NIH), USA (https://clinicaltrials.gov/). We looked for clinical trials that have been already conducted on spinal cord injuries till date (Jan 2018). Overall, among 620 clinical trials that are registered so far, only 38 studies have used stem cells and very few are trails inclusive of scaffold-adjunct treatments have been registered. The detailed description of these studies is described in Table 3.

Conclusion and future perspectives

Cell-based delivery and cells embedded in scaffold-based therapeutic strategies have been developed for various stages of damaged spinal cord. The current therapeutic strategies are aimed at the prevention of further damage to the spinal cord. Current treatment for SCI involves acute resuscitation, aggressive rehabilitation, and further symptomatic treatment of secondary complications. Invasive and non-invasive neuromodulation strategies such as deep brain stimulation, spinal cord stimulation, and motor cortex stimulation are some of the most advanced medical methods for SCI treatment (Chari et al. 2017). Even though these advances showed little improvement in the clinical outcome, no therapeutic approach completely targets the neurological deficits that are caused due to damage of the spinal cord (Tables 2 and 3). Also, only few ongoing clinical trials have currently tested the neuroprotective abilities of certain molecules (riluzole, glyburide, magnesium sulfate, nimodipine, and minocycline) for SCI patients (Tator et al. 2012). Although these molecules have been shown to reduce cell death and decrease the progression of injury, they fail to promote regeneration and spinal cord tissue repair.

Taken together, stem cell therapy has gained significant clinical importance to provide beneficial and efficacious reparative strategies for replenishment of damaged neural tissue (Mothe and Tator 2012). However, due to "harsh" environmental conditions at the site of injury, transplanted cells fail to survive for a long-term period. To increase the cytoprotective effects of stem cells various receptor-based cell survival pathways have been researched upon recently. Among them, activated delta opioid signaling system has been shown to increase the cell survivability of MSCs under various stress conditions (Mullick et al. 2017; Reddy and Sen 2017). In addition to these, the extracellular matrix proteins (collagen, laminin, fibronectin, etc.) of neurogenic niches are highly important for survival, proliferation, and differentiation of the grafted cells. Injectable hydrogels are semisolid gels which are ideal for treatment under the instances of spinal cord damages due to its similar elastic modulus (2-230 kPa) (Tsintou et al. 2015). The different fabrication and micropatterning methods of hydrogels aid in the growth of neural cells in a similar morphological pattern (Shrestha et al. 2014). However, mechanism through which the regenerated axons reach their appropriate target via the hydrogel scaffolds, establishing the neural connections, remains elusive till date. The stem cells on being embedded in the injectable hydrogels may reduce the size of glial scar, regenerate the damaged neurons/glial cells at the site of injury, and modulate the inflammatory cytokines (Khaing et al. 2016; Macaya and Spector 2012; Tukmachev et al. 2016). Further studies are required to address the directionality of newly formed neurons within the biomaterial scaffolds toward both ends of the injured region of spinal cord. Altogether, it can be foresaid that there are no gold-standard methods on neural tissue regeneration. The combination of scaffold embedded with stem cells and/or growth factors are more likely to be beneficial for the regeneration of damaged spinal cord. These therapeutic approaches not only provide structural support but also offer neurotrophic microenvironment, which would mimic neural tissue niche, resulting in proper functional improvement in SCI patients.

Acknowledgements The authors are thankful to Ms. Zera Mariyam for proofreading the manuscript.

Funding Katari Venkatesh (KV) is supported by a National Post-Doctoral Fellowship (N-PDF) (File No: PDF/2016/003652/LS) from Science and Engineering Research Board (SERB), Department of Science and Technology, Govt. of India. Dwaipayan Sen (DS) is supported by a "Fast Track Young Scientist" grant (YSS/2014/000027) from the Science and Engineering Research Board (SERB), Department of Science and Technology, Government of India. DS is also supported by a grant award from the Indian Council of Medical Research (ICMR), Sanction Order No. NCD/Ad-hoc/66/2016-17. The funding sources did not play any role in the research and/or preparation of the article, study design, data collection, analysis/interpretation of data, writing of the report, and decision to submit the article for publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Table 2 Clinical trial reports on the spinal cord injuries using of stem cells and/or scaffolds

