Traumatic Spinal Cord Injury—Repair and Regeneration

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BACKGROUND: Traumatic spinal cord injuries (SCI) have devastating consequences for the physical, financial, and psychosocial well-being of patients and their caregivers. Expediently delivering interventions during the early postinjury period can have a tremendous impact on long-term functional recovery.

PATHOPHYSIOLOGY: This is largely due to the unique pathophysiology of SCI where the initial traumatic insult (primary injury) is followed by a progressive secondary injury cascade characterized by ischemia, proapoptotic signaling, and peripheral inflammatory cell infiltration. Over the subsequent hours, release of proinflammatory cytokines and cytotoxic debris (DNA, ATP, reactive oxygen species) cyclically adds to the harsh postinjury microenvironment. As the lesions mature into the chronic phase, regeneration is severely impeded by the development of an astroglial-fibrous scar surrounding coalesced cystic cavities. Addressing these challenges forms the basis of current and upcoming treatments for SCI.

MANAGEMENT: This paper discusses the evidence-based management of a patient with SCI while emphasizing the importance of early definitive care. Key neuroprotective therapies are summarized including surgical decompression, methylprednisolone, and blood pressure augmentation. We then review exciting neuroprotective interventions on the cusp of translation such as Riluzole, Minocycline, magnesium, therapeutic hypothermia, and CSF drainage. We also explore the most promising neuroregenerative strategies in trial today including Cethrin™, anti-NOGO antibody, cell-based approaches, and bioengineered biomaterials. Each section provides a working knowledge of the key preclinical and patient trials relevant to clinicians while highlighting the pathophysiologic rationale for the therapies.

CONCLUSION: We conclude with our perspectives on the future of treatment and research in this rapidly evolving field.

KEY WORDS: Spinal cord injury, Trauma, Regenerative medicine, Stem cells, Neuroprotection, Management, Clinical trial

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Traumatic spinal cord injuries (SCI) have devastating physical, psychosocial, and vocational implications for patients and caregivers. Direct lifetime costs can reach a staggering $1.1 to 4.6 million per patient with over 1 million people affected in North America alone (Figure 1).[1-3] For treating physicians, a working knowledge of current and emerging therapies in SCI is critical to expediently deliver care and improve long-term functional outcomes for patients.[4,5] This paper summarizes the evidence-based management of a patient with acute SCI and discusses upcoming neuroprotective and neuroregenerative strategies on the cusp of translation. A primer on the unique pathophysiology of SCI is provided to aid in understanding the rationale behind the diverse range of therapeutic approaches discussed below.

PATHOPHYSIOLOGY

Primary and Secondary SCI

SCI can be categorized into primary and secondary phases.[6,7] The primary SCI is the result of physical forces of the initial traumatic event and is often the most important determinant of injury severity; physical forces

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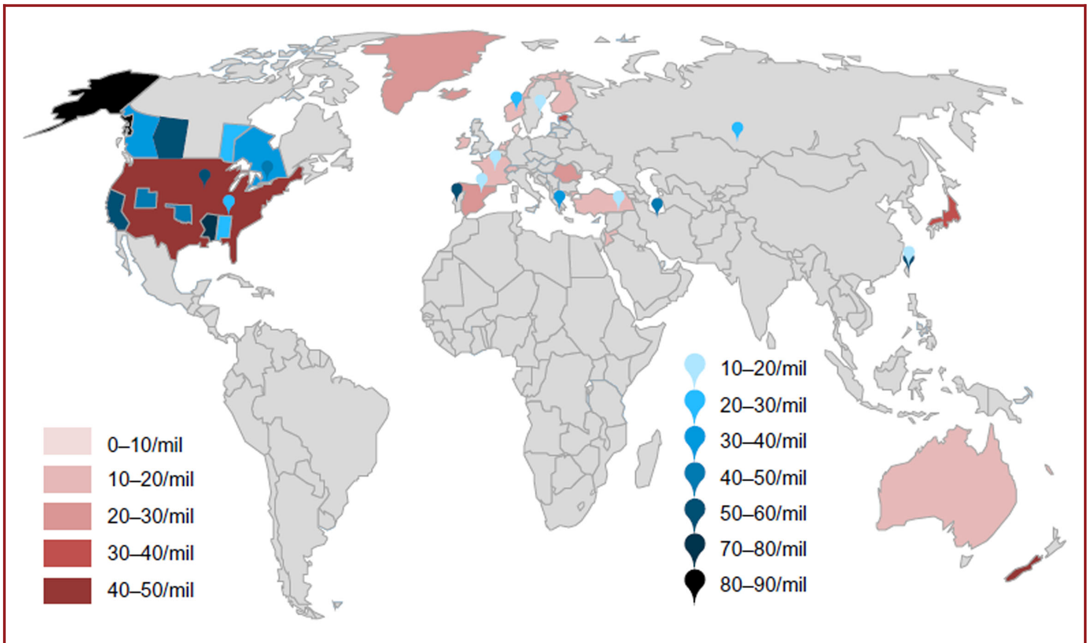

FIGURE 1. *Annual incidence of SCI across reported countries, states/provinces, and regions. Reprinted with permission from Singh A, et al. Clin Epidemiol. 2014;6:309-331.*[137]

involved can include compression, shearing, laceration, and acute stretch/distraction.[8] After the primary injury event, a cascade of secondary injury events is initiated which serves to expand the zone of neural tissue injury and exacerbate neurological deficits and outcomes.[9,10] Secondary SCI is a delayed and progressive tissue injury following the primary SCI. During this secondary injury cascade, inflammatory cells such as macrophages, microglia, T-cells, and neutrophils infiltrate the injury site as a result of disruption of the blood–spinal cord barrier.[138] These cells trigger the release of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1α, IL-1β, and IL-6, with tissue levels of these cytokines peaking at 6 to 12 h after injury and remaining elevated up to 4 days after injury.[11,12] In addition, a loss of ionic homeostasis after SCI results in intracellular hypercalcemia which activates calcium-dependent proteases and causes mitochondrial dysfunction ultimately leading to apoptotic cell death.[13] Oligodendrocytes are particularly susceptible to apoptotic loss and not just at the site of impact. This apoptotic loss has been observed distant from the epicenter of SCI as well as at the lesion epicenter and leads to demyelination of preserved axons.[14-16] In addition, phagocytic inflammatory cells release reactive oxygen species which causes DNA oxidative damage, protein oxidation, and lipid peroxidation. Delayed necrosis and apoptosis are further induced by this process.[17-19] After SCI, upregulated release of excitatory amino acids, such as glutamate and aspartate, is observed due to release from disrupted cells.[20,21] The excessive activation of excitatory amino acid receptors produces excitotoxicity and further propagation of loss of neurons and glia by both necrotic and apoptotic cell death.[22]

