Emerging therapies for acute traumatic spinal cord injury

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There are currently about 85 000 Canadians living with spinal cord injuries, more than half of which are secondary to trauma.[1] As the population ages, the incidence and prevalence of traumatic spinal cord injury are expected to increase, primarily as a result of fall-related injuries among older adults[2]. Therefore, treating spinal cord injuries is relevant not only to spine surgeons and physiatrists, but also to the general clinician who will increasingly encounter such patients in the emergency department or family practice.

Here, we review relevant pathophysiology and recent evidence pertaining to the medical, surgical and cellular-based treatment of acute traumatic spinal cord injury. Most of the identified pharmacologic studies were randomized trials or early phase nonrandomized prospective studies. Research relating to the remaining topics was predominately observational in design (Box 1).

What mechanisms underlie neural injury and repair?

The initial trauma, or primary injury to the spinal cord, starts a sequence of pathological events collectively referred to as secondary injury. These secondary mechanisms begin within seconds of the primary injury and continue for several weeks thereafter, leading to an expanded region of tissue destruction (Figure 1). The initial disruption of the spinal cord vasculature leads to the development of microhemorrhages in the grey and white matter, interstitial edema and the release of coagulation factors and vasoactive amines.[3] These events promote thrombosis and vasospasm of the microvasculature of the spinal cord causing tissue hypoxia and impaired neuronal homeostasis. At the cellular level, impairments include ionic imbalance, peroxidation of membrane lipids, formation of free radicals and release of toxic levels of the excitatory neurotransmitter glutamate.[4] Neuroprotective agents act to mitigate secondary injury mechanisms to reduce the extent of neural damage.

The regenerative capacity of the neurons of the central nervous system (CNS) is severely limited compared with neurons in the peripheral nervous system, largely because of the production of inhibitory molecules that thwart axonal growth, preventing regeneration of injured nerve tracts. Nogo is a family of inhibitory proteins that bind to the Nogo receptor found on regenerating axons.[5] This binding leads to the activation of the Rho pathway, causing inhibition of both axonal growth and neuronal cytoskeletal development.[6] In contrast to neuroprotective therapies, which limit the extent of acute neural injury, neuroregenerative therapies facilitate neuronal regrowth by several mechanisms, including the blockade of these inhibitory pathways.

What supportive and surgical management is effective?

Historically, it was common for patients with spinal injuries to be placed in unmonitored beds on hospital wards for prolonged periods while elements of the bony injury healed. This approach has been supplanted by aggressive medical and surgical methods focused on maintaining cord perfusion, avoiding complications, decompressing the spinal cord and restoring spinal stability.[7]

Medical support

The negative consequences of hypotension on the injured CNS are well established.[8] There is consistent evidence that avoiding hypotension and

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KEY POINTS

- Hemodynamic support to maintain mean arterial pressure at 85–90 mmHg and monitoring in an intensive care unit for the first week after spinal cord injury are recommended.

- Decompressive surgery within 24 hours after injury has been shown to be safe and feasible; in prospective nonrandomized trials, it has been associated with improved rates of neurologic recovery.

- Intravenous methylprednisolone has been used as a neuroprotective strategy based on limited evidence, but this is not a standard of care and may be associated with an increased risk of complications.

- The safety of cellular transplantation in human spinal cord injury is under study in early phase clinical trials, but is currently purely an investigational therapy

- Early phase clinical trials are investigating potential regenerative (e.g., Rho and Nogo inhibitors) and neuroprotective (e.g., riluzole, minocycline, hypothermia) therapies.

maintaining aggressive blood pressure targets during the acute phases after injury improves neurologic recovery and reduces mortality.[9] Based on existing, largely retrospective data, the American Association of Neurological Surgeons recommends that patients' mean arterial pressure be maintained at 85–90 mmHg for the first 7 days after injury.[10] When volume replacement is inadequate to achieve this goal, intravenous vasopressor medications may be introduced.

Patients, particularly those with severe cervical injuries, should receive treatment in an intensive care unit (ICU) with continuous cardiac, hemodynamic and respiratory monitoring for the first 7–14 days after injury. In observational studies, the standardized admission of patients with spinal injuries to an ICU has been associated with reduced mortality and morbidity, in addition to improved neurologic recovery.[11]

Surgical decompression

The preclinical literature provides a strong biological imperative to decompress the spinal cord early after injury.[12] In spite of compelling laboratory findings, for many years, surgeons were reluctant to operate acutely owing to concerns that perioperative hemodynamic changes would compromise cord perfusion.[13] In addition, until the proliferation of instrumented spinal fixation techniques in the 1990s, decompression meant further destabilizing an already unstable spine.

