Time is spine: a review of translational advances in spinal cord injury

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Acute traumatic spinal cord injury (SCI) is a devastating event with far-reaching physical, emotional, and economic consequences for patients, families, and society at large. Timely delivery of specialized care has reduced mortality; however, long-term neurological recovery continues to be limited. In recent years, a number of exciting neuroprotective and regenerative strategies have emerged and have come under active investigation in clinical trials, and several more are coming down the translational pipeline. Among ongoing trials are RISCIS (riluzole), INSPIRE (Neuro-Spinal Scaffold), MASC (minocycline), and SPRING (VX-210). Microstructural MRI techniques have improved our ability to image the injured spinal cord at high resolution. This innovation, combined with serum and cerebrospinal fluid (CSF) analysis, holds the promise of providing a quantitative biomarker readout of spinal cord neural tissue injury, which may improve prognostication and facilitate stratification of patients for enrollment into clinical trials. Given evidence of the effectiveness of early surgical decompression and growing recognition of the concept that "time is spine," infrastructural changes at a systems level are being implemented in many regions around the world to provide a streamlined process for transfer of patients with acute SCI to a specialized unit. With the continued aging of the population, central cord syndrome is soon expected to become the most common form of acute traumatic SCI; characterization of the pathophysiology, natural history, and optimal treatment of these injuries is hence a key public health priority. Collaborative international efforts have led to the development of clinical practice guidelines for traumatic SCI based on robust evaluation of current evidence. The current article provides an in-depth review of progress in SCI, covering the above areas.

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THE physical, financial, and social sequelae of traumatic spinal cord injuries (SCIs) can be devastating for individuals and caregivers alike.[27,128] The direct lifetime costs of care for over 1 million affected North Americans range from $1.1 to $4.7 million USD per person.[128] Timely delivery of specialized care has reduced mortality, but long-term neurological recovery continues to be limited.[6–8,64] Within the last decade, numerous exciting strategies to protect and regenerate the injured spinal cord have emerged.[4,131] In this article, we summarize the most promising preclinical and clinical studies, with an emphasis on the underlying pathophysiological mechanisms

FIG. 1: (c) In the intermediate and chronic phases (2 weeks to 6 months), axons continue to degenerate and the astroglial scar matures to become a potent inhibitor of regeneration. Cystic cavities coalesce to further restrict axonal regrowth and cell migration." Reprinted with permission from Ahuja CS, Wilson JR, Nori S, Kotter MRN, Druschel C, Curt A, Fehlings MG: Traumatic spinal cord injury. *Nat Rev Dis Primers* 3:1–21, 2017. © The authors. Figure is available in color online only.
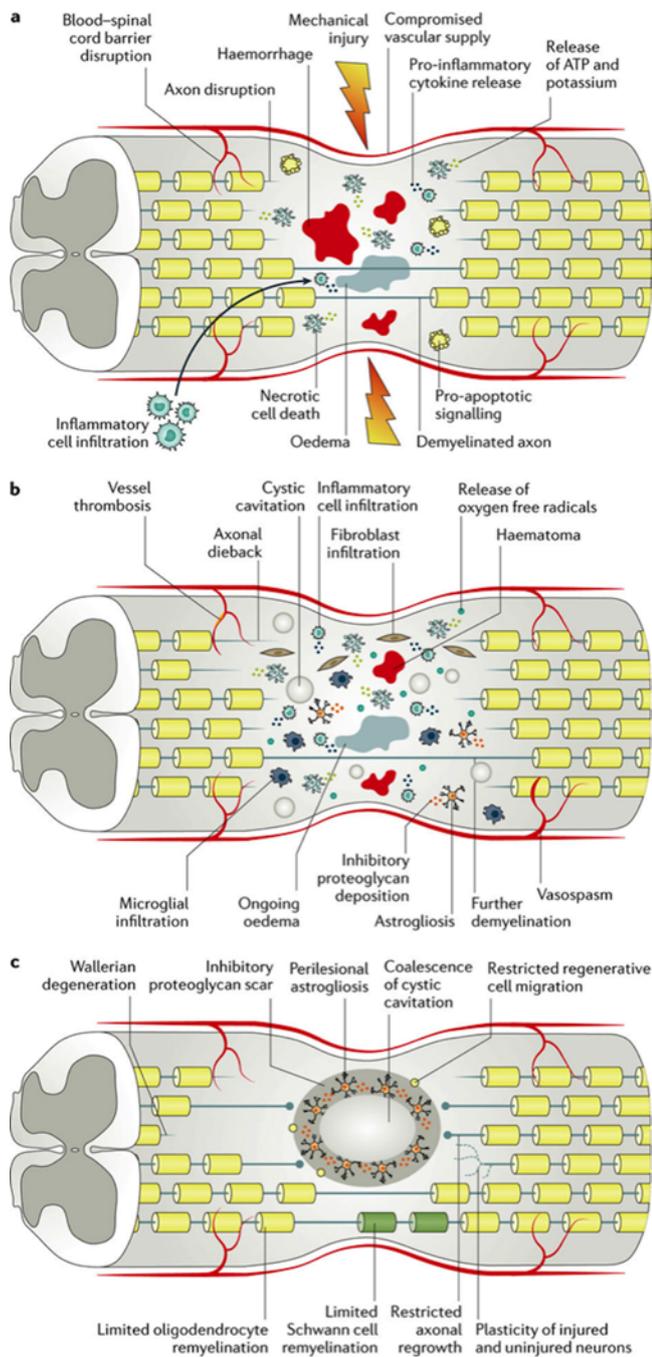
FIG. 1. Pathophysiology of traumatic SCI. "(a) The initial mechanical trauma to the spinal cord initiates a secondary injury cascade that is characterized in the acute phase (that is, 0–48 hours after injury) by oedema, haemorrhage, ischaemia, inflammatory cell infiltration, the release of cytotoxic products and cell death. This secondary injury leads to necrosis and/or apoptosis of neurons and glial cells, such as oligo-dendrocytes, which can lead to demyelination and the loss of neural circuits. (b) In the subacute phase (2–4 days after injury), further isch-aemia occurs owing to ongoing oedema, vessel thrombosis and vaso-spasm. Persistent inflammatory cell infiltration causes further cell death, and cystic microcavities form, as cells and the extracellular architecture of the cord are damaged. In addition, astrocytes proliferate and deposit extracellular matrix molecules into the perilesional area.
FIG. 1. (*continued*)→

of action. We also provide a framework for current management approaches based on internationally recognized guidelines and summarize the next frontiers in the field, such as prognostic biomarkers and advanced imaging.

Epidemiology of SCI

The annual incidence of traumatic SCI varies by region and ranges from 10 to 85 cases per million persons.[1,148,154,184] Nationally, the highest incidence is reported for New Zealand at 49 cases per million, and the lowest for Spain at 8 cases per million.[154] There are over 1 million people living with SCI in North America alone, with aggregate direct costs for acute treatment and chronic care in the United States exceeding $7 billion per year.[33,148] Given the substantial socioeconomic footprint that it exerts, traumatic SCI is a major public health problem.