Barriers to Regeneration

It is widely recognized that regeneration of the adult mammalian central nervous system (CNS), including the spinal cord, is difficult due to limited plasticity.[23] Although recent progress in the field of SCI research has demonstrated that the CNS has more inherent regenerative capacity than that was once thought,[24,25] it does not have the same regenerative capacity that is observed in the peripheral nervous system (PNS). Compared with the PNS, not only is the regenerative capacity of CNS axons lower, but it also decreases with advancing age.[26]

The inhibitory nature of CNS myelin, which starkly contrasts the effects of PNS myelin, was first recognized in 1985.[27] Myelin-associated proteins, including neurite outgrowth inhibitor A (Nogo A),[28,29] myelin-associated glycoprotein,[30,31] and oligodendrocyte-myelin glycoprotein,[32] bind NOGO receptors to activate the GTPase Rho A. Rho-associated protein kinase (ROCK) is the effector of Rho A, which regulates further downstream effectors, and leads to apoptosis and growth cone collapse of regenerating axons along with neurite retraction.

Additional external barriers potently add to the inhibition of regeneration. Hypertrophied astrocytes form a physical barrier called the glial scar, which walls off injured tissue from the healthy tissue.[33] The astrocytes also form a chemical barrier by secreting

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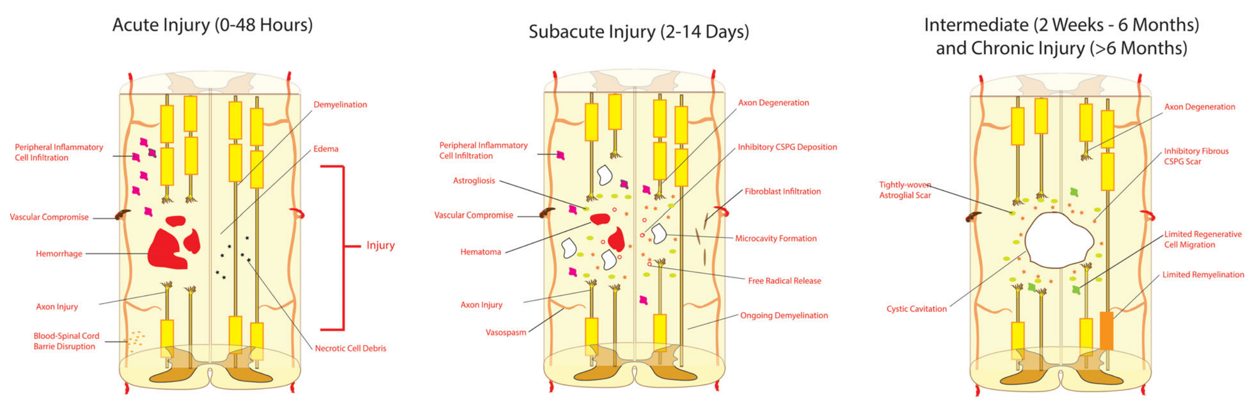

FIGURE 2. *Pathophysiological evolution of SCI. In the acute injury period (0-48 h), hemorrhage, edema, and proapoptotic factors (eg, cytokines, K+, DNA, necrotic debris, etc) contribute to ongoing cell death. Neurons and oligodendrocytes are injured resulting in further loss of function beyond the initial traumatic insult. Astrocytes rapidly activate, proliferate, and infiltrate the site of injury while depositing CSPGs into the microenvironment, and release additional proinflammatory factors which propagate the injury cascade. Demyelinated and injured axons begin to dieback from the inflamed and ischemic perilesional region. In the late subacute and intermediate phases, continued apoptotic and necrotic cell death leaves microcystic cavities which eventually coalesce to form formidable barriers to regeneration in the chronic phase (>6 months). The final chronic phase scar is a dynamic entity consisting of a tightly woven network of astrocytic processes with a dense fibrous deposit of CSPG acting as a physical and biochemical barrier to neurite outgrowth and regenerative cell migration. Based on figure from Ahuja C, Fehlings, M. How can we regenerate the traumatically injured spinal cord? Neurology Central (2016).*

a number of growth inhibitory chondroitin sulfate proteoglycans (CSPGs) including neurocan, versican, brevican, phosphacan, and NG2.[34] Fibroblasts also infiltrate the perilesional region and replace the extracellular matrix with fibrous connective tissue. This is associated with the deposition of inhibitory extracelluar matrix molecules which function as chemical barriers to axonal regeneration similar to myelin-associated inhibitors (Figure 2).[35]

CURRENT MANAGEMENT

The current management of SCI largely follows the American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS) joint section guideline series (Table 1) as well as an upcoming AOSpine 2016 guideline.[36] Initial care in the field prioritizes securing the airway, breathing, and circulation followed by early recognition of SCI and rapid referral to specialized centers in order to expedite delivery of time-sensitive interventions.[36] To limit further insult to the highly vulnerable cord, spinal immobilization should be performed for all patients with suspected or confirmed injuries.[36] This typically involves a rigid cervical collar, backboard for transport, and spinal precautions for patient transfers (eg, logroll maneuver with inline manual cervical stabilization and a transfer board). Systemic hypotension (systolic blood pressure <90 mm Hg), even for brief periods, should be avoided as it is associated with worse long-term neurological outcomes.[36] This can be particularly challenging as hypovolemia is common in polytrauma, and interruption of spinal cord sympathetic fibers can induce a profound loss of vascular tone and bradycardia (neurogenic shock). Resuscitation with large-volume crystalloids is typical; however, alpha-agonists (eg, phenylephrine) or mixed alpha/beta-agonists (eg, dopamine, norepinephrine) may also be required as adjuncts. Once resuscitated, an American Spinal Injury Association (ASIA) International Standards for Neurological Classification of SCI (ISNCSCI) examination should be documented to establish baseline function and the level of neurological injury (Table 2, Figure 3).[36]