Retrospective studies provide conflicting results as to the effect of early surgery on neurologic recovery, but all have shown early decompression to be safe.[14] The Surgical Timing in Acute Spinal Cord Injury Study (STASCIS),[15] a prospective, multicentre, nonrandomized cohort study, compared 313 patients who underwent either early (< 24 h after injury) or late (≥ 24 h after injury) surgical decompression. Early surgery was associated with better neurologic recovery at 6 months as defined by a 2-grade improvement in the American Spinal Injury Association impairment scale (odds ratio [OR] 2.57, 95% confidence interval [CI] 1.11 to 5.97),

with no increase in acute complications compared with late surgery (24.2% v. 30.5%, $p = 0.21$). These results validate those of recent consensus surveys suggesting surgeon preference toward early decompression.[16]

In the specific case of dislocation of the cervical spine, rapid closed reduction of the spine using skeletal traction remains a valid treatment option. In this case, surgery is performed after closed reduction to re-establish spinal stability.

Therapeutic hypothermia

Preclinical studies have suggested that cooling mitigates secondary injury mechanisms.[17] Initial clinical studies involving direct cooling of the cord during surgery failed to show any benefit. However, a recent phase I trial investigated the acute use of modest (33°C) systemic intravascular hypothermia.[18] Complications did not differ between the 14 patients receiving the treatment and the 14 patients to whom they were matched in the control group. At 1-year follow-up, 6 of 14 patients in the treatment group (42.9%) converted from complete (no motor or sensory function below the level of injury) to incomplete (motor or sensory function present below the level of injury) status (3/14 [21.4%] of patients in the control group showed the same degree of recovery), which compares favourably with a neurologic recovery rate of 20% reported in the literature. Although there is currently insufficient evidence to support the use of systemic hypothermia, a multicentre efficacy trial exploring this therapy is being planned.

What drugs have been evaluated for treating spinal cord injury?

To date, 5 pharmacologic therapies have been evaluated in phase III trials (Table 1).[19–23] None of them have become standard of care.

Neuroprotective agents

Methylprednisolone sodium succinate
Methylprednisolone, which attenuates the peroxidation of membrane lipids and post-traumatic inflammation, has consistently been associated with improved neurobehavioural outcomes in preclinical studies.[24] However, the use of methylprednisolone in the clinical setting remains controversial. The most recent Cochrane review pooled the results of 3 studies (meta-analyses) and found no effect for a high-dose 24-hour infusion of methylprednisolone in terms of motor recovery at 6 months (weighted mean difference 0.85, 95% CI –1.79 to 3.49).[25] However, when

started within 8 hours after injury, methylprednisolone was associated with an additional 4-point improvement in NASCIS motor score (weighted mean difference 4.06, 95% CI 0.58 to 7.55).[25] Trends toward increased rates of gastrointesinal hemorrhage (relative risk [RR] 2.18, 95% CI 0.80 to 5.93) and wound infections (RR 2.11, 95% CI 0.81 to 5.49) were seen among patients receiving methylprednisolone.[25] Critics of the drug cite these complications, as well as the use of subgroup analyses to prove effect, as arguments against its use.[26] Balancing the available evidence, consensus guidelines recommend that 24-hour infusion of methylpred-
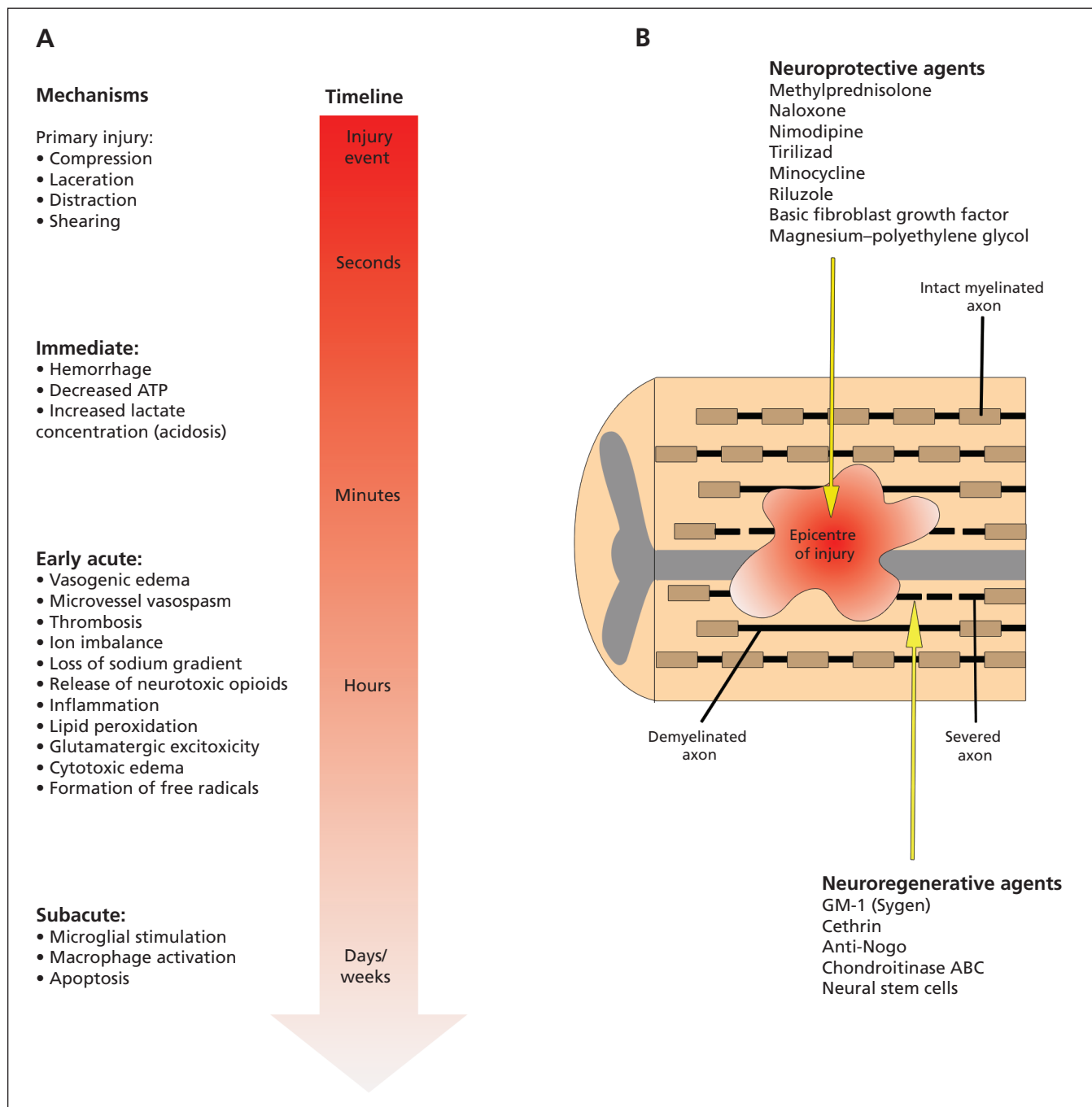