The epidemiology of acute traumatic SCI is evolving, as are injury patterns. In particular, the aging population has given rise to an increased proportion of cervical incomplete SCIs, often without spinal column instability, in older persons from low-energy or fall-related mechanisms.[34,73,103,164,169] Jain et al.[73] recently performed an epidemiological analysis of traumatic SCI in the United States using data from the National Inpatient Sample, the largest American all-payer inpatient healthcare database.[68] This analysis revealed that from 1993 to 2012, the mean age of patients suffering an acute SCI increased from 40.5 years to 50.5 years. The incidence of SCI among the younger male population (16–44 years old) steadily declined; meanwhile, there was a steep rise in SCI incidence among males aged 65 to 74 years, from 84 cases per million in 1993 to 131 cases per million in 2012. The proportion of SCI cases that were due to unintentional falls grew from 19.3% to 40.4%. Similar trends have been reported in much of the developed world,[99,154] including Canada,[28] Japan,[158] Iceland,[86] Spain,[168] and the United Kingdom.[120] By contrast, the proportion of SCI cases due to land transport is growing in developing countries because of increasing transition to motorized transportation, poor infrastructure, and regulatory challenges.[99]

Pathophysiology of SCI

Traumatic SCI is characterized by an initial traumatic insult resulting in mechanical damage of neuronal and glial cell membranes, disruption of the microvasculature, ionic dysregulation, and proapoptotic signaling.[26,96] This initiates a secondary injury cascade that causes further permanent damage and neurological dysfunction. Secondary injury is temporally divided into the acute (within 48 hours), subacute (2–14 days), intermediate (14 days–6 months), and chronic (more than 6 months) phases (Fig. 1).

During the acute phase, hemorrhage and blood–spi-

nal cord barrier (BSCB) disruption expose the cord to a rapid influx of inflammatory cells (e.g., neutrophils, macrophages, etc.) and cytokines (tumor necrosis factor–α [TNF-α], interleukin-1β [IL-1β]).[136] Necrotic cell death releases ATP, potassium ions, and DNA into the microenvironment, which activates microglia to release additional proinflammatory cytokines and recruit peripheral inflammatory cells. Phagocytes rapidly clear debris, but during the process they generate cytotoxic by-products, such as oxygen and nitrogen free radicals, which produce additional cell injury through protein/lipid oxidation and DNA damage.[35,67] During the subacute phase, edema progresses, leading to further vascular compromise. Neuron death and reuptake failure by astrocytes cause accumulation of glutamate in the extracellular compartment and excitotoxicity of nearby neurons.[114,172] Calcium dysregulation, inflammation, and ongoing ischemia cyclically add to the cytotoxic microenvironment.[110,111]

The intermediate and chronic phases of SCI are characterized by dynamic vascular remodeling, alterations in the extracellular matrix composition, and reorganization of local and distal neural circuits.[93] The substantial cell volume loss leads to ex vacuo formation of cystic microcavitations, which coalesce and become a significant barrier to regeneration, cell migration, and axon regrowth.[121,130,159] Within the perilesional region, astrocytes proliferate and tightly interweave their extended processes in an attempt to wall off the lesion core. Astrocytes, pericytes, and ependymal cells generate dense deposits of chondroitin sulfate proteoglycans (CSPGs) as part of the fibrous scar, which bind leukocyte common antigen–related receptors, such as protein tyrosine phosphatase σ (PTPσ). This activates GTPase RhoA and its downstream effector Rho-associated protein kinase (ROCK), leading to axonal growth cone collapse and regenerative failure.[20,22,53,123]

From a systemic perspective, cervical and high thoracic injuries can produce respiratory failure and loss of cardiovascular sympathetic innervation leading to profound hypotension. This can further compound the ischemic insult to the cord. Furthermore, loss of sympathetic innervation to lymphatic organs (e.g., the spleen) can induce a secondary immunodeficiency, termed immune paralysis, which increases patients' susceptibility to infections.[18,166] Together, these and other pathophysiological mechanisms are the target of neuroprotective, rehabilitative, and neuroregenerative strategies in SCI.

"Time Is Spine"—Early Surgery for SCI

For many years, the central dogma guiding the treatment of acute ischemic stroke has been "time is brain." In more recent years, there has been growing recognition that the same principle applies to treatment of acute traumatic SCI—that is, "time is spine." This phrase highlights the concept that there is a critical time window after the primary injury to the spinal cord during which secondary injury mechanisms, which cause further neural tissue destruction, may be curtailed.[5,146] This provides the rationale for early surgery after acute traumatic SCI, which can provide expeditious relief of mechanical compression on the spinal cord and thus attenuate secondary injury cascades

and thereby improve outcomes.[56] The Surgical Timing in Acute Spinal Cord Injury Study (STASCIS) was a prospective, multicenter study that demonstrated that early surgery (< 24 hours) resulted in superior neurological recovery at 6 months compared to late surgery (≥ 24 hours) in patients with cervical SCI.[48] Alongside STASCIS, there has been a growing body of literature favoring early surgical decompression for traumatic SCI.[41,45,48,56,75,170,176,177] Likewise, the efficacy of many acute therapies, including methylprednisolone sodium succinate (MPSS),[16,17] riluzole,[40,59] minocycline,[21] and hypothermia,[104] is time dependent. Further, early optimization of cardiorespiratory and hemodynamic parameters—and management within a specialized acute SCI unit—has been associated with reduced morbidity and mortality as well as improved neurological outcomes.[65,107,167]

Barriers to early surgical intervention for SCI may include lack of operating room availability, transport of patients from the location of injury or from other centers, lack of a specialized operating room nursing team, and lack of surgeon availability on call.[57] Prior studies in North America and Europe have estimated that only 20% to 50% of SCI patients are transferred to an appropriate center and are eligible for surgical decompression within 24 hours of injury.[15,57,161] The implication is that a substantial proportion of patients arrive at a specialized center outside the critical therapeutic time window and are hence deprived of timely therapy that could potentially translate into improved clinical outcomes. From a research standpoint, transport delays also have implications for clinical trials studying acute-phase therapeutics, as the patients' arrival may fall outside of time-based eligibility criteria. There is hence a need to study and modify healthcare system infrastructure and logistics to permit a streamlined path to a specialized acute care center for patients with an acute SCI.

Central Cord Syndrome—Implications of an Aging Population

Today, the prototypical SCI is a cervical incomplete injury without fracture or dislocation—e.g., the so-called "central cord syndrome" (CCS)—in an older person who has sustained a fall or low-energy trauma.[8] In fact, with the continued aging of the population, CCS is expected to soon become the most common form of acute traumatic SCI.[44,164] The first in-depth description of CCS came from Schneider et al.[143] in 1954; they detailed a condition involving "disproportionately more motor impairment of the upper than of the lower extremities, bladder dysfunction, usually urinary retention, and varying degrees of sensory loss below the level of the lesion." It has been postulated that CCS is due to a hyperextension mechanism, particularly in the context of a spondylotic or congenitally narrow canal, resulting in injury to the central portion of the spinal cord.[66,117,142,144] Schneider et al.[144] proposed that sudden compression of the spinal cord between the hypertrophic spondylotic disc–osteophyte complex and the buckled ligamentum flavum caused a hematomyelic cavity to form within the central gray matter of the spinal cord. He hypothesized that there was disruption of the medi-

ally placed corticospinal tract (CST) fibers that controlled hand and upper limb function, but relative sparing of the more laterally placed tracts supplying the lower limbs.[66,144] From a natural history standpoint, patients with CCS have historically demonstrated a relatively favorable profile of neurological recovery, independent of whether early or late surgical management was undertaken.[71,141]

