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REVIEW

Clinical Trials in Traumatic Spinal Cord Injury

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Abstract
Traumatic spinal cord injury (SCI) results in impaired neurologic function that for many individuals is permanent and significantly impacts health, function, quality of life, and life expectancy. Many efforts have been taken to develop effective treatments for SCI; nevertheless, proven therapies targeting neurologic regeneration and functional recovery have been limited. Existing therapeutic approaches, including early surgery, strict blood pressure control, and consideration of treatment with steroids, remain debated and largely focus on mitigating secondary injury after the primary trauma has occurred. Today, there is more research being performed in SCI than ever before. Current clinical trials are exploring pharmacologic, cell-based, physiologic, and rehabilitation approaches to reduce secondary injury and also overcome barriers to neurorecovery. In the future, it is likely that tailored treatments combining many of these strategies will offer significant benefits for persons with SCI. This article aims to review key past, current and emerging neurologic and rehabilitation therapeutic approaches for adults with traumatic SCI.

Key Words Spinal cord injury · trauma · clinical trial · management · neuroprotection · neuroregeneration

Introduction

In the United States (US), it is estimated that 17,500 individuals sustain a traumatic spinal cord injury (SCI) each year and that there are approximately 285,000 people living with chronic SCI [1]. SCI directly results in motor and sensory impairment but also can lead to pain, spasticity, respiratory and cardiovascular alterations, neurogenic bowel, neurogenic bladder, and integumentary complications, affecting overall quality of life and life expectancy. In addition, SCI is associated with a significant economic burden with estimated direct lifetime costs ranging from $1.1 to $4.8 million per patient depending on age and severity of injury [1].

Given the impact of SCI, many efforts have been taken to develop effective treatments. Despite many advances in medical, surgical, and rehabilitation care for persons with SCI, proven treatments specifically targeting neurologic function are limited [2]. With that said, it is an exciting time in the field of SCI research with more current clinical trials being undertaken than ever before. This article aims to review key past, current, and emerging neurologic therapeutic approaches for adults with traumatic SCI. SCI pathophysiology and associated therapeutic targets, current clinical strategies, and investigational therapies for SCI will be discussed.

Pathophysiology and Associated Therapeutic Targets

Traumatic SCI pathophysiology can be divided into primary and secondary injuries. The primary injury occurs due to physical forces associated with a mechanical disturbance of the spinal cord, leading to alterations in axons, blood vessels, and cell membranes. The most common causes include motor vehicle crashes, falls, violence, and sports [1]. Public health campaigns such as motor vehicle safety, fall prevention,

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violence prevention, and safe sport practices are important primary prevention measures for SCI.

Secondary injury occurs after the initial trauma but is nonetheless an important contributor to the overall extent of SCI [3, 4]. Secondary injury occurs through a variety of mechanisms including disruption of the blood spinal cord barrier leading to the infiltration of inflammatory cells, the release of inflammatory cytokines, initiation of proapoptotic signaling cascades, excessive release of excitatory neurotransmitters with resulting excitotoxicity, and ischemia [4–6]. Recognizing potential therapeutic targets for preventing further progression of SCI, much of the past and current research in this field has focused on mitigating the secondary injury cascade.

Finally, once a SCI has occurred, there are several barriers to neurologic recovery. Compared to the peripheral nervous system (PNS), the regenerative capacity of the central nervous system (CNS), and specifically the spinal cord, is limited by a fixed number of available regenerative cells and restricted plasticity [4]. In addition, cystic cavity formation, with limited substrate for axonal growth and cell migration, glial scar, and the release of inhibitory proteins by CNS myelin impede axonal regeneration [4, 6]. Several treatments, ranging from surgical interventions to rehabilitation strategies, are focused on overcoming these obstacles.

Current Clinical Strategies

Timing of Surgical Decompression

The primary objective of early surgery in persons with acute SCI is to provide relief from mechanical pressure in order to reduce spinal cord compression and ischemia to optimize the local environment for neurological recovery. Animal studies demonstrated that persistent compression of the spinal cord after the initial trauma causes ischemia and exacerbates the secondary injury cascade [7–10]. Following these preclinical results, several studies were performed in persons with acute SCI.

The Surgical Treatment of Acute Spinal Cord Injury Study (STASCIS) was a prospective cohort study in persons with cervical SCI and reported that the early decompression group (< 24 h after SCI) were 2.8 times more likely to demonstrate at least a two-grade improvement in American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade at 6 months compared with the late decompression group (≥ 24 h after SCI) [11]. van Middendorp et al. [12] on reanalysis demonstrated a trend toward the efficacy of early decompression, but without statistical significance. Additional studies have reported improvements in AIS grade and/or ASIA motor scores after early surgery (≤ 24 h after SCI), especially in cervical level injuries [13–15]. In one retrospective study of persons with cervical SCI, individuals who underwent surgery within 8 h had better improvement in Spinal Cord Independence Measure (SCIM) scores and AIS grades at 1 year after SCI [16].

Although most recent publications support the effectiveness of early surgery, including the American Association of Neurosurgical Surgeons (AANS) and Congress of Neurological Surgeons guidelines and the current AOSpine guidelines [17–19], a recent systematic review revealed that there have been only low evidence studies that support clinically significant benefit in early intervention to improve long-term functional outcomes after SCI [20]. There is a current randomized controlled trial (RCT) (NCT02673320) comparing early (≤ 48 h after SCI) *versus* delayed (at 15 days postinjury) spinal decompression surgery in persons with tetraplegia (C2-T1, AIS A-D), with follow-up at 2 years looking at numerous functional outcome measures. Given the heterogeneity of SCI patients, future prospective studies are warranted along with studies focusing on the effects of very early intervention, such as 8 or 12 h.