Figure 1: (A) Primary and secondary mechanisms of injury determining the final extent of spinal cord damage. The primary injury event starts a pathobiological cascade of secondary injury mechanisms that unfold in different phases within seconds of the primary trauma and continuing for several weeks thereafter. **(B)** Longitudinal section of the spinal cord after injury. The epicentre of the injury progressively expands after the primary trauma as a consequence of secondary injury events. This expansion causes an increased region of tissue cavitation and, ultimately, worsened long-term outcomes. Within and adjacent to the injury epicentre are severed and demyelinated axons. The neuroprotective agents listed act to subvert specific secondary injuries and prevent neural damage, while the neuroregenerative agents act to promote axonal regrowth once damage has occurred. ATP = adenosine triphosphate.

nisolone, started within 8 hours after injury, is a treatment option that should only be undertaken with knowledge of the potential complications.[27]

Other medications

Other treatments studied for neuroprotection include naloxone, an opioid antagonist that blocks the neurotoxic effects of the endogenous opioid dynorphin A;[19,28] tirilazad, a nonglucocorticoid 21-aminosteroid developed to inhibit the peroxidation of neuronal membranes;[22] and nimodipine, a calcium-channel blocker that prevents calcium-dependent activation of destructive cellular enzymes and presynaptic glutamate release.[21,29] Although each of these agents showed efficacy in animals studies, clinical trials of naloxone versus placebo,[19] tirilazad versus methylprednisolone[22] and nimodipine versus placebo[21] have all failed to show differences in motor recovery.

Neuroregenerative agents

GM-1 (Sygen)

Gangliosides are complex glycolipid molecules comprising an important structural component of neuronal membranes. Laboratory studies have shown that gangliosides can enhance axonal

Table 1: Pharmacologic agents evaluated in phase III trials for acute treatment of traumatic spinal cord injury