Nonetheless, in considering more recent evidence, it is unclear whether identifying CCS as a unique clinicopathological entity is valid or useful. The original account of the etiology of disproportionate upper limb weakness in CCS was predicated upon the work of Foerster,[52] who presumed that the lateral CST, like the fasciculi cuneatus and gracilis, had a somatotopic organization. However, Marchi degeneration studies and neuroanatomical tracer techniques in monkeys have confirmed the absence of laminar organization in the CST.[29,134] In fact, there has not been any neuroanatomical evidence to substantiate the claim of a somatotopic organization of the CST in the spinal cords of humans or higher mammals.[74,106,139] There is increasing thought that the pattern of predominantly arm and hand weakness seen in CCS has little to do with selective injury to the centrally located regions of the CST and more to do with relative preservation of extrapyramidal fiber tracts.[66,74] Evidence from transection studies in monkeys indicates that the CST is more important for arm and hand function than for lower-extremity use, and accordingly, any injury to the CST, even diffuse injuries, may produce a syndrome of disproportionately greater arm and hand dysfunction.[98,106,147] This brings into question the original pathoanatomic basis for CCS. Also, despite previous reports of a comparatively favorable natural history, there is increasing evidence that the pattern of recovery observed in patients with CCS is not substantially different from that of patients with other cervical incomplete SCI syndromes.[66,137,171] From a treatment perspective, in contrast to the situation with other SCI syndromes, operative intervention for CCS has historically been discouraged out of concern for derailing the potential for natural neurological recovery. However, more recent evidence suggests that early surgical management of patients with CCS is not only safe but also effective, with surgical decompression prior to 24 hours having been shown to result in superior neurological and functional recovery at long-term follow-up.[10,102]

With regard to future work needed in this area, there remains a paucity of published literature elucidating how the pathology, imaging features, clinical course, and surgical outcomes associated with CCS differ from those associated with other cervical injury subtypes. Furthermore, beyond CCS, there has been limited research attempting to identify other unique subgroups of cervical incomplete SCI patients that may demonstrate homogeneous recovery patterns. The clinical course of patients with cervical SCI without fracture or dislocation versus patients with fracture or dislocation is also poorly defined. There is a critical unmet need for high-quality clinical studies investigating cervical incomplete SCI and CCS. Indeed, the devastating physical, emotional, and economic burdens these injuries impose on patients, families, and society at large, taken in the context of an aging population, make this area of research a key public health priority.

Clinical Practice Guidelines

Clinical practice guidelines for acute traumatic SCI were recently developed and published under the auspices of AOSpine North America, AOSpine International, and the American Association of Neurological Surgeons/Congress of Neurological Surgeons.[46] Key clinical questions of interest included timing of surgical decompression, use of MPSS, type and timing of anticoagulant thromboprophylaxis, role of baseline MRI in clinical decision making and outcome prediction, and type and timing of rehabilitation. Comprehensive systematic reviews were conducted to synthesize the body of evidence.[11,19,49,89,177] A multidisciplinary guideline development group then used the results of these reviews, in conjunction with their clinical expertise, to develop clinical practice guideline recommendations[39,42,43,45,50] in accordance with the methodology proposed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) working group.[61–63] A summary of the guideline recommendations is provided in Table 1.

Key Preclinical Advances and Phase I/II Trials

Pharmacologics

SCING—Glyburide

Glibenclamide (also known as glyburide) is a sulfonylurea typically used as an oral diabetes type 2 treatment. In SCI, glibencamide has been shown to block upregulated sulfonylurea receptor 1 (Sur1)–regulated nonselective cation channels that may cause persistent post-injury sodium currents. When administered acutely in cervically injured rodents, glibencamide improved 6-week open-field locomotor scores and promoted tissue sparing.[153] The Spinal Cord Injury Neuroprotection with Glyburide (SCING) trial, a phase I/II study (N = 10; NCT02524379) is now underway, delivering glyburide within 8 hours to patients with American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade A/B/C C2–8 injuries. The primary outcome is adverse events after drug administration, and the study is expected to conclude in 2020 (Table 2).

Hepatocyte Growth Factor

Hepatocyte growth factor (HGF) is a c-Met receptor ligand that promotes angiogenesis, mitogenesis, and cell motility in the liver. In models of myocardial infarction and stroke, HGF has been shown to enhance angiogenesis and improve endogenous cell survival.[84,85] In a preclinical study of SCI in non-human primates, intrathecal HGF was found to enhance ventral motor neuron survival, reduce cavitation at the injury epicenter, and improve motor outcomes.[85] In a subsequent non-human primate study, HGF was shown to promote angiogenesis after cervical injury resulting in significant improvements in upper limb recovery.[84] Kringle Pharma Inc. is now recruiting for a phase I/II placebo-controlled study (N = 48; NCT02193334) of KP-100IT (intrathecal HGF) in patients with modified Frankel scale A/B1/B2 cervical injuries within 72 hours of injury; 24-week follow-up results are expected in 2019.

TABLE 1. Summary of clinical practice guideline recommendations for acute traumatic SCI

Recommendation	Quality of Evidence	Strength of Recommendation
Timing of surgical decompression[44]		
We suggest that early surgery (≤24 hrs after injury) be considered as a treatment option in adult patients w/ traumatic CCS.	Low	Weak
We suggest that early surgery be offered as an option for adult acute SCI patients regardless of level.	Low	Weak
Use of MPSS[49]		
We suggest not offering a 24-hr infusion of high-dose MPSS to adult patients who present after 8 hrs w/ acute SCI.	Moderate	Weak
We suggest a 24-hr infusion of high-dose MPSS be offered to adult patients w/in 8 hrs of acute SCI as a treatment option.	Moderate	Weak
We suggest not offering a 48-hr infusion of high-dose MPSS to adult patients w/ acute SCI.	No included studies	Weak
Type & timing of anticoagulant thromboprophylaxis[42]		
We suggest that anticoagulant thromboprophylaxis be offered routinely to reduce the risk of thromboembolic events in the acute period after SCI.	Low	Weak
We suggest that anticoagulant thromboprophylaxis, consisting of either subcutaneous low-molecular-weight heparin or fixed, low-dose unfractionated heparin, be offered to reduce the risk of thromboembolic events in the acute period after SCI. Given the potential for increased bleeding events w/ the use of adjusted-dose unfractionated heparin, we suggest against this treatment option.	Low	Weak
We suggest commencing anticoagulant thromboprophylaxis w/in the first 72 hrs after injury, if possible, in order to minimize the risk of venous thromboembolic complications during the period of acute hospitalization.	Low	Weak
Role of baseline MRI in clinical decision making & outcome prediction[38]		
We suggest that MRI be performed in adult patients w/ acute SCI prior to surgical intervention, when feasible, to facilitate improved clinical decision making.	Very low	Weak
We suggest that MRI should be performed in adult patients in the acute period following SCI, before or after surgical intervention, to improve prediction of neurologic outcome.	Low	Weak
Type & timing of rehabilitation[43]		
We suggest that rehabilitation be offered to patients w/ acute SCI when they are medically stable & can tolerate required rehabilitation intensity.	No included studies	Weak
We suggest offering body weight support treadmill training as an option for ambulation training in addition to conventional overground walking, dependent on resource availability, context, & local expertise.	Low	Weak
We suggest that individuals w/ acute & subacute cervical SCI be offered functional electrical therapy as an option to improve hand & upper-extremity function.	Low	Weak
Based on the absence of any clear benefit, we suggest not offering additional training in unsupported sitting beyond what is currently incorporated in standard rehabilitation.	Low	Weak

Granulocyte Colony Stimulating Factor

Granulocyte colony stimulating factor (G-CSF) is a glycoprotein that has demonstrated neuroprotective effects in SCI by enhancing ischemic central nervous system (CNS) cell survival and inhibiting inflammatory cytokine pathways.[79] This resulted in white matter sparing and improved motor scores in small animal models. A phase I/IIa (N = 16) trial found that both low- and high-dose regimens of intravenous (IV) G-CSF within 48 hours of injury improved AIS scores without increasing serious adverse events. A double-blind, randomized, placebo-controlled phase III study (N = 120) from Iran of chronic AIS grade B/C/D patients is expected to report in 2018 on 6-month ASIA motor score improvements and Spinal Cord Independence Measure (SCIM) outcomes.