S. No.	Transplant type	Injury grade and No. of patients	Transplantation specifications	Neurological outcome	Shortcomings	References
Cells						
1	BM-HSCs	ASIA-A grade; $n = 9$	Intralesional, arachnoid space	ASIA grade A to B or C, non-carcinogenic, effective and safe	$n = 9$, short-term follow-up	Deda et al. 2008
2	BM-HSCs	ASIA-A to C; $n = 18$	Intrathecal	78% by one grade, 22% by two grade, feasible and safe	$n = 18$, headaches (9%), increased temperature, (6%) improvement ≥ 3 grades	Kakabadze et al. 2016
3	BM-HSCs	ASIA-A; $n = 20$	Intra-arterial and intravenous	Motor and/or sensory Safe and no complications	$n = 20$	Sykova et al. 2006
4	Autologous ex vivo cultured BM-MSCs	ASIA-A; $n = 30$	Intrathecal	Safe and no adverse events	No description about neurological outcome	Pal et al. 2009
5	BM-aspirated cells	ASIA-A; $n = 21$	Intrathecal or intralesional route	Safe and feasible No adverse events	No significant improvement	Chhabra et al. 2016
6	Autologous ex vivo cultured BM-MSCs with physical therapy	ASIA-A and B; $n = 70$	Intrathecal + physical therapy	46% of patients showed functional improvements	No sustained neurological improvement (54%)	El-Kheir et al. 2014
7	Autologous ex vivo cultured BM-BMSCs	ASIA-A; $n = 5$	Inter-vertebral	Safe and feasible No adverse events	$n = 5$, no significant neurological improvements	Saito et al. 2012
8	BM-MSCs	ASIA-A; $n = 14$	Intralesional	Tactile sensitivity, lower limbs motor, hip flexors, sacral sparing and urological function Safe and feasible	$n = 14$, post-operative symptoms (incision pain, cerebrospinal fluid leak)	Mendonca et al. 2014
9	Autologous ex vivo cultured BM-MSCs	ASIA-A; $n = 5$	Percutaneous, intralesional	Bowel movements, tactile functions Safe, no adverse effects	$n = 14$, no description about carcinogenesis	Larocca et al. 2017
10	Autologous ex vivo cultured BM-MSCs and Schwann cells	ASIA-A; $n = 6$	Intralesional	bladder functions and axonal regeneration	No motor functions, n = 6	Oraee-Yazdani et al. 2016
11	BM-MSCs, labeled with iron oxide nanoparticles	ASIA-A; n = 1	Intrathecal	No clinical improvements	Side effects like fever, headache Neurological functions are not improved	Chotivichit et al. 2015
12	Autologous BM-MSCs	ASIA-A; $n = 40$	Near to lesion site	Motor functions, light touch, pin prick sensory, urinary functions	Short-term follow-up	Dai et al. 2013
13	Autologous ex vivo cultured Schwann cells	AIS A; $n = 6$	Intrathecal space	No additional spinal cord damage, mass lesion, or syrinx formation	No electrophysiological studies, no follow-up after 1 year	Anderson et al. 2017
14	BM-MSCs	AIS A; $n = 16$	Intramedullary, subdural space	Limited neurological improvement	Only 2 patients showed improvement No significant neurological improvement	Oh et al. 2016
Scaffold and stem cells						
15	NeuroRegen scaffolds + autologous BM-mononuclear cells	AIS A; $n = 5$	NeuroRegen scaffold with 1×10^9 cells	Improvements in lower limbs	No adverse effects No scaffold degradation report	Xiao et al. 2016
16	NeuroRegen scaffold combined with human MSCs	AIS A; $n = 8$	NeuroRegen scaffolds with 4×10^7 cells	Improvements in motor and autonomous functions	Side effects—infection, allergic reaction, and aggravation of neurological status	Zhao et al. 2017

Table 3 Cell/scaffold-based clinical trials that are enrolled for spinal cord injuries