Surgery for Central Cord Syndrome

In the past, surgical decompression was delayed for persons with acute central cord syndrome (CCS) until their neurological recovery plateaued out of fear that surgery may interfere with recovery [21–23]. Additionally, some studies support delayed decompression for CCS [24, 25] to allow for medical stability particularly in elderly patients, which can decrease mortality rates [25]. However, recent studies have shown a trend toward improvement with early surgical decompression in CCS [26, 27]. Lenehan et al. [28] reported that patients with CCS who underwent early decompression (< 24 h after SCI) had improved ASIA motor scores (6.31 points), and a greater chance of AIS improvement at 12-month follow-up than those with late decompression (≥ 24 h after SCI). A prospective RCT (COSMIC, NCT01367405) was initiated in 2013 [29], but was terminated in 2016 because of difficulties with patient enrollment.

In the most recent clinical practice guidelines from AOSpine, the recommendation was to consider early surgery (≤ 24 h after SCI) in CCS [19]. Although early surgical decompression for SCI is generally suggested, more evidence is recommended. A current trial (NCT01485458) is underway for persons with acute (< 48 h) cervical (C5–8) SCI (AIS C) with canal stenosis without bony injury, between the age of 20 and 79 years, comparing early (< 24 h after SCI) *versus* delayed (> 2 weeks after SCI) decompression surgery on outcomes at 1 year.

Methylprednisolone in SCI

The National Acute SCI Study (NASCIS) trials remain an important, albeit controversial, aspect of SCI research and clinical care. NASCIS 1, evaluated the effect of

methylprednisolone (MP) (1000-mg loading dose, followed by 250 mg q6hrs × 10 days vs MP 100 mg load followed by 25 mg q6hrs × 10 days), a corticosteroid thought to inhibit the inflammatory cascade contributing to secondary damage in SCI, in persons ($n = 330$) with acute SCI [30]. Although the trial was terminated early, there was no difference between the two groups in terms of motor recovery at 6 weeks or 6 months.

NASCIS-2 then randomized 487 patients with acute (≤ 12 h) SCI into three groups; MP (30 mg/kg bolus followed by 5.4 mg/kg/h × 23 h), naloxone (5.4 mg/kg bolus then 4 mg/kg/h × 23 h), and a placebo arm [31]. The primary analysis found no statistically significant improvement in outcomes; however, secondary subgroup analyses revealed significant motor recovery (~5 points) in patients receiving high-dose MP within 8 h of injury at 6 weeks, 6 months, and 1 year [31, 32]. Subsequently, NASCIS-3 sought to determine the ideal length of MP therapy and as such subjects ($n = 499$) with acute (< 8 h) SCI were randomized into three groups: 24 h of MP (NASCIS-2 conditions), 48 h of MP, or 48 h of tirilazad [33]. Results of NASCIS-3 suggested that for patients in whom MP therapy was initiated within 3 h of injury, 24 h of therapy was sufficient. If treatment began between 3 and 8 h of injury, 48 h of MP was associated with better neurologic outcomes (although with an increased risk of infection including severe pneumonia and sepsis) [33].

The benefits and safety of utilizing the NASCIS protocol (mostly NASCIS-2) has been debated. Concerns include patient selection and randomization, use of pre-defined primary endpoints that were felt to favor the investigator's conclusions, methodology of the analysis, limited replication of findings, and increased morbidity and mortality in persons administered MP [34–36]. In 2002, the Neurosurgery Clinical Practice Guidelines [37] recommended MP for either 24 or 48 h "as an *option* in the treatment of patients with acute SCI injuries that should be undertaken only with the knowledge that the evidence suggesting harmful side effects is more consistent than any suggestion of clinical benefit." In 2012, a Cochrane review summarizing 6 large-scale studies on MP in acute SCI found an overall 4-point increase in ASIA motor scores when MP was administered within 8 h of injury [38]. In 2013, however, the Neurosurgical Guidelines updated their recommendation to state that high-dose MP was "not recommended" and "associated with harmful side effects including death" [39]. In a counterpoint in 2014, Fehlings and Wilson [40] questioned the dramatic change in the Neurosurgical Guideline recommendations, given no significant change in evidence used for the recommendations in 2003 and 2012 and the exclusion of the 2012 Cochrane analysis from their review.

More recently, a number of papers have continued the debate regarding use of MP in acute traumatic SCI [41–47]. Evaniew et al. [41] reported on persons with acute SCI who received either the NASCIS-II regimen of MP within 8 h ($n = 46$) or no steroid treatment ($n = 1555$) and found no significant differences for motor recovery, with a higher rate of complications (61 vs 36%; $p = 0.02$) in the MP group. A critique of this paper in a letter to the editor followed along with a response [42, 43]. In a subsequent review by Evaniew et al. [44], they concluded that "pooled evidence does not demonstrate a significant long-term benefit for MP in patients with acute traumatic SCIs and suggested it may be associated with increased GI bleeding."

Bowers et al. [45] reported results of a survey completed by 77 persons with chronic SCI on treatment with MP from the patients' perspective and found that 59.4% reported that the small neurological benefits were "very important" to them and that they had "little concern" for the potential side effects of MP. This led this group and others to consider that "conscious patients should be given greater opportunity to decide their treatment." In the most recent AOSpine 2017 Guidelines [46], administration of intravenous (IV) MP for 24 h was recommended to be considered within 8 h of cervical injury in patients without significant medical contraindication, although the evidence level was reported as "weak."

The debate over the use of MP in acute traumatic SCI in the last two decades has not abated and there is evidence that can be used to substantiate each position. Protocols in regard to treatment with MP in acute SCI still seemingly remain hospital dependent. There are no current ongoing trials in this area.