ASCENT-ASCI—Basic Fibroblast Growth Factor

Basic fibroblast growth factor (bFGF) is a critical pat-terning morphogen during embryonic development that is used to maintain many cell types in a primitive state in vitro, including NSCs. In animal models of SCI, bFGF protects against excitotoxic cell death and can reduce free radical generation.[151] Daiichi Sankyo Inc. and Asubio Pharmaceuticals Inc. completed the ASCENT-ASCI (Asubio Spinal Cord Early Neuro-recovery Treatment for Acute Spinal Cord Injury), a phase I/II randomized, placebo-controlled study (N = 62; NCT01502631) of SUN13837, a bFGF analog, in patients with acute C4–7 AIS grade A injuries. While the primary endpoint was not reached, by 16 weeks there were no serious adverse events reported and no significant difference in SCIM outcome score between groups.[108]

Cell Therapies

Exogenous cell therapies represent an exciting strategy to neuroprotect and regenerate the injured spinal cord

TABLE 2. Summary of select, ongoing therapeutic phase I/II trials for traumatic SCI

Trial	Sponsor	Target N	Eligibility Criteria	Intervention	Control	Primary Outcome	Secondary Outcomes
SCING (gly-buride)	Ohio State University	10	Age 18–80 yrs; AIS grade A, B, or C; neurological level btwn C2 & C8; able to receive drug w/in 8 hrs of injury	DiaBeta PO 1.25 mg then 0.625 mg q 6 hrs ×11 doses	None	AEs over 1 yr	None
KP-100IT (HGF)	Kringle Pharma Inc.	48	Age 18–75 yrs; modified Frankel grade A, B1, or B2; neurological level below C3	HGF intrathecal 0.6 mg at 72 hrs; repeat wkly ×5	Placebo at 72 hrs; repeat wkly ×5	AEs over 24 wks; ASIA motor score at 24 wks	P-100 concentration in plasma & CSF at 6 wks; ASIA motor score at 12 wks; ASIA sensory score at 24 wks; modified Frankel scale at 24 wks
G-CSF	Tehran University of Medical Sciences	120	Age 18–60 yrs; AIS grade B, C, or D; injury more than 6 mos prior	G-CSF 300 mg once daily ×7 days	Normal saline ×7 days	ASIA motor & sensory scores at 6 mos	SCIM-III & IANR-SCIFRS at 6 mos; AEs up to 1 yr
CSF Drain-age in Acute SCI	St. Joseph's Hospital and Medical Center	60	Age 18–75 yrs; AIS grade A, B, or C; neurological level btwn C4 & C8; injury less than 24 hrs prior	CSF drainage by lumbar drain (target ITP 10 mm Hg) & elevation of MAP (target MAP 100–110 mm Hg) ×5 days	Lumbar drain w/o CSF drainage & maintenance of MAP (target MAP 85–90 mm Hg) ×5 days	Intrathecal pressure at 5 days; ASIA motor score at 180 days	AIS grade at 180 days; ASIA sensory score at 180 days; SCIM at 180 days; pain numeric rating scale at 180 days
AST-OPC1	Asterias Biotherapeutics Inc.	35	Age 18–69 yrs; AIS grade A or B; neurological level btwn C4 & C7; able to receive cells btwn 21 & 42 days after SCI	AST-OPC1s—dose escalation across patients w/ 2, 10, or 20 million cells	None	AEs over 1 yr	Upper-extremity ISNCSCI motor score at 1 yr
NSI-566	Neuralstem Inc.	8	Age 18–65 yrs; AIS grade A; neurological level btwn C5 & C7 or T2 & T12; able to receive cells btwn 1 & 2 yrs after SCI	Human spinal cord–derived NSC (NSI-566) transplant	None	AEs over 6 mos	Graft survival on MRI & potential autopsy at 60 mos; EMG, SCIM, ISNCSCI at 60 mos
Safety of ahSC in Chronic SCI	The Miami Project to Cure Paraysis	10	Age 18–65 yrs; AIS grade A, B, or C; neurological level btwn C5 & T12; at least 1 yr since injury	Autologous human sural nerve Schwann cell transplant	None	ISNCSCI at 6 mos; MRI at 6 mos; neuropathic pain inventory at 6 mos	SCIM-III, SCI–functional index computer adaptive testing, walk test, MEP, SSEP, & others at 6 mos
CELLTOP (adipose stem cells for SCI)	Allan Dietz	10	Age >18 yrs; AIS grade A or B; SCI btwn 2 wks & 1 yr prior	100 million intrathecal autologous, adipose-derived MSCs	None	AEs over 4 wks	CBC, CRP, Cr, BUN, & blood electrolytes at 4 wks; AEs over 48 wks; AIS grade at 96 wks; SSEP & MEP at 96 wks
Stem Cell Therapy in SCI	Neurogen Brain and Spine Institute	500	Age 1–65 yrs	Intrathecal autologous bone marrow mononuclear cell transplant	No intervention	Clinical symptoms at 6 mos	FIM at 6 mos

AE = adverse event; ahSC = adult human Schwann cells; BUN = blood urea nitrogen; CBC = complete blood count; Cr = creatinine; CRP = C-reactive protein; EMG = electromyography; IANR-SCIFRS = International Association of Neurorestoratology Spinal Cord Injury Functional Rating Scale; ISNCSCI = International Standards for Neurological Classification of Spinal Cord Injury; ITP = intrathecal pressure; MAP = mean arterial pressure; MEP = motor evoked potential testing; PO = by mouth; q = every; SSEP = somatosensory evoked potential testing.

through mechanisms such as paracrine signaling, immune modulation, extracellular matrix deposition, induction of plasticity, and direct neuroglial cell replacement.[12] As living and reactive therapies, the actions of these treatments are dependent on the specific cell type, route of administration (IV, intrathecal, intraparenchymal), cell state, and timing of delivery.[82,126,129]

Mesenchymal stem cells (MSCs), olfactory ensheathing cells (OECs), and Schwann cells can be harvested from allogenic sources to produce standardized stocks or can be autologously derived to reduce the risk of post-transplant rejection. Neural stem cells (NSCs) and oligodendrocyte progenitor cells (OPCs) are more challenging to isolate in large numbers from adult allogenic sources. Typically these cells are derived from pluripotent stem cells such as embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs).[12,81] While both cell types can proliferate and generate cells of all 3 germ layers, iPSCs avoid the ethical issues surrounding the use of embryonic tissue. More recently, technology has emerged to directly reprogram somatic cells into NSCs[127] and MSCs[23] without an interceding pluripotent stage.

Mesenchymal Stem Cells

MSCs are rapidly proliferating, multipotent connective tissue progenitor cells capable of differentiating into myocytes, chondrocytes, adipocytes, and osteoblasts.[51,97] MSCs are readily found throughout the body and can be harvested from accessible tissue such as bone marrow, abdominal fat, and skeletal muscle.[31,149] MSCs are currently under study for their immunomodulatory properties in multiple sclerosis,[37] sepsis,[94] and arthritis.[185] In preclinical SCI studies, MSCs have demonstrated the ability to enhance tissue sparing and functional recovery through immunomodulation, neurotrophic factor secretion, and pro-angiogenic signaling.[5,8,56] MSCs derived from various sources are being assessed in multiple ongoing clinical trials.