S. No.	NCT number	Title	Interventions	Age (years)	Phases, status	Enrolment	Last updated	Sponsor/collaborators
1	NCT03105882	Pilot study of the Neuro-Spinal Scaffold for the Treatment of AIS A Cervical Acute SCI	Neuro-spinal scaffold	16 to 70 (Child, Adult, Senior)	1; recruiting	10	26-Jul-2017	InVivo Therapeutics, Massachusetts
2	NCT02138110	The INSPIRE Study: Probable Benefit of the Neuro-Spinal Scaffold for Treatment of AIS A Thoracic Acute Spinal Cord Injury	Neuro-spinal scaffold	16 to 70 (child, adult)	1, 2; active, not recruiting	20	20-Jul-2017	InVivo Therapeutics, Massachusetts
3	NCT02302157	Dose Escalation Study of AST-OPC1 in Spinal Cord Injury	Oligodendrocyte progenitor cells derived from pluripotent stem cells	18 to 69 (adult, senior)	1, 2; recruiting	35	11-Jul-2017	Asterias Biotherapeutics, Inc. California
4	NCT02688049	NeuroRegen Scaffolds Combined with Stem Cells for Chronic Spinal Cord Injury Repair	NeuroRegen scaffolds, mesenchymal stem cells transplantation, and NeuroRegen scaffold/ neural stem cells transplantation	18 to 65 (adult)	1; completed	30	1-Jun-2017	Chinese Academy of Sciences|Affiliated Hospital of Logistics University of CAPF, China
5	NCT03167138	Microfragmented Adipose Tissue (LipogemsÂ®) Injection for Chronic Shoulder Pain in Persons With Spinal Cord Injury	Autologous microfragmented adipose tissue, Lipogems System	18 to 60 (adult)	3	6	24-May-2017	Kessler Foundation, USA
6	NCT01899664	Upper Extremity Surgery in Spinal Cord Injury	Nerve transfer surgery	18 to 60 (adult)	1; recruiting	50	12-May-2017	Washington University School of Medicine, Missouri
7	NCT02481440	Umbilical Cord Mesenchymal Stem Cells Transplantation to Patients With Spinal Cord Injury	Biological: umbilical cord mesenchymal stem cells	18 to 65 (adult)	1, 2; active, not recruiting	44	7-May-2017	Limin Rong|Third Affiliated Hospital, Sun Yat-Sen University, China
8	NCT02152657	Evaluation of Autologous Mesenchymal Stem Cell Transplantation in Chronic Spinal Cord Injury: a Pilot Study	Mesenchymal stem cell transplantation	18 to 65 (adult)	1; completed	5	25-Apr-2017	Hospital Sao Rafael, Brazil
9	NCT01772810	Safety Study of Human Spinal Cord-derived Neural Stem Cell Transplantation for the Treatment of Chronic SCI	Human spinal cord stem cells	18 to 65 (adult)	1; recruiting	8	7-Apr-2017	Neuralstem Inc., Maryland
10	NCT02861612	Nerve Transfers to Restore Hand Function in Spinal Cord Injury	Procedure: nerve transfer surgery	18 to 60 (adult)	1, 2; recruiting	5	13-Mar-2017	Ottawa Hospital Research Institute|Ontario Neurotrauma Foundation|Canadian Society of Plastic Surgeons| Washington University School

Table 3 (continued)

S. No.	NCT number	Title	Interventions	Age (years)	Phases, status	Enrolment	Last updated	Sponsor/collaborators
								of Medicine|Rick Hansen Institute, Canada
11	NCT02354625	The Safety of ahSC in Chronic SCI With Rehabilitation	Autologous human Schwann cells	18 to 65 (adult)	–; recruiting	10	8-Mar-2017	W. Dalton Dietrich|The Miami Project to Cure Paralysis |University of Miami, Florida
12	NCT02510365	Functional Neural Regeneration Collagen Scaffold Transplantation in Acute Spinal Cord Injury Patients	Functional collagen scaffold	18 to 65 (adult)	2, 3; active, not recruiting	20	7-Feb-2017	Chinese Academy of Sciences |Affiliated Hospital of Logistics University of CAPF|The First Affiliated Hospital of Soochow University, China
13	NCT02688062	NeuroRegen Scaffoldâ„¢ with Bone Marrow Mononuclear Cells Transplantation vs. Intradural Decompression and Adhesiolysis in SCI	NeuroRegen Scaffold with BMMCs transplantation, surgical intradural decompression and adhesiolysis	18 to 60 (adult)	1, recruiting	22	7-Feb-2017	Chinese Academy of Sciences |First Hospitals affiliated to the China PLA General Hospital, China
14	NCT02981576	Safety and Effectiveness of BM-MSC vs AT-MSC in the Treatment of SCI Patients	Autologous mesenchymal stem cells	18 to 70 (adult, senior)	1, 2; active, not recruiting	14	30-Jan-2017	University of Jordan, Jordan
15	NCT01739023	Safety of Autologous Human Schwann Cells (ahSC) in Subjects with Subacute SCI	Autologous human Schwann cells	18 to 60 (adult)	1, 2; recruiting	9	10-Jan-2017	W. Dalton Dietrich|The Miami Project to Cure Paralysis|University of Miami, Florida
16	NCT02923817	Clinical Trial Using Bone Marrow-Derived Mononuclear Cells for Spinal Cord Injury	Transplantation of autologous bone marrow-derived mononuclear cells by lumbar injection	20 to 60 (adult)	1, 2; completed	30	9-Jan-2017	Da Nang Hospital|Kitano Hospital|Translational Research Informatics Center, Kobe, Hyogo, Japan
17	NCT02687672	Transplantation of Autologous Bone Marrow or Leukapheresis-Derived Stem Cells for Treatment of Spinal Cord Injury	Stem cell transplantation	5 to 55 (child, adult)	2; active, not recruiting	50	17-Oct-2016	Stem Cells Arabia, Jordan
18	NCT01676441	Safety and Efficacy of Autologous Mesenchymal Stem Cells in Chronic Spinal Cord Injury	Mesenchymal stem cell transplantation	16 to 65 (child, adult)	1; completed	32	6-Oct-2016	Pharmicell Co., Ltd., South Korea
19	NCT02009124	Stem Cell Therapy in Spinal Cord Injury	Autologous bone marrow mononuclear cell transplantation	12 to 65 (child, adult)	1; recruiting	500	23-Sep-2016	Neurogen Brain and Spine Institute, India
20	NCT01714349	Nerve Transfer After Spinal Cord Injuries	Nerve transfer	18 to 65 (adult)	1; completed	20	21-Sep-2016	Washington University School of Medicine |United States Department of Defense, Missouri