Blood Pressure Management after SCI

Blood pressure (BP) management in the acute period after SCI is extremely important, as persistent hypotension can increase spinal cord ischemia and secondary damage. The current AANS and Congress of Neurological Surgeons guideline [37] provides level III recommendations for continuous hemodynamic monitoring, and interventions to maintain mean arterial blood pressure (MAP) between 85 and 90 mmHg for the first 7 days in persons with cervical SCI [39]. This includes using IV fluids and vasopressors to improve blood flow to the injured cord. Recent reports have recommended norepinephrine as a first line agent given its lower side effect profile than dopamine [48, 49].

Although recent studies have confirmed these published guidelines [50, 51], others have suggested that such an arbitrarily elevated MAP goal may not be efficacious and that maintenance of the recommended sustained systemic hypertension may be associated with risks to the patient [49, 52, 53].

Currently, there are two studies evaluating the medical management of BP for persons SCI. One is a phase III randomized controlled double blinded (RC-DB) parallel group study (NCT02232165) for persons within acute (≤ 12 h) cervical and thoracic (to T12) SCI (AIS A-C) comparing a target MAP of ≥ 65 *versus* ≥85 mmHg for 7 days on year 1 motor scores. The second (NCT02878850) is comparing BP being maintained in a higher range (MAP 85–90 mmHg) *versus* in a

normal range (MAP 65–70 mmHg) for 7 days in persons with acute cervical and thoracic (to T8) SCI (AIS A and B). These studies are expected to conclude in 2019 and 2020 respectively.

It is important to recognize that MAP support principally aims to maintain an appropriate spinal cord perfusion pressure (SCPP), determined by the difference between MAP and intraspinal pressure (ISP). Since the intraspinal pressure may increase independently of MAP, maintenance of a low ISP or a high SCPP (or both) has gained interest in the initial management of SCI [54–56]. Although initial studies have shown encouraging results about the predictive value of low ISP or high SCPP in neurological recovery, larger multicenter studies are needed to validate these preliminary data.

Investigational Therapies for SCI

Over the last three decades, many studies have explored treatments for SCI. There are also numerous investigational trials currently taking place [57, 58]. We will describe these therapies by the nature of their approach including pharmacological, cell based, physiological, and rehabilitation.

Pharmacological Approaches

Minocycline

Minocycline is a FDA-approved second-generation tetracycline antibiotic with CNS-penetrating abilities. It has anti-inflammatory, anti-oxidant, and anti-apoptotic properties [59]. Given these effects, it is also being investigated in preclinical models of other CNS disorders [5]. In animal SCI studies, it protects against neuronal loss and minimizes lesion size [60–62].

A phase II single-center double-blind randomized placebo-controlled study of 7 days of IV minocycline administration in persons ($n = 27$) with acute traumatic SCI (vs placebo, $n = 25$) demonstrated safety, stable SCI drug levels, and a trend toward improved motor scores, especially for individuals with tetraplegia [63]. An on-ongoing multisite phase III RCT (NCT01828203) is investigating the effect of twice daily IV minocycline over 7 days *versus* placebo for individuals with acute (< 12 h) cervical SCI on recovery at 3 months and 1 year postinjury.

Riluzole

Riluzole is another FDA-approved medication being studied in SCI. It is a benzothiazole anti-epileptic which reduces excitotoxicity by sodium blockade and reduction of presynaptic release of glutamate. Riluzole received marketing authorization in the US as a disease-modifying agent for treatment of amyothrophic lateral sclerosis in 1995, although its efficacy remains modest [64, 65]. In preclinical animal SCI models, riluzole attenuates the secondary injury cascade, promoting tissue sparing at the injury site and improved neurological recovery [66].

A prospective, multicenter phase I matched comparison group trial performed by the North American Clinical Trials Network (NACTN) of persons ($n = 36$) with acute (< 12 h) cervical and thoracic SCI who received 14 days of riluzole demonstrated safety. Temporary elevations of liver enzymes were seen in 14–70% of patients for different enzymes but there were no reported severe adverse events. In addition, significant neurologic motor improvement (15.5 point mean ASIA motor score difference) for individuals with cervical SCI at 90 days postinjury was reported [67].

A multicenter phase IIb/III randomized, placebo-controlled, 2-arm parallel group superiorly trial (RISCIS, NCT01597518) began in January 2014 to assess the efficacy and safety of riluzole for patients with acute (< 12 h) cervical (C4-8) SCI (AIS A-C). The primary outcome is ASIA motor score at 6 months. The study is expected to conclude in December 2018.

Magnesium with Polyethylene Glycol

Magnesium acts to antagonize *N*-methyl-D-aspartate (NMDA) receptors to reduce inflammation and excitotoxicity. Co-administration with polyethylene glycol (PEG) allows for improved penetration to the CNS allowing for reduced dosing and decreased peripheral side effects [68]. In animal models, magnesium improves tissue sparing and motor recovery [69–71].

A phase I/II RC-DB study (NCT01750684) sponsored by Acorda Therapeutics evaluating the role of magnesium with PEG (AC105) for individuals with acute traumatic SCI (C4-T11) began in 2013 but was terminated in 2015 due to limited enrollment. A total of 13 subjects received at least 1 infusion of AC105 or placebo, although full results have not been reported as of yet. A subsequent study of AC105 in a porcine SCI model did not find improvements in locomotor recovery or weight-supported treadmill walking [72].

Gacyclidine

Gacyclidine is also a NMDA receptor antagonist. In animal SCI models, it attenuates spinal cord damage and promotes recovery [73, 74]. A multicenter phase II prospective, RC-DB study investigated the role of IV Gacyclidine injection *versus* placebo in persons ($n = 280$) with acute (< 2 h) cervical and thoracic SCI. No significant differences in ASIA motor or sensory score were seen at 1 month and 1 year [75].