Pharmicell Co. is assessing bone marrow–derived MSCs in a phase II/III trial (N = 32; NCT01676441). Patients with chronic cervical AIS grade B injuries are receiving 3.2×10^7 intrathecal MSCs and 1.6×10^7 intraparenchymal MSCs. Outcomes include ASIA motor scores, MR-based diffusion tensor imaging (DTI), and electrophysiological tests; results are expected in 2020.

Adipose-derived MSCs are being assessed at the Mayo Clinic in the Adipose Stem Cells for Traumatic Spinal Cord Injury (CELLTOP) study, a phase I trial (N = 10; NCT03308565) delivering 1×10^8 autologous MSCs into the cerebrospinal fluid (CSF) of patients with 2-week- to 1-year-old AIS grade A/B/C injuries. Results are expected in 2023. Umbilical cord–derived MSCs are also being tested in multiple recently registered phase I/II trials (NCT03521323; NCT03505034; NCT02481440) for both subacute and chronic injury.

Olfactory Ensheathing Cells

OECs are highly phagocytic cells that surround olfactory neurons and rapidly clear pathogens and debris at the CNS–nasal mucosa border.[38,152,178,188] They also generate a favorable environment by expressing neurotrophins and facilitating olfactory regeneration after injury.[9] OECs have been harvested from the olfactory bulb and the nasal mucosa for transplant into the cord.[112] In SCI models, they enhance neuron and glial cell survival in the early phases, promote remyelination, and reduce neuroinflammation.[113,140,173] Numerous clinical trials have been completed demonstrating the safety and feasibility of OEC transplants for SCI. A meta-analysis of 1193 cases across several clinical trials found no increase in serious adverse events; however, efficacy could not be determined due to methodological and technical concerns.[109]

Schwann Cells

Schwann cells provide structural scaffolding and promote a favorable microenvironment to facilitate the robust regeneration observed in the peripheral nervous system. In preclinical SCI studies, intraparenchymal and intrathecal Schwann cell transplants have been shown to reduce cystic cavitation, enhance tissue sparing, and promote remyelination, resulting in sensory and motor recovery.[14,70,76,155,175]

The Miami Project to Cure Paralysis completed a phase I (N = 6; NCT01739023), nonrandomized, dose-escalation study of autologous intraparenchymal Schwann cell therapy in individuals with subacute-intermediate AIS grade A T3–11 injuries. At 1 year's follow-up, no serious complications were reported. The same group is currently recruiting for a phase I (N = 10; NCT02354625), open-label, nonrandomized trial of autologous MSCs in patients with AIS grade A/B/C injuries occurring at least 12 months prior to enrollment. Results are expected by 2019.

Neural Stem Cells

NSCs are self-renewing, multipotent progenitor cells capable of differentiating to neural cells, oligodendrocytes, and astrocytes.[83] Although they populate the central nervous system (CNS) during fetal development, in adults they are found in limited regions such as the subventricular zone and around the central canal of the spinal cord.[58,124,133] NSCs derived from primary and reprogrammed autologous, allogeneic, and xenogeneic sources have demonstrated efficacy in small and large animal models of SCI.[12,78,135,157] A recent meta-analysis of 74 preclinical studies found significant motor recovery (pooled SMD [standardized mean difference] 1.45; p < 0.001) after NSC transplant.[186] While multiple mechanisms of action likely exist, studies suggest that NSCs enhance neurotrophic signaling, promote remodeling of neural circuitry, improve remyelination, and modify the extracellular matrix.

Two phase II trials in cervical (N = 31; NCT02163876) and thoracic (N = 12; NCT01321333) SCI led by Stem Cells Inc. transplanted human fetal brain–derived CNS stem cells. The trials were terminated early in 2016; according to a recent report, there was no significant increase in the rate of serious adverse events with escalating doses, suggesting that the therapy was well tolerated.[105] Neuralstem Inc. is now recruiting for an open-label, single-site phase I (N = 8; NCT01772810) safety study of human spinal cord–derived NSCs in individuals with 1- to 2-year-old AIS grade A injuries at C5–7 or T2–12. Results are expected in 2022.

Oligodendrocyte Progenitor Cells

OPCs are self-renewing, multipotent cells that most commonly differentiate into oligodendrocytes. They secrete neurotrophic factors, and their oligodendroglial progeny are capable of remyelinating denuded axons after SCI in animals, resulting in tissue sparing and neurobehavioral recovery.[80,150]

Asterias Biotherapeutics Inc. is assessing AST-OPC1, human ESC–derived OPCs, as part of a phase I/IIa (N = 35; NCT02302157) dose-escalation study. Between 21 and 42 days after SCI, patients with AIS grade A/B/C4–7 injuries will receive 2×10^6, 10×10^6, or 20×10^6 AST-OPC1s. Patients will be assessed for 1 year, with results expected at the end of 2018.

Biomaterials

Biomaterials represent an emerging strategy to enhance recovery after SCI by acting as a structural scaffold for endogenous regeneration, providing directional guidance cues, delivering drugs locally, and supporting the survival of transplanted cells. Numerous materials are demonstrating promising results in clinically relevant animal models.

QL6

QL6 is a biodegradable, neutral-pH, peptide biomaterial that is water soluble and self-assembles into a nanometer-scale lattice-like conformation in vivo. QL6 demonstrates a neuroprotective effect in SCI and can be delivered prior to or with NSCs to enhance graft survival, reduce inflammation and glial scarring, and improve motor function in small animal models.[72,115,189]

Hyaluronan/Methylcellulose

Hyaluronan/methylcellulose (HAMC) is an injectable, biodegradable polymer blend[60] that is capable of supporting the engraftment of NSCs[125] and OPCs[54] in SCI to enhance functional recovery. The polymer can also be modified to deliver growth factors (e.g., PDGF-AA [platelet-derived growth factor AA]),[125] small peptide ligands (e.g., RGD),[54] and CSPG scar-degrading drugs (e.g., chondroitinase ABC)[132] using affinity release.

INSPIRE—Neuro-Spinal Scaffold

The Neuro-Spinal Scaffold (InVivo Therapeutics Corp.) is a porous bioresorbable polymer scaffold that promotes appositional healing, spares white matter, decreases post-traumatic cyst formation, and normalizes intraparenchymal tissue pressure.[163] The polymer is composed of poly(lactic-co-glycolic acid) covalently conjugated to poly-L-lysine and is designed to facilitate favorable cell-material interactions. Polymer scaffold seeded with neural stem cells has been shown to improve functional recovery in animal hemisection models.[138,162]

A pilot study evaluating the safety and feasibility of implantation of the Neuro-Spinal Scaffold (InVivo Study of Probable Benefit of the Neuro-Spinal Scaffold™ for Safety and Neurologic Recovery in Subjects with Complete Thoracic AIS A Spinal Cord Injury) has completed recruitment and is currently in the follow-up phase (NCT02138110). Eligibility criteria included age 16 to 70 years; AIS A trau-matic SCI with a neurological level between T2 and T12/L1; ability to receive the scaffold within 96 hours of injury; and non-penetrating contusion injury no less than 4-mm diameter as determined by MRI. A case report of the first patient to undergo implantation of the scaffold as part of this trial has been published previously.[163] The patient was a 25-year-old man with a T11–12 fracture-dislocation sustained in a motocross accident resulting in a T11 AIS A SCI. A 2×10–mm scaffold was implanted directly into the traumatic cavity within the spinal cord parenchyma at T12 through a dorsal root entry zone myelotomy. At 3 months, neurological function had improved to an L1 AIS C incomplete injury. No procedural complication or safety concern resulting from implantation of the scaffold was seen at 6 months' follow-up.