Table 3 (continued)

S. No.	NCT number	Title	Interventions	Age (years)	Phases, status	Enrolment	Last updated	Sponsor/collaborators
21	NCT02570932	Administration of Expanded Autologous Adult Bone Marrow Mesenchymal Cells in Established Chronic Spinal Cord Injuries	Autologous mesenchymal bone marrow cell	18 to 70 (adult, senior)	1; completed	10	5-Sep-2016	Puerta de Hierro University Hospital, Spain
22	NCT01769872	Safety and Effect of Adipose Tissue Derived Mesenchymal Stem Cell Implantation in Patients with Spinal Cord Injury	Autologous adipose tissue derived MSCs transplantation	19 to 70 (adult, senior)	1; completed	15	1-Aug-2016	Biostar|Korea University Anam Hospital, Korea
23	NCT02482194	Autologous Mesenchymal Stem Cells Transplantation for Spinal Cord Injury—a Phase I Clinical Study	Autologous, mesenchymal stem cells	18 to 50 (adult)	1; completed	9	28-Jun-2016	Armed Forces Bone Marrow Transplant Center, Rawalpindi, |Armed Forces Institute of Regenerative Medicine, Pakistan
24	NCT02165904	Subarachnoid Administration of Adult Autologous Bone Marrow Mesenchymal Cells Expanded in Incomplete (SCI)	Adult autologous mesenchymal bone marrow cell	18 to 70 (adult, senior)	1, 2; active, not recruiting	10	13-Jun-2016	Puerta de Hierro University Hospital, Spain
25	NCT02260713	Autologous Bone Marrow Cell Transplantation in Persons With Acute Spinal Cord Injury—an Indian Pilot Study	Autologous bone marrow cell	18 to 55 (adult)	2; recruiting	21	23-Feb-2016	Indian Spinal Injuries Centre|Indian Council of Medical Research, India
26	NCT02326662	Neural Stem Cell Transplantation in Traumatic Spinal Cord Injury	Biological: autologous stem cell transplantation	18 to 50 (adult)	1; completed	30	26-Oct-2015	Federal Research Clinical Center of Federal Medical & Biological Agency,,Novagenesis Foundation |Ophiuchus Technologies AG, Russia
27	NCT02574572	Autologous Mesenchymal Stem Cells Transplantation in Cervical Chronic and Complete Spinal Cord Injury	Autologous mesenchymal cells transplantation	18 to 65 (adult)	1, 2; completed	10	9-Oct-2015	Hospital Sao Rafael, Brazil
28	NCT01909154	Safety Study of Local Administration of Autologous Bone Marrow Stromal Cells in Chronic Paraplegia	Mesenchymal stromal cell therapy	18 to 60 (adult)	–; recruiting	12	17-Jun-2015	Puerta de Hierro University Hospital, Spain
29	NCT01321333	Study of Human Central Nervous System Stem Cells (HuCNS-SC) in Patients with Thoracic Spinal Cord Injury	Human central nervous system stem cells	18 to 60 (adult)	–; recruiting	12	16-Jun-2015	StemCells, Inc., California
30	NCT01624779	Intrathecal Transplantation Of Autologous Adipose Tissue Derived MSC in the Patients with Spinal Cord Injury	Autologous adipose tissue derived mesenchymal stem cells	19 to 70 (adult, senior)	1, 2; completed	15	11-Feb-2015	Bukwang Pharmaceutical, South Korea
31	NCT01354483	Umbilical Cord Blood Mononuclear Cell Transplant To Treat Chronic Spinal Cord Injury	Umbilical cord blood mononuclear cell, methylprednisolone and lithium carbonate tablet	18 to 60 (adult)	2; recruiting	20	20-Aug-2014	China Spinal Cord Injury Network|Chengdu PLA General Hospital, China