Fibroblast Growth Factor

Fibroblast growth factor (FGF) is a heparin-binding protein that stimulates axonal regeneration, facilitates survival of injured neurons, and reduces inflammation, astrocyte activation, and scar formation [76]. A multicenter, phase II, RC-DB parallel group study was initiated in 2012 in persons with complete cervical injuries to evaluate the efficacy, safety, and pharmacokinetics of SUN13837 injection (a FGF mimetic) in adults with acute SCI. This trial was called the ASCENT (Asubio Spinal Cord Early Neurorecovery Treatment) trial and the criteria were later expanded to include AIS A, B, and C injuries. In this study, 65 subjects were randomized (1:1) within 12 h of injury to IV SUN13837 (SUN) or matching placebo for no less than 7 and no more 28 days. The efficacy measures included the mean total SCIM III, combined SCIM III Self-Care and Mobility subscales and ASIA motor scores. Analyses of primary and secondary outcomes showed nonsignificant trends consistently favoring SUN13837 treatment although there were no safety concerns [77]. No current studies are documented.

Cethrin

The Rho signaling pathway is upregulated after SCI. This pathway is a significant barrier to axon regulation [78]. C3 transferase is a toxin produced by *clostridium botulinum* blocks Rho-mediated inhibition of axonal growth. In SCI rat models, it promotes neural regeneration and axonal growth [79, 80].

In 2011, Fehlings et al. [81] published the results of a phase I/IIa clinical trial of a C3 transferase, BA-210 (trademarked as Cethrin). A single dose of BA-210 (0.3 to 9 mg), a permeable material, was applied to the dura matter at the site of SCI during decompressive surgery, for persons ($n = 48$) with acute (< 7 days) complete SCI (C4-T12). No serious adverse events were attributed to the drug [81]. Increased motor recovery and AIS grade conversion at 12 months in persons with cervical injury were seen compared to historical controls.

A multicenter phase IIb/III, RC-DB study (NCT02669849) led by Vertex Pharmaceuticals Incorporated to assess the efficacy and safety of VX-210 in individuals with acute traumatic cervical SCI began in 2016 and is ongoing. Eligibility criteria include C4-7 AIS A or B, upper extremity motor score (UEMS) < 16 points on each side, and planned spinal decompression/stabilization within 72 h of initial injury. Participants receive a single 9-mg dose of VX-210 in a fibrin sealant *versus* placebo. The primary outcome is change from baseline in UEMS at 6 months. Estimated study completion date is June 2018.

Anti-Nogo-A Antibody

Nogo-A is a neurite growth inhibitory myelin protein which restricts neurorecovery [82]. In rat SCI models, administration of anti-Nogo-A antibody leads to enhanced regeneration and reorganization of the SCI and to superior recovery of locomotor training [83, 84]. A multicenter phase I open-label cohort study (NCT00406016) of humanized anti-Nogo antibody, ATI-355, in persons ($n = 51$) with acute SCI (C5-T12) was completed in Europe in September 2011. Results have not been published to date. A phase II study of ATI-355 is anticipated in Europe but has not been reported to clinical-trials.gov or the European Union Clinical Trials Register to date [4].

Hepatocyte Growth Factor

Hepatocyte growth factor (HGF) is secreted by mesenchymal cells. After SCI, HGF is upregulated and contributes to the migration of mesenchymal cells to the area of injury [85]. HGF reduces the formation of glial scar and promotes functional recovery in animal SCI models [86, 87].

A phase I/II randomized parallel-arm study (NCT02193334) of intrathecal injections of HGF beginning at 72 h of injury and repeated weakly for 5 weeks in individuals with cervical (C4–C8) motor complete SCI was launched in Japan in 2014 with an estimated study completion date of October 2018.

GM-1 Ganglioside

Gangliosides are acidic glycolipids present in cell membranes throughout the CNS that contribute to neural development, cellular recognition, and neuronal communication. Two RCTs have been performed in humans with SCI in the 1990s and 2000s. A phase II prospective, RC-DB trial of daily GM-1 ganglioside (brand name Sygen) for 18–32 days postinjury in persons ($n = 37$) with acute cervical and thoracic demonstrated improvement in year 1 ASIA motor scores [88]. A multicenter phase III RC-DB clinical trial of two doses of Sygen *versus* placebo in persons ($n = 797$) with acute SCI suggested accelerated motor and bowel/bladder recovery in the first 3 months postinjury but no significant effects were found after the study period had ended [89].

Difference in timing of administration of GM-1 ganglioside is postulated as one potential contributor to the variation in outcomes between the two studies [90]. A Cochrane Database Systematic Review sited significant methodological weaknesses in the collection and presentation of the data for these trials. The review concluded that the available evidence does not support the use of ganglioside treatment to reduce the death rate in SCI patients and that there is no evidence for improved motor recovery or quality of life after treatment [91]. No follow-up studies have been performed to date.

Granulocyte Colony-Stimulating Factor

Granulocyte colony-stimulating factor (G-CSF) is a cytokine glycoprotein found in many tissues throughout the body. It is a

FDA-approved drug used to treat neutropenia and mobilize hematopoietic stem cells for transplantation. More recently, it has demonstrated a role in neuroprotection, neural tissue repair, and sensorimotor recovery [92]. In rat SCI models, it reduces cell apoptosis and promotes motor recovery [93, 94].

Takahashi et al. [95] performed a phase I/IIa nonrandomized clinical trial of G-CSF in persons ($n = 16$) with acute (≤ 48 h) cervical and thoracic SCI who received IV G-CSF for 5 days following injury. No severe adverse effects were observed. Increased motor recovery at 1 year was reported compared to controls [96]. A follow-up cohort study showed improved motor recovery in individuals receiving G-CSF at 3 months compared to historical high-dose MP [97].

A current multicenter phase III RC-DB, parallel group comparative study (GSPIRIT, JMA-IIA00217) is investigating 5 days of IV G-CSF in individuals with acute (< 48 h) cervical incomplete (AIS B and C) SCI. The primary endpoint is change in ASIA motor score from baseline to 3 months. The study is expected to conclude in April 2019.