Key Phase III Trials

A number of phase III randomized controlled trials (RCTs) testing the safety and efficacy of neuroprotective and regenerative therapies for acute traumatic SCI are currently underway (Table 3).

RISCIS—Riluzole

Riluzole is a sodium channel–blocking benzothiazole anticonvulsant drug. Riluzole modulates excitatory neurotransmission and has been shown to improve survival in the setting of amyotrophic lateral sclerosis (ALS).[122] The drug is currently approved for use in ALS by regulatory authorities in several countries.[122] Its well-defined human safety record makes riluzole an attractive agent for translation into clinical trials of SCI treatment. With regard to mechanism of action, during the secondary injury cascade of SCI, there is thrombosis and vasospasm of the spinal cord microvasculature, leading to ischemia. This triggers neuronal membrane dysfunction, with increased Na^+ influx from continuous activation of voltage-gated Na^+ channels and decreased Na^+ efflux from dysfunction of the membrane-bound Na^+-K^+-ATPase pump.[2] The marked increase in intracellular Na^+ leads to an influx of Ca^{2+} through the Na^+-Ca^{2+} exchange pump. This in turn activates a number of Ca^{2+}-dependent enzyme systems, such as calpains and phospholipases, leading to regional cell death.[156] This pathophysiological pathway, which centers on Na^+ overload, affords an opportunity to curb the extent of injury, preserve remnant viable neurological tissue, and improve clinical outcomes, and it provides the rationale for the use of sodium channel–blocking agents for neuroprotection in SCI.[160] In addition to its ability to reduce intracellular levels of Na^+ and Ca^{2+}, riluzole functions as an anti-glutamatergic agent via inhibition of glutamate release, prevention of glutamate receptor hypofunction, and activation of glutamate transporters to increase glutamate uptake.[55,87] The multifaceted effects of riluzole on excitotoxicity and neuromodulation make it a promising neuroprotective treatment option for patients who have suffered SCI.

There is strong evidence from a number of independent studies, using several different animal models of brain and spinal cord ischemic and traumatic injury, that riluzole is neuroprotective and promotes functional recovery.[13,95,145,181] In preclinical animal models of SCI, riluzole has been

TABLE 3. Summary of active phase III RCTs for traumatic SCI

Trial	Active Centers	Target N	Eligibility Criteria	Intervention	Control	Primary Outcome	Secondary Outcomes
RISCIS (riluzole)	23 (3 Canada, 16 USA, 4 Australia)	351	Age 18–75 yrs; AIS grade A, B, or C; neurological level btwn C4 & C8; able to receive drug w/in 12 hrs of injury	Riluzole PO/NG 100 mg BID ×24 hrs then 50 mg BID ×13 days after injury	Placebo PO/NG BID ×14 days	Change in ASIA motor score at 180 days	AIS grade, ASIA sensory scores, SCIM, SF-36, EQ-5D, pain NRS, GRASSP (180 days)
MASC (minocycline)	4 (3 Canada, 1 Australia)	248	Age ≥16 yrs; neurological level btwn C0 & C8; able to receive drug w/in 12 hrs of injury	Minocycline IV BID ×7 days: 800 + 700 mg day 1; 600 + 500 mg day 2; 400 + 400 mg days 3–7	Placebo (normal saline) IV BID ×7 days	Change in ASIA motor score from baseline to btwn 3 mos & 1 yr post-injury	ASIA sensory scores, SCIM, SF-36, AIS grade
SPRING (VX-210)	36 (28 USA, 8 Canada)	150	Age 14–75 yrs; AIS grade A or B; motor level btwn C4 & C7 on each side; scheduled to undergo surgery w/in 72 hrs of injury	VX-210 9 mg in fibrin sealant (local admin)	Placebo (buffer solution) in fibrin sealant (local admin)	Change in ASIA upper-extremity motor score at 6 mos	SCIM, CUE-T, GRASSP, AIS grade conversion, motor level change (6 mos); pharmacokinetic parameters of VX-210 (Tmax, Cmax, AUC) at 48 hrs after treatment
FES	1 (Canada)	25	Age ≥18 yrs; incomplete SCI btwn C4 & C7; less than 6 mos post-injury; unable to grasp objects	FES (balanced, biphasic, current regulated electrical pulses; pulse amplitude from 8 to 50 mA; pulse width from 250 to 300 μsec; pulse frequency from 20 to 70 Hz)	Conventional OT	Change in FIM score from baseline at 8 wks & at 6-mo follow-up	GRASSP, Jamar hydraulic hand dynamometer, Action Research Arm Test, TR-HFT, ReJoyce therapy device, SCIM (8 wks, 6 mos)
ES135/rhFGF1	3 (Taiwan)	100	Age 18–65 yrs; AIS grade A	ES135 administered intrathecally	Placebo administered intrathecally	Change in ASIA motor score at 48 wks	

Admin = administration; BID = twice daily; CUE-T = Capabilities of Upper Extremity Test; NG = nasogastric (by nasogastric tube); NRS = numeric rating scale; OT = occupational therapy; TR-HFT = Toronto Rehabilitation Institute Hand Function Test.

found to attenuate secondary injury pathways, increase neural tissue preservation at the site of injury, and improve neurobehavioral outcomes in comparison to placebo and other sodium channel–blocking medications.[145,146,182,183] On the basis of promising preclinical data, a phase I clinical trial investigating the safety and pharmacokinetics of riluzole in the setting of acute traumatic SCI was undertaken (NCT00876889).[59] For the 36 enrolled patients, this study found improved ASIA motor scores, particularly for cervical SCI cases, and a similar complication profile compared to 36 matched patients in the North American Clinical Trials Network (NACTN) SCI Registry. These results provided the impetus for a phase IIb/III clinical trial, Riluzole in Acute Spinal Cord Injury Study (RISCIS), which commenced in January 2014 and is currently ongoing (NCT01597518).[40]

RISCIS is a multicenter, double-blinded, placebo-controlled, 2-arm parallel group superiority RCT with a sequential adaptive design. Adult patients (age 18–75 years) with AIS grade A, B, or C SCI and a neurological level between C4 and C8 presenting within 12 hours of injury are randomized in a 1:1 ratio to receive riluzole (100 mg twice a day for 24 hours, then 50 mg twice a day for 13 days after injury) or placebo. The primary outcome is change in ASIA motor score from baseline to 180 days after injury. Secondary outcomes include overall neurological recovery (AIS grade), sensory recovery (ASIA Light Touch and Pin Prick scores), functional outcomes (SCIM), quality of life (SF-36, EQ-5D), pain (numeric rating scale), sensorimotor upper limb function (Graded Redefined Assessment of Strength Sensibility and Prehension [GRASSP]), mortality, and adverse events. Patients, physicians, and data collectors remain blinded to treatment group allocation throughout randomization and follow-up.

MASC—Minocycline

The antibiotic minocycline has demonstrated neuroprotective properties in preclinical studies.[187] Specifically, minocycline has been found to reduce apoptosis of oligodendrocytes and microglia and improve neurological recovery in rodent models of SCI.[100,174] A phase II trial of minocycline for acute traumatic SCI was completed and published in 2012.[21] Fifty-two patients were randomly as-

signed to receive minocycline (N = 27) or placebo (N = 25). Compared to patients in the placebo arm, patients treated with minocycline experienced a 6-point greater recovery in ASIA motor score at 1 year, although the difference was not statistically significant. While no difference was observed for thoracic injuries, a trend toward improved motor recovery with minocycline (14-point difference in ASIA motor score) was observed for cervical cases (p = 0.05). A phase III RCT, Minocycline in Acute Spinal Cord Injury (MASC), has been initiated (NCT01828203).