Early localization and classification of osseoligamentous and neurological injuries is necessary to expediently provide the outcome-altering therapies discussed below.[4,5,37,38] Computerized tomography (CT) imaging is recommended for all patients with suspected SCI as x-rays can miss up to 6% of injures.[39] When evaluating patients with high-energy mechanisms and confirmed cervical injuries, thoracolumbar imaging is recommended to rule out concomitant injuries that may not be clinically apparent.[40] The role of magnetic resonance imaging (MRI) in the initial workup of patients remains unclear; however, urgent MRI is strongly recommended, particularly in cases with unexplained neurological deficits to rule out ongoing spinal cord compression due to occult ligamentous injuries, epidural hematomas, or critical disk herniations. The utility of MRI in prognostication is also becoming more apparent as validated prediction scores continue to be published.[41]

Concurrent with the diagnostic workup, patients should be transferred to a critical care unit providing continuous respiratory, cardiac, and hemodynamic monitoring.[36] Immediate life- or limb-threatening injuries should be managed by the appropriate teams while maintaining strict spinal immobilization. Delivering effective care in SCI requires a collaborative

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TABLE 1. "Current best practices for the diagnosis and management of SCI. The table displays several key recommendations, many of which are from the 2013 updated guidelines from the Joint Section on Disorders of the Spine and Peripheral Nerves of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons"[135,a]

Topic	Level of AANS/CNS recommendation	Guideline/recommendation
Hypotension	Level III	Correction of hypotension to systolic blood pressure > 90 mm Hg) as soon as possible
	Level III	Maintenance of mean arterial blood pressure between 85 and 90 mm Hg for 7 days
Hypoxia	None	Hypoxia (PaO2 < 60 mm Hg or O2 saturation < 90%) should be avoided [3]
ICU monitoring	Level III	SCI patients should be managed in an intensive care unit (ICU) setting with cardiac, hemodynamic, and respiratory monitoring to detect cardiovascular dysfunction and respiratory insufficiency
Immobilization	Level II	Patients with SCI or suspected SCI (except in penetrating injury) should be immobilized
	Level III	Spinal immobilization should be performed with rigid cervical collar and supportive blocks on a backboard with straps
Specialized centers	Level III	SCI patients should be transferred expediently to specialized centers of SCI care
Examination	Level II	The ASIA ISNCSCI examination should be performed and documented
Imaging	Level I	No cervical imaging is required in awake trauma patients that have no neck pain/tenderness, normal neurological examination, normal range of motion, and no distracting injuries
	Level I	CT is recommended in favor of cervical x-rays
	Level I	CT angiography is recommended in patients that meet the modified Denver screening criteria [9]
Neuroprotection	Level I	Methylprednisolone is not recommended[b]
Spinal cord decompression	None	Surgical decompression prior to 24 h after SCI can be performed safely and is associated with improved neurological outcome [10]
	Level III	Early closed reduction of fracture/dislocation in awake patients without a rostral injury is recommended, and pre-reduction MRI does not appear to influence outcome

[a]Reprinted with permission of Springer from Martin AR, Aleksanderek I, Fehlings MG. Diagnosis and acute management of spinal cord injury: current best practices and emerging therapies. Current Trauma Reports. 2015;1(3):169-181.
[b]The authors do not agree with this guideline given the balance of trial data available and the 2012 Cochrane review on steroids for SCI. An upcoming 2016 AOSpine guideline will recommend MPSS as a treatment option for patients within 8 h of injury. See the 'Steroids for SCI' section for a full discussion.

multidisciplinary approach including fiberoptic intubation by anesthesia/critical care, modified intraoperative positions for general surgery/orthopedic procedures, and early recognition of therapeutic windows, which can positively alter long-term outcomes.

Early Surgical Decompression

After SCI, ongoing mechanical compression of the spinal cord can impair blood flow causing ischemia and an expanded zone of neural tissue injury. The goal of early surgical decompression after SCI is to relieve this compression, thereby improving the vascular supply to the injured area and limiting the zone of secondary injury expansion. A sizable body of preclinical literature supports the positive effects of early surgical decompression on behavioral and pathological outcomes in animal SCI models.[42]

With respect to clinical evidence on this topic, a number of comparative cohort studies have been published investigating the clinical impact of performing decompressive surgery prior to several thresholds. Notably, to investigate the efficacy of early decompression prior to a 24-h threshold, the Surgical Treatment of Acute Spinal Cord Injury Study (STASCIS) enrolled 313 cervical SCI patients.[38] Patients receiving early decompression (<24 h after SCI) experienced 2.8 times greater odds of experiencing an ASIA Impairment Scale (AIS) improvement of at least 2 grades at 6 months as compared with patients who underwent late decompression (≥24 h after SCI). Although not statistically significant, early decompression was associated with a reduced incidence of acute in-hospital complications. A prospective Canadian cohort study (including cervical, thoracic, and lumbar SCI, n = 84) confirmed the findings observed in STASCIS, reporting that in the adjusted analysis early decompression was associated with a statistically greater improvement in ASIA motor score recovery at the time of rehabilitation facility discharge.[43] Moreover, an observational Canadian cohort study showed that AIS A (complete injury) and AIS B (complete motor injury with incomplete sensory injury) patients who received

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TABLE 2. Summary of International Standards for Neurological Classification of Spinal Cord Injury