Cell-Based Therapies

Cell-based therapies for the treatment of SCI is also being explored. Possible uses include modulating the inflammatory response, providing trophic support, axon remyelination, and neuronal regeneration [5]. Nevertheless, many challenges with cell-based therapies have been cited, including safety, efficacy, deliverability, reproducibility, manufacturing, cost-effectiveness, and regulation [98].

Schwann Cells

Schwann cells (SCs) produce myelin and support axons in the PNS. They have also been shown to be capable of remyelinating demyelinated axons of the CNS [99]. A systematic review and meta-analysis found moderate improvement in motor function recovery after SC administration in SCI animal models [100].

An early autologous SC transplantation trial was performed in Iran in 4 persons with stable chronic mid-thoracic SCI. No adverse effects at 1 year were reported, although all participants experienced transient paresthesias or increased muscle spasms [101]. A subsequent study of persons ($n = 33$) with cervical and thoracic SCI (AIS A and B) reported partial sensorimotor recovery and no adverse events or associated tissue abnormalities [102].

Anderson et al. at the Miami Project to Cure Paralysis recently reported the results of a phase I open-label, nonrandomized, nonplacebo-controlled trial of autologous SCs harvested from a sural nerve (within 5–30 days postinjury) and injected into the epicenter of the SCI lesions (within 4–7 weeks of injury) in persons ($n = 6$) with complete paraplegia (T3–11). At 1-year post-transplantation, there were no reported significant surgical, medical, or neurological safety concerns [103].

A second phase I open-label, nonrandomized, nonplacebo-controlled study (NCT02354625) of autologous SCs by the same group began in January 2015. This study is investigating the safety of autologous SCs in subjects with chronic (≥ 12 months) SCI (C5-T12, AIS A-C) receiving rehabilitation. Primary outcomes assessed at 6 months post-transplantation include the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) exam, MRI imaging of the spinal cord, neuropathic pain symptoms inventory, International SCI (ISCI) basic pain dataset version2, pain diagram, and quantitative sensory testing. The study is expected to conclude in January 2019.

Olfactory Ensheathing Cells

Olfactory ensheathing cells (OECs) are specialized glial cells residing in both the PNS and CNS that share properties of both astrocytes and SCs. In animal SCI models, they have been shown to mediate regeneration and functional reconnection [104]. Functional gains in these models have also been reported [105].

The first reported study of autologous OECs in SCI was a phase I single blind clinical trial of persons ($n = 3$) with chronic (6 to 32 months) complete thoracic paraplegia who received injected OECs into the region of the injured spinal cord. No safety concerns were reported [106]. In 2006, Lima et al. [107] reported on a pilot study of persons ($n = 7$) with chronic (6 months to 6.5 years) complete SCI (C4-T4) who were transplanted with olfactory mucosa autografts. Some improvement in neurologic function was reported. Initial adverse events included decreased sensation in one individual and transient pain.

In 2014, Dlouhy et al. [108] reported the first human spinal cord mass complicating spinal cord cell transplantation in an 18-year-old woman with T10-11 SCI after OEC implantation at her site of injury. She developed back pain 3 years after implantation and was found to have an intramedullary spinal cord mass at the site of cell implantation requiring resection. This report raised significant safety concerns in the research community.

A phase I/IIa clinical trial of human OECs in chronic SCI confirmed no adverse events up to 3 years following transplant. However, no functional improvements were seen [109]. Since this time, several additional phase I trials have been performed. In a systematic meta-analysis, OECs were reported to have substantial overall efficacy in SCI when injected to the rostral-caudal parenchyma compared to multiple small volume injections [110]. A recent systematic review and meta-analysis of 10 studies including 1193 patients with chronic SCI treated with OEC transplantation reported overall low

methodological quality [111]. The most frequently reported adverse events included fever, anemia, and syringomeyelia. Statistically significant adverse events included cerebrospinal fluid (CSF) leakage, sensory deterioration, and both motor and sensory deterioration. The authors concluded that overall transplantation with OECs appears to be safe but the evidence for efficacy is modest and prospective randomized trials in a larger number of patients are needed. A current study (NCT02870426) is examining the role of OECs donation to individuals with SCI with the aim of optimizing collection, culture, and storage to address the limitations in autologous transplantation.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are of mesodermal lineage found in bone marrow, cartilage, adipose tissue, placenta, umbilical cord, and the perivascular region of most organs that can differentiate into osteocytes, adipocytes, and chondrodytes [104]. They produce growth factors, neuroprotective cytokines, and chemokines, reduce inflammation, modulate glial scar formation, and mediate apoptosis [112]. They can be provided by intrathecal, intraspinal, and IV administration. A systematic review and meta-analysis of MSCs in 83 rat model SCI studies showed substantial benefit on locomotor recovery [113].

Early studies confirm the safety of MSCs in humans [114, 115]. A single-center phase II/III trial (NCT01676441) of autologous bone marrow derived MSC transplantation to the spinal cord in persons with chronic (> 12 months) cervical SCI (AIS B) sponsored by Pharmicell Co. Ltd. began in 2008 and is expected to complete in 2020. The primary outcome measure is ASIA motor score.

Neural Precursor Cells

Neural precursor cells are multipotent CNS cells found in the subventribular zone, subgranula zone, and dentate gyrus of the brain and ependymal region of the central canal of the spinal cord that can differentiate into neurons, astrocytes, and oligodendrocytes. They can function to reduce inflammation, secrete neuroprotective cytokines, replace lost cells, provide local trophic support, and act as a scaffold for axonal regeneration [4, 98]. In animal SCI models, they reduce cystic cavitation, remyelinate injured axons, and improve behavioral outcomes [116, 117].