MASC is a multicenter, placebo-controlled, double-blinded RCT. The target enrollment is 248 patients. Adult patients (age ≥ 16 years) with cervical SCI presenting within 12 hours of injury are randomly assigned to IV minocycline (800-mg initial dose tapered to 400 mg by 100 mg at each dose and then administered to the end of day 7) or placebo. The primary outcome is recovery in ASIA motor score measured between 3 months and 1 year post-injury. Secondary outcomes include ASIA sensory recovery, functional outcome (SCIM), quality of life (SF-36), and overall neurological function (AIS grade).

SPRING—VX-210

Following CNS injury, there is inhibition of axonal growth and regeneration. Several growth inhibitory pathways converge in signaling to Rho, an intracellular GT-Pase.[36] Activation of Rho and downstream activation of Rho-associated kinase leads to an imbalance in the phosphorylation state of myosin light chain and, as a consequence, a collapse of the growth cone scaffold and axon growth arrest.[47] C3 transferase, an enzyme derived from *Clostridium botulinum*, locks RhoA in the inactive state and thereby inhibits Rho signaling. C3 transferase has been shown to promote axonal outgrowth on inhibitory substrates both in vitro and in vivo.[36,116] VX-210 is a recombinant engineered variant of C3 transferase that can readily cross the spinal cord dura and permeate across the cell membrane through a receptor-independent mechanism.[116] In a rodent thoracic spinal cord contusion model, local delivery of VX-210 to the injury site has been found to inactivate RhoA, reduce the extent of the lesion, and improve locomotor function.[116] A phase I/IIa clinical trial was undertaken.[47] Forty-eight patients with an AIS A cervical or thoracic SCI received 0.3 to 9 mg Cethrin applied locally onto the anterior or posterior dural surface overlying the injured spinal cord at the time of surgery. Changes in ASIA motor scores were small in all thoracic SCI patients (1.8 ± 5.1) and larger in cervical SCI patients (18.6 ± 19.3). Cervical SCI patients treated with 3 mg of Cethrin experienced the greatest improvement in ASIA motor score at 1 year (27.3 ± 13.3). Based on this experience, a phase IIb/III trial of VX-210 for acute traumatic cervical SCI, the SPRING (SPinal Cord Injury Rho INhibition InvestiGation), is now underway (NCT02669849).

The SPRING trial is designed as a multicenter, double-blinded, placebo-controlled, prospective randomized study. Eligibility criteria are age 14 to 75 years; AIS A or B acute traumatic SCI with a motor level between C4 and C7; and ability to undergo surgery within 72 hours of injury. The target enrollment is 150 patients. The primary outcome is change in ASIA upper-extremity motor score from baseline to 6 months post-injury. Secondary outcomes at 6 months include functional status (SCIM), sensorimotor upper limb function (GRASSP), AIS grade conversion, and ASIA motor level change, in addition to pharmacokinetic parameters of VX-210 (Tmax [time taken to reach the maximum concentration], Cmax [maximum concentration], and AUC [area under the curve]).

ES135/rhFGF1

Fibrin glue containing acidic fibroblast growth factor (aFGF) has been studied as a possible repair strategy for SCI. In animal studies, aFGF, in conjunction with a peripheral nerve graft, has demonstrated potential to support axonal regeneration and formation of white matter to gray matter connections.[24,101] This was tested in a human for the first time in 2004.[25] The patient was a young male with chronic paraplegia and a complete spinal cord gap resulting from a stabbing injury. The technique involved bridging the spinal cord gap with sural nerve grafts and applying fibrin glue mixed with aFGF to the grafted area. This patient improved from being wheelchair-bound to being able to ambulate independently with a walker. A phase I pilot study tested local application of fibrin glue with aFGF without nerve grafting in 9 patients with chronic SCI (> 5 months).[180] The procedure was well tolerated, and the patients demonstrated significant improvement in ASIA motor and sensory scores. In a subsequent larger trial that involved 49 chronic SCI patients, application of aFGF with fibrin glue and duraplasty performed via laminectomy was combined with adjuvant booster treatment of combined aFGF and fibrin glue at 3 and 6 months postsurgery via lumbar puncture.[179] Again, the use of aFGF was found to be safe and feasible; significant improvements were seen in ASIA motor and sensory scale scores, AIS grade, neurological level, and Functional Independence Measure (FIM) score at 24 months after treatment. A phase III multicenter, double-blinded, placebo-controlled, randomized trial of aFGF (ES135; EUSOL Biotech Co., Ltd.) is currently enrolling patients (NCT03229031). Eligible patients are 18 to 65 years of age and have an AIS A SCI. The target enrollment is 100 patients. The primary outcome is change in ASIA motor score at 12 months.

Functional Electrical Stimulation

Functional electrical stimulation (FES) involves the application of electrical stimulus to generate muscle contractions in a carefully timed and orchestrated fashion that allows for functional limb use. FES has been successfully applied to improve ambulatory ability in patients with incomplete SCI.[77,165] Similarly, muscle contraction may be coordinated to produce grasp opening and closing; thumb opening, closing, and positioning; wrist flexion and extension; forearm pronation; and elbow extension.[69] A phase III multicenter randomized trial (NCT01292811) of FES compared to conventional occupational therapy for restoration of upper limb function is currently ongoing. The primary outcome is change in burden of care from baseline at 8 weeks to 6-month follow-up, as evaluated by FIM. Secondary outcomes include change in sensorimotor upper limb function (GRASSP), grip force (measured using a Jamar hydraulic hand dynamometer), and SCIM score.
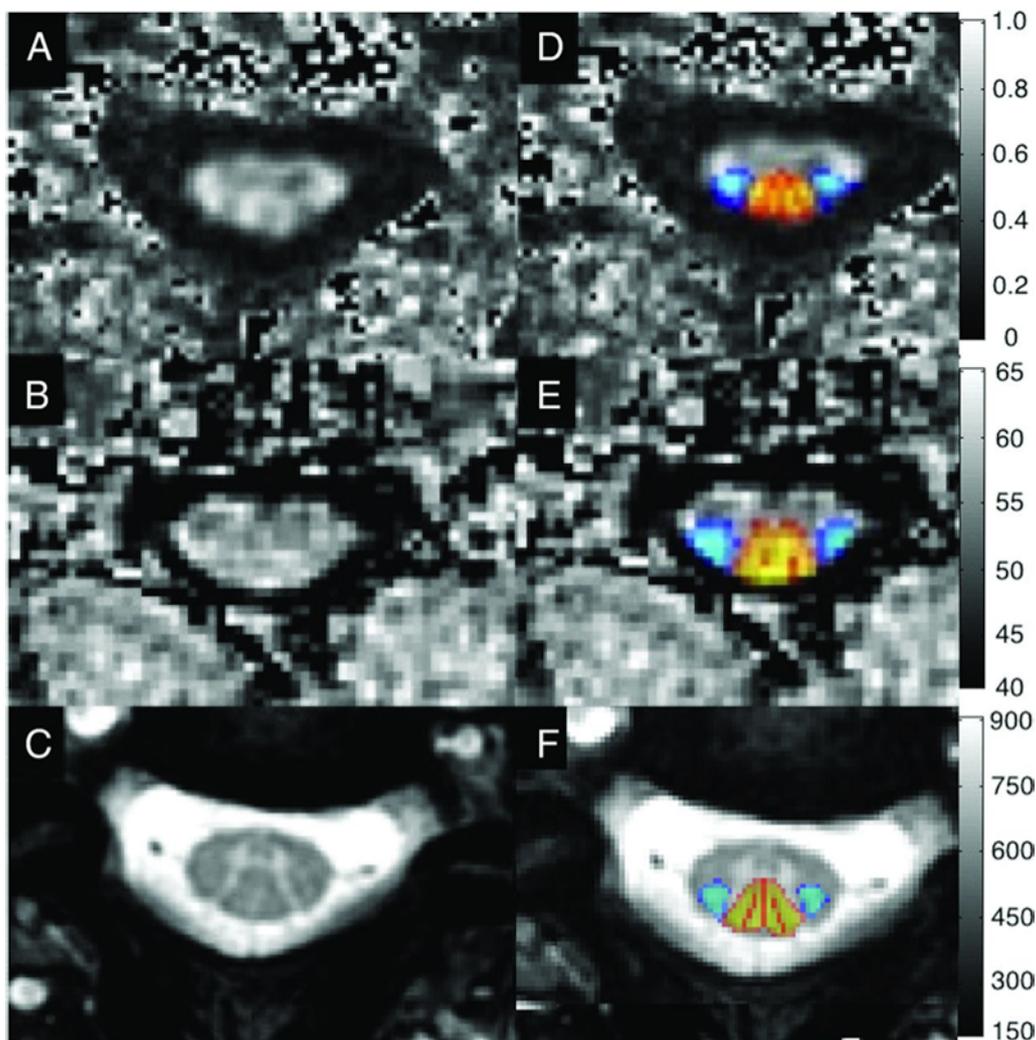
FIG. 2. Representative axial MR images showing functional anisotropy (FA) mapping (**A**), MTR mapping (**B**), and T2*-weighted imaging (**C**) with probabilistic maps of the lateral corticospinal tracts (*blue*) and dorsal columns (*red-yellow*) overlaid (**D–F**) following registration to the Spinal Cord Toolbox (SCT; https://www.nitrc.org/projects/sct/)[31] atlas. Reprinted with permission from Martin AR, De Leener B, Cohen-Adad J, Cadotte DW, Kalsi-Ryan S, Lange SF, et al: Clinically feasible microstructural MRI to quantify cervical spinal cord tissue injury using DTI, MT, and T2*-weighted imaging: assessment of normative data and reliability. *AJNR Am J Neuroradiol 38*:1257–1265, 2017. Figure is available in color online only.