Parameter	Definition
Motor score	Score out of 100 points representing motor power in 5 key myotomes (each grade out of 5) in each limb
Sensory score	Score out of 224 points representing light touch and pin prick sensation in 28 dermatomes bilaterally
AIS grade	Cumulative measure of injury severity ranging from AIS grade A (most severe motor sensory complete lesion) to AIS grade E (least severe no neurological deficit)
AIS grade A	No motor or sensory preservation below the neurological level of injury (including the distal sacral segments)
AIS grade B	Sensory, but no motor, preservation below the neurological level of injury (including the distal sacral segments)
AIS grade C	Motor preservation below the neurological level of injury (including the distal segments) with less than half of key muscles below the neurological level graded antigravity or better
AIS grade D	Motor preservation below the neurological level of injury (including the distal segments) with at least half of key muscles below the neurological level graded antigravity or better
AIS grade E	Neurological normal in a patients who previously had deficit
Neurological level of injury	The lowest segment where motor and sensory function is normal on both sides
Zone of partial preservation	In AIS grade A patient, lowest dermatome or myotome with partial innervation

Based on Kirshblum et al. J Spinal Cord Med. 2011;34(6):535-546.[136]

early decompression experienced shorter length of hospital stay, while AIS B, C, and D incomplete injury patients decompressed in an early fashion demonstrated an additional 6.3 points in motor recovery as compared to those decompressed late.[4] Taken together, these findings support the concept of "Time is Spine", emphasizing the importance of early diagnosis and intervention to enhance long-term outcomes.

Central cord injury is the most common form of incomplete SCI. It is defined as greater weakness in the upper extremities than the lower extremities, typically present without spinal instability, with patients typically experiencing substantial spontaneous neurological recovery. Historically, early decompression has been avoided in cases of central cord injury due findings of poor outcomes after surgery.[44] However, an analysis of prospective data performed by the Spine Trauma Study Group associated early decompression (<24 h after SCI) with an additional 6.3 points of ASIA motor score recovery and 2.8 times odds of AIS grade improvement at 12-month follow-up as compared to late decompression (≥24 h after SCI).[45] In 2013, a randomized control trial Comparing Surgical Decompression Versus Conservative Treatment in Incomplete Spinal Cord Injury (NCT01367405; n = 72) trial was initiated by Raboud University. The study will compare surgical decompression within 24 h to normal conservative treatment without surgery and is currently recruiting participants.

Steroids for SCI

Methylprednisolone (MPSS) is a potent synthetic glucocorticoid which upregulates anti-inflammatory cytokine release and reduces oxidative stress to enhance neural cell survival in preclinical models of traumatic SCI. The National Acute Spinal Cord Injury Study trial series (1990,[46] 1997[47]) found an increase in the number of infection-related complication (eg, severe sepsis, severe pneumonia) with the high-dose 48-h protocol, which outweighed the potential neurological benefits. However, a shorter 24-h course of IV MPSS (30 mg/kg bolus + 5.4 mg/kg/h × 23 h) had a substantially lower complication rate and, when administered to a subgroup of patients within 8 h of injury, was still found to improve neurological outcomes. These subgroup analyses and the purported methodology have been a source of controversy for the last 3 decades. A 2012 Cochrane review meta-analysis pooling 6 key randomized trials and observational studies was completed which found that patients receiving MPSS within 8 h of injury had a 4-point greater ASIA motor score improvement.[48] This modest benefit can have tremendous functional implications for patients when those motor points are recovered in key myotomes such as hand strength and deltoid function. As a result, an upcoming AOSpine 2016 guideline developed by an international expert panel will suggest 24 h of IV MPSS be considered within 8 h of injury for patients without significant medical contraindication.

Blood Pressure Augmentation

Vascular injury and localized edema contribute to ongoing ischemia in the perilesional region. Blood pressure augmentation has emerged as a viable strategy to neuroprotect at-risk tissue by enhancing perfusion. Current AANS/CNS guidelines recommend maintenance of mean arterial pressure

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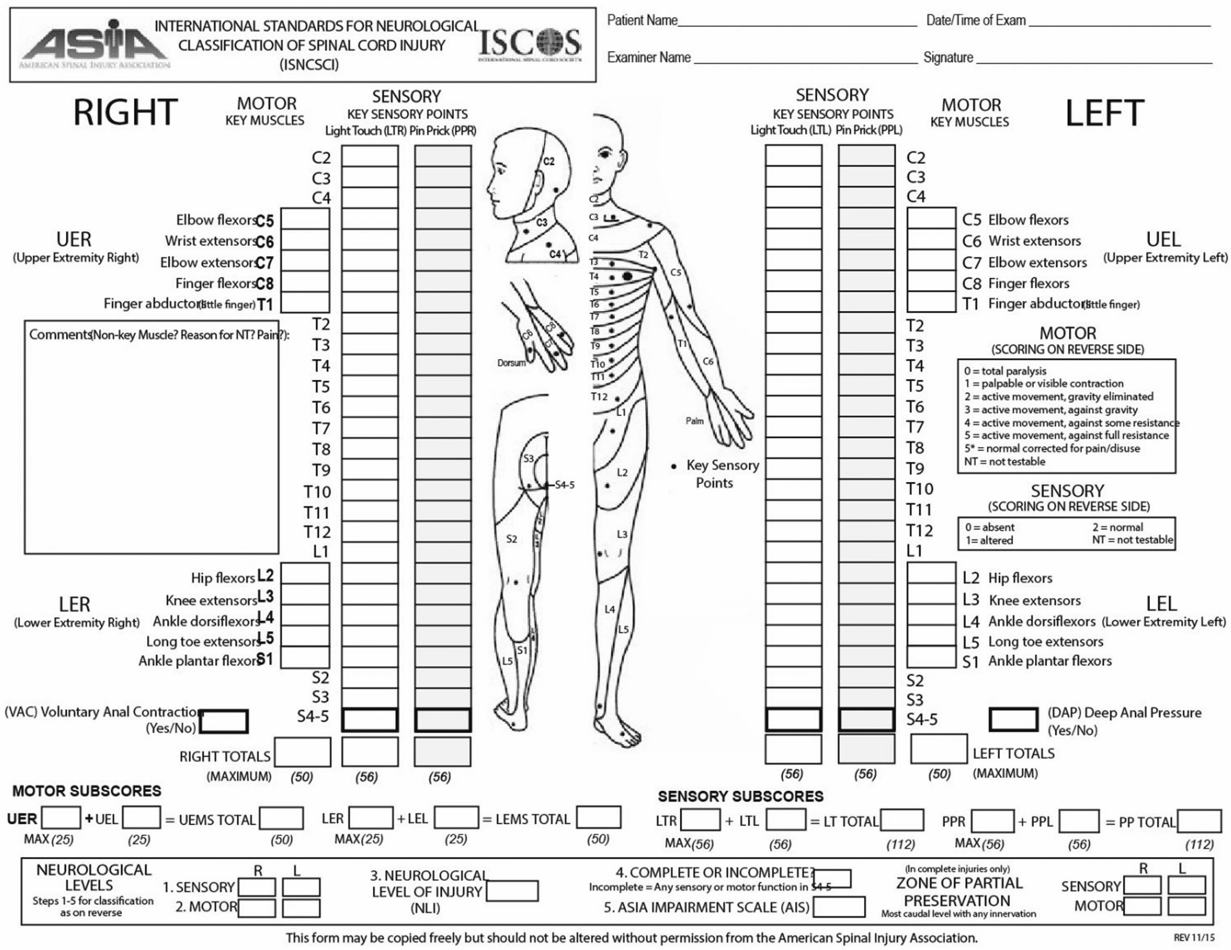