A phase I/II open-label single-arm trial (NCT01321333) of a single dose of allogenic human CNS stem cells in persons with thoracic SCI (AIS A-C, at least 6 weeks postinjury) sponsored by Stem Cells Inc. began in 2011 and completed in 2015. No results have been published to date. A phase II single-blind, randomized, parallel-arm study (NCT02163876) of intramedullary transplantation of human CNS stem cells in individuals with cervical (C5-7) SCI (AIS B or C, > 3 months postinjury) by the same group began in 2014 with a primary outcome of change in UEMS at 1 year. The study was terminated in 2016. Full results have not been published to date.

Oligodendrocyte Progenitor Cells

Oligodendrocyte progenitor cells (OPCs) are found in the white and gray matter of the CNS and preferentially differentiate to oligodendrocytes [118]. Potential functions after SCI include production of neurotrophic factors, suppression of inflammation, and remyelination of axons [118]. Spontaneous remyelination by OPCs at the injury site after SCI is limited and transplantation of exogenous cells is more effective in improving outcomes [98]. In animal SCI models, OPC cell transplantation has showed evidence of remyelination and functional recovery [119, 120].

An initial study of OPC transplantation in persons with acute (< 14 days) thoracic complete SCI by the Geron Corporation terminated in 2011 after 5 patients underwent transplantation. This phase I/IIa dose escalation study (NCT02302157) of OPCs for persons with cervical (C4-7) SCI (AIS A and B) between 14 and 21 days was reopened by Asterias Biotherapeutics, Incorporated in 2015. The primary outcome is number of adverse events, with secondary outcomes measures including UEMS and motor level. Although 25 additional subjects have been to date enrolled, the study currently remains active but is not recruiting. Completed 12-month data shows improvement of 2 or more motor levels in 4/6 participants [121]. Estimated study completion date is December 2018.

Activated Macrophages

The CNS has often been referred to as having "immune privilege," in which the macrophage immune response to injury is blunted and delayed compared with the PNS that may enhance regeneration [122]. Initial animal model studies after peripheral nerve-activated (in a spinal cord transection model) and skin-activated macrophages (in a contusion model) showed recovery of some motor function, electrophysiological activity, and nerve fiber continuity across the lesion site [123, 124]. It was theorized that co-incubation of monocytes with excised skin will produce macrophages with an "alternatively activated" wound-healing phenotype that could remove growth inhibitory myelin components from the cellular environment and potentially secrete trophic factors, as well as provide indirect benefit through cytokine signaling and activation of the local adaptive immune response [123].

A phase I open-label clinical trial of autologous incubated macrophages was completed in 8 subjects with a complete injury, in which 3 improved in their AIS grade from A to C [125]. Subsequently in 2003, a phase II RCT was initiated at 6 treatment sites around the world for subjects with acute (<

14 days) traumatic complete SCI (C5 and T11); the first RCT of a cell-based intervention for patients with acute SCI. Subjects were randomly assigned in a 2:1 ratio to the treatment (autologous incubated macrophages) or control (standard of care) groups [126]. Of the 43 subjects (26 treatment, 17 control), there was a trend that conversion to motor incomplete status (AIS C) favored the control group, in part due to a high conversion rate of the control group [126]. No further studies have been published in this area.

Biomaterials

Spinal Scaffolds

The use of scaffolds to provide guidance for axonal regrowth is being investigated. In rat SCI models, decellularized scaffolds have been shown to promote axonal regeneration and lead to enhanced motor recovery [127]. In 2016, Thoedore et al. [128] reported the first human implantation of a porous bio-resorbable polymer scaffold in a young man with T11 AIS A SCI. No safety issues were reported. Neurological exam at 3 months post-implantation showed conversion to L1 AIS C injury [128].

The INSPIRE Study (NCT02138110) sponsored by InVivo Therapeutics began in 2014 and is a phase III Humanitarian Device Exemption (HDE) multisite open-label study investigating the effect of neural-spinal scaffold transplantation in individuals with acute (≤ 96 h) thoracic (T2-T12/L1) complete SCI on AIS grade at 6 months. The study is currently active but not recruiting (Jan 2018). Original estimated primary completion date was September 2017. A pilot study (NCT03105882) of neural-spinal scaffold transplantation in individuals with recent traumatic complete SCI (C5-T1) by the same group started in March 2017 and is active but not recruiting at this time.

In China, several studies investigating the NeuroRegen Scaffold with stem cells transplantation are being investigated for individuals with chronic SCI (NCT02352007, NCT02688049, NCT02688062). In addition, the same group is conducting a phase I open-label trial (NCT02510365) of collagen scaffold transplantation and comprehensive rehabilitation in individuals with acute (≤ 21 days) complete SCI (C5-T12).

Physiological Approaches

Therapeutic Hypothermia

Therapeutic hypothermia is used to treat a variety of medical conditions, most notably hypoxic encephalopathy after cardiac arrest. Rapidly decreasing the body's core temperature to 32–34 degrees Fahrenheit (°F) reduces the basal metabolic rate and attenuates the systemic inflammatory response [129]. SCI animal studies suggest improved behavior recovery [130].

A pilot study of endovascular hypothermia in persons (n = 14) with acute cervical complete SCI demonstrated feasibility. Complications included atelectasis, pneumonia, ARDS, and arrhythmia [131]. In 2010, follow-up data was published noting AIS grade conversion in 6/14 participants (42.8%) [132]. Significant attention was brought to this approach after a case report of a NFL football player with a cervical complete SCI was treated with moderate systemic hypothermia, surgical decompression, and MP who had significant neurologic recovery (AIS D) [133]. In a case-control study of 35 patients with cervical SCI, Dididze et al. [134] noted improvement in AIS grade in 15 participants at 11 months. More recently, Hansenbout and Hansenbout [135] reported a prospective case series using a combination of dural cooling, surgical decompression and steroids in 20 patients with complete SCIs with a reported 65% conversion rate.