Biomarkers

There is a critical need for improved prognostication in SCI. To this end, there has been much interest in identifying and characterizing imaging, serum, and CSF biomarkers that may quantify the degree of neural tissue injury and predict neurological outcomes. In addition to guiding patient counseling and calibration of expectations, these may facilitate stratification of patients for enrollment into clinical trials. The use of biomarkers could also permit the enrollment of patients who cannot be adequately examined because of head injury, multisystem trauma, drug intoxication, or pharmacological sedation, and in doing so, may facilitate the translation of novel therapies for acute traumatic SCI.

Imaging

Our ability to image the injured spinal cord at high res-olution has improved substantially over recent years. With the development of advanced spinal MRI protocols with acquisition times under 35 minutes, it is now clinically feasible to obtain microstructural MRI sequences, including DTI, magnetization transfer (MT), and T2*-weighted imaging, in the setting of acute traumatic SCI.[118] Quantitative metrics derived from these modalities have potential to serve as biomarkers to quantify cervical spinal cord tissue injury. In particular, the signal intensity ratio of white matter to gray matter on T2*-weighted imaging has been found to correlate strongly with focal motor and sensory deficits, more so than cross-sectional area, fractional anisotropy, or MT ratio (MTR) (Fig. 2).[119]

Cerebrospinal Fluid

Molecular profiling of CSF in the setting of SCI has been an active area of investigation. Kwon et al.[90] random-

ly assigned 22 patients with acute traumatic SCI to CSF-drainage (via lumbar intrathecal catheter) or no-drainage groups. This trial confirmed the safety of CSF drainage, but it also enabled biochemical analysis of CSF samples collected through the drains. Key inflammatory cytokines (e.g., interleukin [IL]-6, IL-8, and monocyte chemotactic protein [MCP]-1) and structural proteins (e.g., tau, S100β, and glial fibrillary acidic protein [GFAP]) were temporally profiled. An ordinal logistic regression model could predict the observed AIS grade with 89% accuracy based on concentrations of S100β, GFAP, and IL-8 at 24 hours post-SCI.[91] Moreover, in patients with cervical injury, concentrations of these proteins could predict upper-extremity motor recovery at 6 months better than baseline AIS grade. In addition, CSF levels of TNF-R1 at 24 hours correlated strongly with neuropathic pain. This study has been expanded to a prospective, multicenter initiative, known as the Canadian Multicentre CSF Monitoring and Biomarker Study (CAMPER; NCT01279811). Analysis of the first 50 patients enrolled in this study found CSF concentrations of IL-6, tau, S100β, and GFAP at 24 hours to be significantly different between patients with AIS A, B, and C injuries.[92] Discriminant analysis based on levels of IL-6, IL-8, MCP-1, tau, S100β, and GFAP showed 83.3% accuracy in predicting AIS grade conversion at 6-month follow-up. Additionally, all of these CSF biomarkers showed significant correlation with ASIA motor score improvement, especially for cervical SCI patients. A recent study of MRI (intramedullary lesion length, hematoma length, hematoma extent, CSF effacement, cord expansion, maximal spinal cord compression) and CSF (IL-6, IL-8, MCP-1, tau, GFAP, S100β) biomarkers found that both correlated with baseline AIS grade; however, ability to predict baseline AIS grade was maximized when both were combined together.[30] In direct head-to-head comparison, CSF biomarkers were found to better discriminate between injury severities, and more accurately predict neurological recovery (AIS grade conversion, ASIA motor score improvement) than MRI biomarkers.

Serum

Evaluation of serum proteins, too, holds promise. In a cohort of 35 patients with acute traumatic SCI, Ahadi et al.[3] observed increased serum levels of GFAP, neuron-specific enolase (NSE), and the phosphorylated form of the heavy subunit of neurofilament (pNF-H). GFAP levels correlated with severity of SCI. Kuhle et al.[88] found that serum neurofilament light chain (NF-L) concentrations closely correlated with ASIA motor score at baseline and after 24 hours and with 3- to 12-month motor outcome. Further, minocycline treatment was associated with lower levels of NF-L in patients with motor complete SCI. This last finding highlights the possibility of using biomarkers as surrogate outcomes in SCI clinical trials.

Future Directions

A number of promising neuroprotective and regenerative therapies for acute traumatic SCI are under active investigation, and several more are coming down the translational pipeline. There is reason to hope that in the near future development of a biomarker readout from a combi-nation of imaging, serum, and CSF analysis may improve prognostication for patients with SCI and further facilitate the translation of novel therapeutics from bench to bedside through clinical trials. With the organization of large, multicenter, and in some cases multinational, prospective registries of SCI and the collection of mass data relating to clinical characteristics, imaging features, serum markers, and CSF markers, the application of machine learning and big data analytical approaches may pave the way toward precision and personalized medicine for traumatic SCI. Further, regional and national efforts to organize healthcare systems infrastructure to facilitate early transfer of SCI patients to centers specializing in the care of patients with these injuries may improve clinical outcomes on a large scale.

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Disclosures

Dr. Fehlings reports a consultant relationship with Fortuna Fix.

Author Contributions

Conception and design: all authors. Acquisition of data: Badhiwala, Ahuja. Analysis and interpretation of data: Badhiwala, Ahuja. Drafting the article: Badhiwala, Ahuja. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fehlings. Administrative/technical/material support: Fehlings. Study supervision: Fehlings.

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