FIGURE 3. *International Standards for Neurological Classification of Spinal Cord Injury clinical examination form. The standardized assessment and calculation of motor and sensory scores is demonstrated on this template. Reprint of the 2015 American Spinal Injury Association and International Spinal Cord Society ISNCSCI assessment form retrieved from http://asia-spinalinjury.org/wp-content/uploads/2016/02/International_Stds_Diagram_Worksheet.pdf.*

(MAP) $\geq$ 85 to 90 mm Hg for 7 days postinjury as this has been found to enhance long-term AIS grade outcomes for patients.[5] In application, this most often necessitates invasive blood pressure monitoring, IV fluid therapy, and central venous access for continuous infusion of vasopressors.[49] These substantial requirements have prompted a noninferiority trial entitled Mean Arterial blood Pressure Treatment for Acute Spinal Cord Injury (NCT02232165) comparing MAP $\geq$ 85 mm Hg vs MAP $\geq$ 65 mm Hg with results expected by 2017.[3]

These requirements can also be a significant hindrance to early mobilization, an important component of cardiorespiratory and dermatologic complication prevention. A collaborative interdisciplinary approach utilizing adjunctive measures such as prophylactic vasopressors, abdominal binding, and assistive devices is often required to safely elevate patients. The precise timing of mobilization is dictated by the patient's hemodynamic status and the expertise of the treating team.[50]

KEY TRIALS IN NEUROPROTECTION

In addition to early decompression, MAP augmentation and IV MPSS, several other neuroprotective strategies targeting key components of the secondary injury cascade have emerged in preclinical research.[51] The most promising therapies currently being translated are discussed in this section.

Pharmacological Therapies

Riluzole

Riluzole is a benzothiazole sodium channel blocker currently approved by the US Food and Drug Administration, European

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Medicines Agency, and Health Canada for the treatment of amyotrophic lateral sclerosis.[52,53] It protects against excitotoxic cell death by blocking sodium influx in injured neurons and restricting the presynaptic release of glutamate.[54] Animal studies in SCI have demonstrated its ability to reduce neuronal loss and cavity size while improving sensorimotor and electrophysiological outcomes.[55-58] A collaborative effort to study Riluzole for SCI is being led by the corresponding author (MGF) and includes the North American Clinical Trials Network, AOSpine, the Ontario Neurotrauma Foundation, and the Rick Hansen Institute. This phase II/III randomized controlled trial (RCT) (n = 351) entitled "Riluzole in Spinal Cord Injury Study" (RISCIS; NCT01597518) is currently recruiting patients with acute C4-8 ASIA grade A/B/C injuries and will assess multiple outcomes including the AIS, Brief Pain Inventory, and Spinal Cord Independence Measure.[3] The study is expected to conclude in 2018.

Magnesium

Magnesium can act as an N-methyl-D-aspartate (NMDA) receptor antagonist to decrease excitotoxicity and also functions as an anti-inflammatory agent. Stable cerebrospinal fluid (CSF) levels can be generated by delivering magnesium with an excipient such as polyethylene glycol (PEG).[59-61] In animal models, the Mg-PEG combination has been shown to enhance tissue sparing and lead to behavioral recovery.[62,63] A phase I trial (n = 15; NCT01750684) of an Mg-PEG combination (AC105) led by Acorda Therapeutics Inc. (Ardsley, New York) concluded in February 2015 with results pending report.[3]

Minocycline

Minocycline is a second-generation bacteriostatic tetracycline antibiotic that has demonstrated neuroprotective properties in preclinical models of CNS disorders including Huntington's disease and multiple sclerosis.[64,65] This stems in part from its significant anti-inflammatory effect mediated by inhibition of microglial activation, IL-1β, TNF-α, cyclooxygenase-2, and matrix metalloproteinases.[66-69] In animal studies, minocycline treatment after acute SCI has been shown to reduce lesion size and promote tissue sparing.[70,71] A phase II trial demonstrated that patients with acute incomplete cervical SCI (n = 25) may benefit from early minocycline administration as they found a 14-point ASIA motor score improvement compared to placebo ($P = .05$).[72] This exciting result led to the development of a phase III trial (n = 248) entitled 'Minocycline in Acute Spinal Cord Injury' (NCT01828203) which will assess intravenously administered minocycline for 7 days vs placebo and is expected to report by 2018.[3]

Monosialotetrahexosylganglioside (GM-1) Ganglioside

GM-1 is a glycosphingolipid found in cell membranes with the ability to activate receptor tyrosine kinases to enhance neural plasticity and regeneration. It has been successfully used for neuroprotection in animal models of SCI where it enhanced tissue sparing.[73] A successful phase II trial (n = 37) found improved 1-year ASIA motor scores for those receiving daily GM-1 for 18 to 32 days postinjury.[74] Unfortunately, a follow-up phase III RCT (n = 797) found no statistically significant improvement with treatment.[75] No further studies have been registered.