A larger phase II/ III trial (ARCTIC, NCT02991690) by the Miami Project to Cure Paralysis was initiated in May 2017. In this prospective multicenter case-controlled study of systemic hypothermia in acute (≤ 24 h) cervical SCI (AIS A-C) patients receive modest (33 °F) intravascular hypothermia for 48 h. Primary outcomes include AIS, ASIA motor index, FIM, and SCIM scores.

Cerebrospinal Fluid Drainage

Cerebrospinal fluid (CSF) drainage aims to improve spinal cord perfusion and reduce ischemia by relieving pressure, similar to external ventricular drainage (EVD) for elevated intracranial pressure (ICP) [5]. It is used routinely for thoracoabdominal aortic aneurysm surgery but is not regularly implemented for treatment of acute traumatic SCI [136]. In animals, a combination of CSF drainage and MAP elevation maximizes spinal cord blood flow after SCI [137].

A phase I study of CSF drainage in humans (n = 22) was published in 2009 with no significant adverse events. No differences in ASIA motor scores were noted between cases and controls at 6 months; however, the study was underpowered [138]. A single site phase IIb randomized control open-label trial (NCT02495545) of CSF drainage and MAP elevation *versus* MAP elevation alone was initiated in 2015 and is recruiting participants with acute (≤ 24 h) cervical (C4-8) SCI (AIS A-C).

Acute Intermittent Hypoxia

Acute intermittent hypoxia (AIH), breathing mild bouts of low oxygen, elicits serotonin and brain-derived neurotrophic factor (BDNF)-dependent motor plasticity within somatic motor nuclei in rats [139]. Functionally, when combined with ladder walking, AIH improves forelimb placement in rats with

chronic cervical SCI [140]. An early study in humans ($n = 13$) with chronic motor incomplete SCI showed that a single dose of acute hypoxia increased ankle strength [141]. This was followed by a RC-DB crossover study of persons ($n = 19$) with chronic motor incomplete SCI who received daily AIH and over ground walking training. Treatment resulted in improved walking speed and endurance [142]. Similarly, improved walking speed, endurance, and dynamic balance were recently reported from a second RCT of AIH for persons ($n = 35$) with chronic motor incomplete SCI; however, no difference in standing balance was seen [143, 144].

Expanding investigations to the effects on upper extremity function, Trumbower et al. [145] recently reported improved hand dexterity, function, and maximum hand opening in a preliminary study of 6 persons with chronic motor incomplete C5 tetraplegia. To date, no significant adverse events from use of AIH have been described. Navarrete-Opazo et al. [146] did not find visual or verbal memory impairment after a 4-week protocol of moderate AIH in this population.

There are several ongoing trials investigating the role of AIH for persons with SCI. Three phase I/II RC-DB crossover studies (NCT02274116, NCT02323945, NCT02323698) examining the effectiveness of AIH in persons with chronic motor incomplete SCI commenced in 2014. Outcomes include walking speed, endurance, and ankle strength. In 2015, a RC-DB parallel group trial (NCT02323945) of AIH *versus* room air in non-ambulatory and ambulatory persons with subacute (2–4 months) motor incomplete SCI (C2-T12) to determine the effect on recovery of walking function was launched. More recently, a multisite RC-DB study (NCT03262766) of AIH and task-specific upper training in persons with chronic (> 1 year) motor incomplete SCI (C2-T2) and a RC-DB crossover trial (NCT03071393) on the effects of a single session of AIH on motor function (including respiratory function) on persons with SCI (C4-T12) > 6 months were initiated.

Functional and Rehabilitation Interventions

Locomotor Training

Locomotor training (LT) is based on the concept that activity-dependent plasticity can be driven by neuromuscular activation below the injury, either intrinsically using task-specific sensory cues or extrinsically by using stimulation [147, 148]. Activity-based therapy often uses body-weight support treadmill training (BWSTT) for locomotor training in which the body weight supported can be progressively decreased as walking improves. This technique has been studied by numerous groups, including the NeuroRecovery Network (NRN), in which recovery of walking was found in some individuals with motor incomplete SCI (AIS C and D), even years after injury [149]. A limitation of NRN data is that there is no control group and as such no data available for comparison. Other improvements have been reported including strength, coordination, and sense of well-being [150–152].

Locomotor training can also occur over ground and with supplemental electrical stimulation. A number of recent meta-analyses that compared locomotor training via BWSTT to other forms of gait training, however, did not show significant improvement in walking distance or speed relative to over ground training [153–155]. Limitations of these analyses include variations in the methodology including study sample sizes, stepping protocols, length of intervention, sessions, and time from injury.

Most recently, results from individuals with chronic motor incomplete SCI who completed at least 120 NRN therapy sessions of locomotor training via BWSTT with progression to over ground activities were reported [156]. Gait improved by a median of 0.29 m/s and 70 m, which surpasses the minimally clinically important difference for gait speed and distance, and a majority retained this performance after follow-up. As there was no control group, it is unclear if this could have been achieved with over ground training alone. Of note however, the rate of improvement was variable and that many patients exhibited detectable cumulative improvement for the first time at 60, 80, 100, and 120 sessions.

At this point, there is insufficient evidence to determine whether locomotor training via BWSTT will improve walking function after a SCI as compared with over ground training with a therapist alone. Larger scale studies with consistent methodology may be needed.

Spinal Cord Stimulation

Similar to LT, spinal cord stimulation is based on activity-dependent plasticity of spinal and supraspinal networks. Subthreshold stimulation of the spinal cord, through epidural or transcutaneous stimulation, is an important way to modulate motor function [157]. Animal studies have also been performed looking at the combination of spinal stimulation and other treatments. Musienko et al. [158] reported that a combination of epidural stimulation, pharmacology to manipulate serotonergic, dopaminergic, and noradrenergic pathways and rehabilitation restored hindlimb locomotion in rats with SCI.