Table 3 (continued)

S. No.	NCT number	Title	Interventions	Age (years)	Phases, status	Enrolment	Last updated	Sponsor/collaborators
32	NCT01325103	Autologous Bone Marrow Stem Cell Transplantation in Patients with Spinal Cord Injury	Bone marrow stem cells	18 to 50 (adult)	1; completed	20	27-May-2014	Hospital Sao Rafael|Oswaldo Cruz Foundation|Irep Sociedade de Ensino Superior MÃ©dio e Fundamental Limitada|Hospital Espanhol, Brazil
33	NCT02027246	Safety and Efficacy of Stem Cell Therapy in Spinal Cord Injury	Autologous bone marrow mononuclear cell transplantation	8 to 63 (child, adult)	1, 2; completed	166	10-Mar-2014	Neurogen Brain and Spine Institute, India
34	NCT01046786	Safety and Feasibility of Umbilical Cord Blood Cell Transplant into Injured Spinal Cord	Umbilical Cord blood mononuclear cell, methylprednisolone and lithium	18 to 60 (adult)	–; completed	8	27-Jan-2014	China Spinal Cord Injury Network|Chinese University of Hong Kong|The University of Hong Kong
35	NCT01217008	Safety Study of GRNOPC1 in Spinal Cord Injury	Human embryonic stem (hES) cell-derived oligodendrocyte progenitor cells (OPCs)	18 to 65 (adult)	1, 2; completed	5	6-Jan-2014	Asterias Biotherapeutics, Inc., California
36	NCT01355549	Platelet-Rich Plasma Therapy for Shoulder Pain in Persons with Spinal Cord Injury	Platelet-rich plasma (PRP) therapy	18 to 60 (adult)	1, 2; recruiting	6	14-Jan-2013	Kessler Foundation, USA
37	NCT01186679	Safety and Efficacy of Autologous Bone Marrow Stem Cells in Treating Spinal Cord Injury	Autologous bone marrow stem cells	20 to 55 (adult)	−, recruiting	12	20-Aug-2010	International Stemcell Services Limited, India
38	NCT00816803	Cell Transplant in Spinal Cord Injury Patients	Autologous bone marrow transplant	10 to 36 (child, adult)	1, 2; completed	80	2-Jan-2009	Cairo University|Al-Azhar University|Medical Military Academy, Egypt|Alexandria University, Egypt

Abbreviations SCI, Spinal cord injury; NSCISC, National Spinal Cord Injury Statistical Center; GDP, Gross domestic product; NSCT, Neural stem cell transplantation; NSC, Neural stem cell; ASIA, American Spinal Cord Injury Association; TNFα, Tumor necrosis factor alpha; IL-β, Interleukin 1 beta; GFAP, Glial fibrillary acidic protein; BBB, Blood-brain barrier; GCV, Ganciclovir; CSPGs, Chondroitin sulfate proteoglycans; GAG, Glycosaminoglycan; CNS, Central nervous system; CNS, Central nervous system; OPCs, Oligodendrocyte progenitor cells; cABC, Chondroitinase ABC; ATP, Adenosine triphosphate; NO, Nitric oxide; NADPH, Nicotinamide adenine dinucleotide phosphate; ROS, Reactive oxygen species; LPS, Liposaccharides; MAG, Myelin-associated glycoprotein; Omgp, Oligodendrocyte myelin glycoprotein; MPSS, Methylprednisolone; GK-11, Gacyclidine; NTX, N-terminal telopeptide; bALP, Bone alkaline phosphatase; FIM, Functional Independence Measure; COT, Common Object Test; SVZ, Subventricular zone; SGZ, Subgranular zone; ESCs, Embryonic stem cells; PSCs, Pluripotent stem cells; NS/PCs, Neural stem/progenitor cells; MSCs, Mesenchymal stem cells; HSCs, Hematopoietic stem cells; G-CSF, Granulocyte colony-stimulating factor; HBO, Hyperbaric oxygen; BSCB, Blood-spinal cord barrier; NES, Neuroepithelial stem cells; OECs, Olfactory ensheathing cells; SCs, Schwann cells; hGPCs, Human glial progenitor cells; HGF, Hepatocyte growth factor; BDNF, Brain-derived neurotrophic factor; ECM, Extracellular matrix; PGA, Poly(glycolic acid); PLA, Poly(lactic acid); BPA, Blood pressure augmentation; BMMCs, Bone marrow mononuclear cells

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