Fibroblast Growth Factor

Fibroblast growth factor is a heparin-binding protein found to be neuroprotective against excitotoxicity while also reducing oxygen-free radical generation.[76] In animal models, it has been shown to reduce motor neuron loss and improve respiratory deficits.[77,78] A phase I/II trial (n = 62; NCT01502631) of the fibroblast growth factor-analog, SUN13837 (Asubio Pharmaceuticals Inc., Edison, New Jersey), completed in 2015 with results pending publication.[3]

Granulocyte Colony-stimulating Factor

Granulocyte colony-stimulating factor (G-CSF; CSF 3) is a cytokine glycoprotein found in numerous tissues throughout the body. It is capable of promoting cell proliferation, survival, and mobilization. In the CNS, it has been shown to facilitate survival of ischemic cells and reduce inflammatory cytokine expression (eg, TNF-α, IL-1β).[79-81] A recent pair of nonrandomized phase I/IIa trials showed no increase in serious adverse events with G-CSF administration while also demonstrating improvement in AIS outcomes.[82,83] Additional well-designed RCTs will be required to establish the efficacy of G-CSF for SCI.

Hepatocyte Growth Factor

Hepatocyte growth factor (HGF) is a prosurvival, promotility c-Met receptor ligand. In small animal SCI models, HGF increases neuron survival and decreases oligodendrocyte apoptosis resulting in improved behavioral outcomes.[84-86] More recently, HGF has been shown to promote angiogenesis and enhance upper limb recovery in a primate model of cervical SCI.[85] A phase I/II randomized trial (n = 48; NCT02193334) of KP-100IT (HGF; Kringle Pharma Inc., Osaka, Japan) is now underway with results expected in 2017.[3]

Nonpharmacologic Therapies

Therapeutic Hypothermia

Therapeutic hypothermia (TH; 32°C-34°C) significantly reduces the basal metabolic rate of the CNS and decreases inflammatory cell activation.[87] It has been successfully applied in neonatal hypoxic-ischemic encephalopathy and after in-hospital cardiac arrest.[88-90] In preclinical SCI models, it has been shown to enhance tissue sparing and promote behavioral recovery prompting a pilot study (n = 14) of early systemic TH for patient with AIS A injuries which found no increase in complication rates and a trend toward increased neurological recovery (43% vs 21%).[91,92] A phase II/III trial entitled Acute Rapid Cooling Therapy for Injuries of the Spinal Cord has been planned to definitively assess efficacy.

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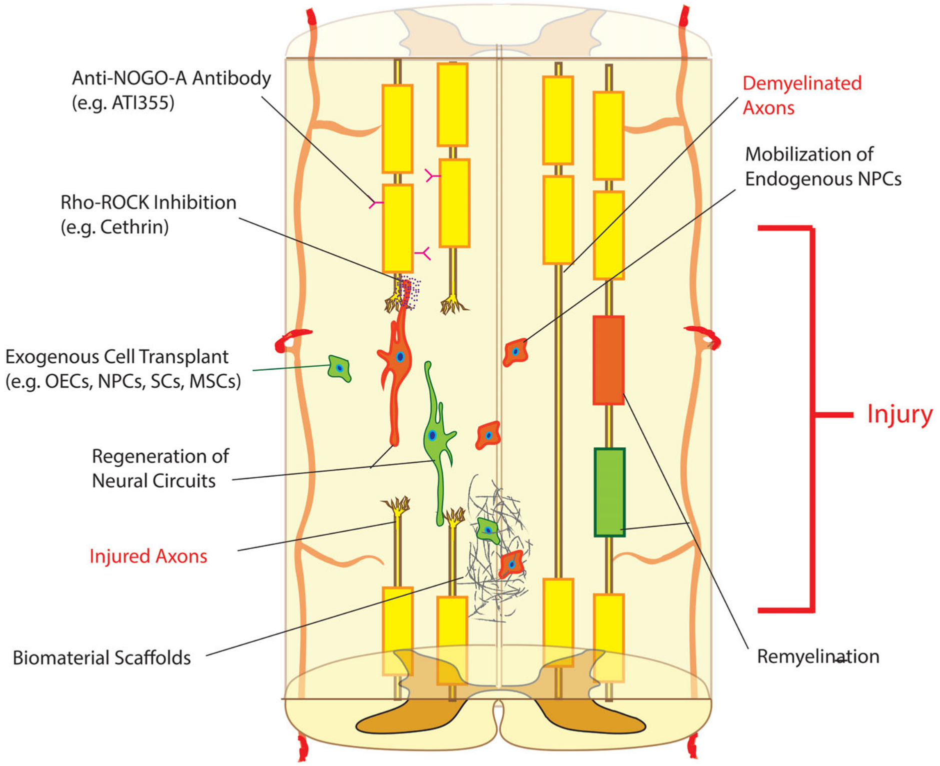

FIGURE 4. *Neuroregenerative strategies for spinal cord injury. Schematic of a traumatic SCI with demyelination and loss of axons. Regenerative therapies actively being translated are shown including anti-NOGO-A antibody treatment (eg, ATI355), Rho-ROCK inhibition (eg, Cethrin [Vertex Pharmaceuticals]), cell transplants (eg, iPSC-NPC, ES-NPC, OEC, SC, BMC, MSC), implantation of biomaterials, and mobilization of endogenous cell pools (eg, Metformin). Adapted from Ahuja C, Fehlings, M. How can we regenerate the traumatically injured spinal cord? Neurology Central (2016), © Michael Fehlings.*

CSF Drainage

CSF drainage attempts to prevent cord hypoperfusion in the critical postinjury period by relieving pressure analogous to external ventricular drainage (EVD) for raised intracranial pressure (ICP). A phase I/II trial (n = 22) completed in 2009 found no significant improvement outcomes with drainage; however, the study was not sufficiently powered to demonstrate efficacy.[93] Recent large-animal trials have found that CSF drainage acts synergistically with MAP augmentation to improve cord blood flow.[94] Based on these key results, a phase IIB trial (N = 60; NCT02495545) of MAP elevation with CSF drainage has been launched with results expected by December 2017.[3]

KEY TRIALS IN NEUROREGENERATION

While timely neuroprotective interventions can have tremendous benefits in the acute injury period, the majority of our patients are in the chronic phase of their injuries where further recovery is limited. This section discusses emerging neuroregenerative therapies in clinical trial or on the cusp of translation (illustrated in Figure 4).