Harkema et al. [159] published the first case report of the use of epidural stimulator implantation and use of a neurorehabilitation protocol, including manual facilitation of standing and gait, in an individual with chronic (> 2 years) T1 AIS B SCI in 2011. After a few months of training, the subject regained the ability to maintain continuous minimally assisted full weight bearing for up to 4 min. By 7 months post-implantation, voluntary control of the lower limbs was also reported [159]. A subsequent report, noted similar findings in an additional three individuals with motor complete (AIS A and B) cervical and thoracic SCI [160]. Recently, one of the patients with chronic paraplegia treated with epidural electrical

stimulation of the lumbosacral spinal cord was reported to gain volitional control of task-specific muscle activity, independent standing, and step-like rhythmic muscle activity while side lying and upright with partial body-weight support [161].

Transcutaneous electrical stimulation, a non-invasive technique using painless stimulation waveforms transmitted via electrodes placed on the skin of the spine, is also showing promising results for individuals with SCI. This stimulation is presumed to travel through the dorsal roots to activate spinal circuitry [157]. In 2015, Gerasimenko et al. [162] published the first report of transcutaneous stimulation in five individuals with motor complete paraplegia. Involuntary locomotor-like stepping was induced in each subject within a single test session and all participants regained the ability to create voluntary stepping movements with stimulation over a 4-week period [162].

Several trials are underway to further investigate the role of epidural spinal stimulation for treatment of SCI. A variety of outcomes are being studied in individuals with chronic SCI including recovery of autonomic control of cardiovascular function, recovery of voluntary movement, ability to stand independently, ability to coordinate stepping and change in volitional response index magnitude (NCT02037620, NCT03364660, NCT025922668, NCT03026816, NCT02339233). Similarly, transcutaneous spinal stimulation for individuals with chronic SCI is being vigorously examined. Outcomes for some of the current trials include hand impairment/dexterity, knee extension strength, change in walking speed, lower extremity motor control, spasticity, and bladder function (NCT0469675, NCT03184792, NCT03046875, NCT03384017, NCT03137108, NCT03240601, NCT02331979).

Transcranial Stimulation

Transcranial magnetic stimulation (TMS), electromagnetic stimulation applied at the cranial level, is an emerging treatment for individuals with SCI. Recent meta-analyses showed that TMS is effective in reducing spasticity of spinal origin and may reduce SCI-associated neuropathic pain and, however, further studies are encouraged [163, 164]. In addition to symptom control, the role of TMS related to motor recovery after SCI is also being investigated. TMS has the potential to modulate corticospinal, cortical, and subcortical pathways to promote functional recovery but results to date have been mixed and further investigation is needed [165]. A large randomized crossover study (NCT01915095) of persons with chronic (> 6 months) SCI with some hand and lower extremity function evaluating the effects of repetitive TMS and training on changes in motor evoked potentials began in 2016 and is estimated to be completed in 2021.

Another type of non-invasive transcranial stimulation, transcranial direct current stimulation (tDCS), is similarly being studied to determine the effects on motor recovery. A randomized double blind parallel-arm study (NCT01539109) of the effect of tDCS and rehabilitation on upper limb function in individuals with chronic (> 6 months) incomplete SCI is ongoing.

Exoskeletons

Powered robotic exoskeletons, wearable orthoses which can be used as an assistive device for over ground walking or a rehabilitation tool, are also being studied in regard to their impact on improving functional mobility after SCI. In the US, five specific exoskeleton devices are being studied, the Rex, Ekso, ReWalk, Indego, and Phoenix (NCT03057652, NCT01701388, NCT02600013, NCT03144830, NCT02314221, NCT02324322, NCT02943915, NCT02322125, NCT02944669, NCT02658656, NCT03340792, NCT02793635, NCT03082898, NCT03175055). There are an increasing number of facilities with clinically based programs for the EKSO and ReWalk. The ReWalk system and Indego are approved for home use.

A systematic review concluded that powered exoskeletons can provide non-ambulatory individuals with thoracic motor complete SCI the ability to walk at modest speeds [166]. Ongoing studies in individuals with acute and chronic SCI are looking at the impact of exoskeletons on cardiorespiratory status, bone mineral density, ambulation speed, functional ambulation, and muscle volume. Nevertheless, the impact of exoskeletons on other outcomes, including neurorecovery, remains unclear.

In the future, it is likely that increased evaluation of exoskeletons used in conjunction with other therapies will be studied. For example, Gad et al. recently reported the use of buspirone, transcutaneous electrical stimulation, and use of an exoskeleton for and individual with chronic complete paraplegia and found that spinal cord stimulation and drug administration enhanced the level of effort the subject could generate while stepping in the exoskeleton [167]. An ongoing open-label study (NCT03096197) is examining the effects of exoskeleton-assisted walking with simultaneous TCS in non-ambulatory individuals with chronic (>6 years) SCI (C6-T10) with lower extremity motor scores greater than or equal to 16 on gait speed.

Conclusion

A substantial amount of research has been performed to develop effective treatments for persons with traumatic SCI. Nevertheless, current therapeutic approaches focused on neurorecovery remain limited and highly debated. Although

many of the interventions previously studied have not led to changes in the standard of care to date, much has been learned and understanding the experiences of the past will hopefully help lead researchers to finding new answers in the future. Today, the number of clinical trials in SCI continues to increase. Strategies discussed include surgical, pharmacologic, cell-based, physiologic, and rehabilitation interventions with vast therapeutic targets. Moving forward, it is likely that research and clinical treatments incorporating many of these approaches will be tailored to specific sub-populations using quantifiable imaging and biochemical markers to offer significant benefits for persons with SCI.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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