Pharmacological Therapies

Rho-ROCK Inhibitor

Components of the injured adult CNS including CSPGs, myelin-associated glycoproteins, and NOGO potently inhibit axon outgrowth and attempts at regeneration via the Rho-ROCK signaling pathway. Cethrin/VX-210 (Vertex Pharmaceuticals, Boston, Massachusetts) is a direct Rho inhibitor applied intraoperatively within a fibrin glue sealant to the epidural space.[95] A mixed open-label phase I/IIa trial (n = 48; NCT00500812) of patients with cervical or thoracic injures found no increase in serious adverse events and a significant improvement in long-term motor scores (18.5 ASIA points) for cervical patients.[96] These very exciting results have led to a phase III trial in patients with acute cervical SCI which has commenced in 2016.

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Anti-NOGO Antibody

Anti-NOGO is a monoclonal antibody against NOGO-A, a major inhibitor component of adult CNS myelin. Anti-NOGO treatment delivered by intrathecal injection has been shown to promote axonal sprouting and functional recovery in animal models by clearing the source of this inhibitory signaling.[97] A phase I trial (n = 51; NCT004060160) of humanized anti-NOGO antibody (ATI-355; Novartis, Basel, Switzerland) has been completed with results pending dissemination.[3] A European group led by Professor Armin Curt is planning on carrying forward with additional trials with the anti-NOGO antibody in patients with SCI.

Nonpharmacologic Therapies

Spinal Cord Stimulation

Spinal cord stimulation (SCS) has been used to successfully treat refractory chronic pain for disorders ranging from SCI to phantom limb pain. In animal models, weakly imposed DC electrical fields have been shown to promote cathode-directed neurite outgrowth while oscillating DC fields can promote bidirectional regeneration.[98] Recently, a small human study has shown that SCS combined with rehabilitation can provide gradual recovery of voluntary lower limb movement even years after a complete injury.[99] Additional trials (NCT02592668, NCT02313194) are now ongoing to assess safety/feasibility and validate this exciting finding with results expected by 2018. Another potential application, shown in a rodent model, is the application of SCS in combination with stem cell transplants to enhance the survival and migration (galvanotaxis) of grafted cells beyond the region of injection.

Cell Therapies

Cell-based regenerative therapies are an exciting field as transplanted cells are capable of filling many roles including providing trophic support, modulating the inflammatory response, regenerating lost neural circuits, and remyelinating denuded axons.[100-102] Early research utilized embryonic stem cells (ESCs), however, ethical concerns and limited supplies have driven the field towards induced pluripotent stem cell (iPSCs) which can be derived from any somatic cell, including autologous sources.[103] While unanticipated challenges have arisen, including early senescence and retained epigenetic memory, iPSCs remain a key therapeutic approach moving forward. Numerous animal studies over the last 3 decades have demonstrated the beneficial effects of a range of transplanted cell types. The most clinically relevant approaches are discussed here.

Neural Stem/Precursor Cells

Derived from stem cells, multipotent neural precursor cells (NPCs) are capable of differentiating to CNS-specific neurons, oligodendrocytes, and astrocytes, making them a particularly promising strategy. In animal studies, they are capable of integrating with host circuits to enhance behavioral recovery over several weeks.[104,105] A pair of phase II trials by Stem Cells Inc. (Newark, California) of human CNS stem cell transplants for cervical (n = 31; NCT02163876) and thoracic (n = 12; NCT01321333) injury were terminated in 2016 prior to completion. While results regarding sensorimotor outcomes are pending dissemination, preliminary data suggest no increase in complications rates related to the treatments.[3] This provides confirmation of existing safety data that intraparenchymal stem cell transplants are feasible and suggests further optimization of the cells and/or their environment is required to produce meaningful changes in functional recovery.

A parallel strategy to specifically target postinjury demyelination is the transplant of oligodendrocyte precursor cells (OPCs) which preferentially differentiate to functional oligodendrocytes. Asterias Biotherapeutics Inc. (Fremont, California) has launched an open-label phase I/II dose-escalation trial (n = 35; NCT02302157) of their AST-OPC1 cell line with long-term outcome measures including adverse events and serial ISNCSCI exams. The study is expected to complete in 2018.[3]

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are multipotent cells capable of repairing connective tissues by differentiating to myocytes, osteoblasts, chondrocytes, and adipocytes.[106] They can also modulate local and systemic inflammation which has been exploited in animal models of SCI where MSC treatment led to a decrease in peripheral inflammatory cell infiltration and an increase in parenchymal tissue volume.[107-111] A phase II/III RCT (n = 32; NCT01676441) by Pharmicell Co. (Seoul, South Korea) studying intraparenchymal and intrathecal MSC treatment for patients with acute AIS B injuries is ongoing with results expected in 2016.[3]

Schwann Cells

The robust regeneration seen in the PNS is thought to be mediated in large part by Schwann cells (SCs). In animal models of SCI, peripheral SCs transplanted into the CNS were found to remyelinate axons, reduce cystic cavitation, and enhance recovery.[112] An open-label phase I trial (n = 10; NCT02354625) by the Miami Project to Cure Paralysis is now investigating SCs in the treatment of patients with chronic AIS A, B, and C cervical or thoracic injuries with results expected by 2018.[3]

Olfactory Ensheathing Cells

Olfactory ensheathing cells (OECs) protect olfactory neurons exposed to the harsh conditions of the nasal mucosa. They rapidly phagocytose debris and microbes while also providing trophic support through growth factor signaling.[113-116] In animal models, OECs have been shown to induce regeneration in reapposed dorsal roots after brachial plexus avulsion injuries resulting in substantial recovery of proprioception.[117] Clinical studies of OECs for brachial plexus avulsions are now in preparation by researchers in the UK. OECs harvested from the

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nasal mucosa have also been transplanted into the spinal cord for SCI and have been shown to improve neurite outgrowth and endogenous remyelination resulting in impressive behavioral recovery in animal models.[118] Numerous clinical trials of OECs for chronic SCI have been completed worldwide and analyzed in a meta-analysis (cumulative n = 1193) which found no significant increase in complication rates related to the transplant. Efficacy could not be definitively established due to the quality of the studies.[119]

Biomaterials

Regeneration is often hindered by the presence of a substantial postinjury cystic cavity, which lacks the substrate to support cell migration and axon growth. Biomaterials have emerged as an exciting strategy to fill cavitation defects and reproduce the complex structural architecture of the extracellular matrix.[120-124] Many of these materials can be engineered to biodegrade over time, release growth factors, and can even be seeded with stem cells to enhance engraftment.[97,98] Several biomaterials have been shown to be effective in animal models of SCI from the acute to chronic phases (eg, HAMC,[121] QL6,[125,126] fibrinogen,[127] etc). As the technology evolves, more niche-specific biomaterials are expected to emerge with extended drug-release and cell support capabilities. Currently, a phase III trial (n = 20; NCT02138110) of InVivo Therapeutics' Neuro-Spinal Scaffold (Cambridge, Massachusetts) is now recruiting patients with acute AIS A thoracic injuries.[3] Results are expected in 2017.

FUTURE DIRECTIONS

The next substantial changes in the management of patients with SCI are likely to be translated from research that adapts to the heterogeneity of SCI. Modified trial designs which specifically target SCI subpopulations are likely to have the greatest impacts on long-term functional recovery. Stratifying patients in this way will require a combination of existing metrics (eg, clinical exam, radiography) and novel assessment techniques (eg, advanced imaging, biochemical biomarkers).

While many novel treatments show promise in animal models of SCI, these experimental paradigms typically involve very controlled injury and recovery conditions after biomechanically precise injuries in animals matched for age, weight, gender, species, and, in some cases, genetic background. This obviously pales in comparison to the natural variability that occurs in the acute human SCI setting. The appreciation of the heterogeneity of human SCI is partly the result of the challenges that have been experienced in the execution of clinical trials of novel therapies, particularly in the acute setting. Variability in neurological recovery requires that many patients be recruited to complete such acute clinical trials in order to be sufficiently powered. Difficulties in achieving such recruitment has plagued the conduct of virtually all acute clinical studies, and the failure to enroll sufficiently large patient cohorts within realistic time frames has resulted in the premature cessation of numerous clinical trial programs. New approaches to overcome this will be needed in the future to facilitate the conduct of such clinical trials and enhance the speed with which novel treatments for SCI can be validated. Such approaches include narrowing the inclusion window to be more specific in the types and severities of cord injuries being studied, and establishing objective biomarkers for the stratification of injury severity and more precise prediction of neurological outcome.

Seminal large-scale clinical trials for SCI have typically used broad inclusion criteria to bolster recruitment across participating centers. However, post hoc subgroups analyses have now demonstrated that patient characteristics, presentations, and the underlying pathophysiology in SCI can be highly heterogeneous which can influence the relationship between treatments and outcomes.[46-48,128,129] As a result, more recent studies are recruiting carefully selected populations. The upcoming Riluzole in Spinal Cord Injury (RISCIS; NCT01597518) trial is an example where recruitment is limited to patients with C4-8 injuries and ASIA grades A, B, or C.[3,58] Other clinical initiatives have similarly restricted inclusion both with regard to the level of injury (cervical vs thoracic), severity of injury (AIS grade A, B, or C), and timing of intervention. While logistically demanding, this careful selection will allow a more valid assessment of the drug's efficacy.

The next generation of trials will also need to further define subpopulations based on quantifiable imaging and biochemical biomarkers. MRI is a key imaging modality for most CNS pathologies; however, its adoption in SCI trials has been limited. This is likely because the most common sequences (T1- and T2-weighted) rely on gross measurements of hemorrhage and compression providing only modest utility in predicting outcomes. Future MR imaging will need to quantify the cord microstructure to better estimate damage and recovery potential. Emerging techniques for this include diffusion tensor imaging (axon integrity), myelin water fraction (myelination), MR spectroscopy (gliosis or ischemia), and functional MRI (connectivity).[130,131]

Biochemical biomarkers are also being extensively explored. The Canadian Multicentre CSF Monitoring and Biomarker Study (NCT01279811) is testing CSF over 5 days for inflammatory cell proteins, interleukins, and other cytokines.[3] Specific proteins, such as IL-6, S100β, and tau within the CSF of acute SCI patients have been shown to be able to objectively stratify injury severity and predict AIS grade and motor score improvement.[132,133] An additional class of biomarkers currently under study through the Rick Hansen Institute is micro RNAs (miRNA), which are short noncoding RNA segments that can regulate post-transcriptional gene expression. miRNAs are specifically up- or downregulated with varying grades of SCI, and may hold important prognostic information as they are further understood.[134] Together these biomarkers will yield important data to help identify subgroups within the heterogeneous SCI population, and when combined with clinical examination, will

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allow patients to be stratified by their specific pathophysiologic niche into targeted trials.

CONCLUSION

The breadth of therapeutic approaches discussed within this review and the rapidly evolving management of a patient with SCI highlight the excitement and progress continuing to be made in the field. The collaborative effort of thousands of physicians, scientists, and allied health professionals has generated a treatment pipeline with numerous promising therapies likely to see translation over the next decade.

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