Drug	Purported mechanism	No. of RCTs evaluating drug	Evidence for use
Methylprednisolone sodium succinate	• Attenuates peroxidation of the neuronal membrane • Reduces TNF-α release • Improves perfusion of spinal cord • Reduces influx of neuronal calcium	3 (evaluating high-dose 24-h infusion v. placebo)[19–21] 1 (evaluating high-dose 48-h infusion v. high-dose 24-h infusion)[22]	High-dose 24-h infusion:* • No difference in NASCIS† motor score recovery v. placebo in overall analysis (weighted MD 0.85 [95% CI –1.79 to 3.49]) • Improved NASCIS motor score recovery in subgroup receiving treatment within 8 h of injury v. placebo (weighted MD 4.06 [95% CI 0.58 to 7.55]) • Trend toward increased wound infection rates (RR 2.11 [95% CI 0.81 to 5.49]) and GI bleeding (RR 2.18 [95% CI 0.80 to 5.93]) in steroid group High-dose 48-h infusion: • No difference in NASCIS motor score recovery in overall analysis v. 24-h infusion (MD 3.37 [95% CI –0.54 to 7.28]) • Trends toward increased rates of severe sepsis (RR 4.0 [95% CI 0.45 to 35.38]) and pneumonia (RR 2.25 [95% CI 0.71 to 7.15]) v. 24-h infusion
Naloxone	• Blocks the neurotoxic effects of the endogenous opioid dynorphin A	1 (v. placebo)[19]	• No difference in NASCIS motor score recovery between treatment and placebo groups
Nimodipine	• L-type calcium-channel blocker • Prevents activation of calcium-dependent apoptotic enzymes and blocks presynaptic release of glutamate	1 (v. placebo)[21]	• No difference in motor neurologic status between treatment (ASIA motor score‡ 67 [95% CI 50 to 95]) and placebo groups (ASIA motor score 72 [95% CI 50 to 94] at 1 year
Tirilazad mesylate	• Attenuates peroxidation of neuronal membrane	1 (v. 24-h infusion of methylpred-nisolone)[22]	• No difference in NASCIS motor score recovery between tirilazad and 24-h infusion of methylprednisolone • No placebo-controlled evaluation available
GM-1 ganglioside (Sygen)	• Important component of CNS neuronal membranes • Facilitates regrowth and regeneration of axons • Several neuroprotective properties	1 (v. placebo)[23]	• No difference in marked neurologic recovery between treatment and placebo groups as defined by at least a 2-grade improvement in modified Benzel scale§ grade

Note: ASIA = American Spinal Injury Association, CI = confidence interval, GI = gastrointestinal, CNS = central nervous system, MD = mean difference, NASCIS = National Acute Spinal Cord Injury Study, RCT = randomized controlled trial, RR = relative risk, TNF = tumour necrosis factor.
*Results of a meta-analysis combining the results of 3 studies.
†Ordinal score between 0 and 35 reflecting the motor power in 7 key muscle groups on the right side of the body. A higher score suggests better motor function.
‡Orginal score between 0 and 100 reflecting the motor power in 10 key muscle groups on both sides of the body. A higher score suggests better motor function.
§Ordinal scale between 1 and 7. A higher score suggests superior neurologic status.

regeneration after injury.[30] In addition, a variety of neuroprotective effects have been attributed to these compounds. However, a randomized placebo-controlled trial of the ganglioside compound GM-1 (Sygen) involving 760 patients[23] reported no difference in the proportion of patients achieving marked neurologic recovery at 6 months, although quantitative results were not presented.

What drugs are in development for treating spinal cord injury?

Several neuroprotective and neuroregenerative agents targeting specific pathological mechanisms are currently in the midst of clinical translation. Although promising, these agents have yet to show efficacy in phase III trials.

Neuroprotective agents

Riluzole
Riluzole is a sodium-channel blocker approved by the US Food and Drug Administration and Health Canada for the treatment of amyotrophic lateral sclerosis (ALS), in which it reduces motor neuron degeneration, thereby prolonging survival.[31] In preclinical models of spinal cord injury, riluzole mitigates secondary injury by blocking pathological activation of sodium channels and reducing the release of neuronal glutamate.[4] A phase I/II trial evaluating the safety and pharmacokinetics of riluzole for injuries in humans began in 2010 and was completed in January 2012, with full results awaiting publication.[32,33]

Minocycline
Minocycline, a chemically modified form of tetracycline, has shown to be neuroprotective in animal injury models, although its exact mechanisms of action remain incompletely understood.[34] Its use in other clinical conditions, such as acne, shows it has a favourable safety profile in humans. In a randomized placebo-controlled phase II trial, minocycline was associated with a trend toward improved motor recovery at 1 year (difference in American Spinal Injury Association motor score 6 points, 95% CI –3 to 14, $p = 0.20$).[35] A single case of transiently elevated serum transaminases was the only drug-related complication reported.

Basic fibroblast growth factor
Injection of basic fibroblast growth factor has been shown to improve functional and respiratory parameters in animal injury models, presumably by reducing glutamate-mediated excitotoxicity.[36] A recombinant version of this molecule is the subject of a phase I/II trial currently recruiting patients.

Neuroregenerative agents

Cethrin
BA-210 is a bacterial-derived toxin that inhibits the Rho pathway of inhibitory proteins and promotes axonal growth in vitro. When combined with a biohemostatic adhesive, BA-210 forms a permeable paste called Cethrin that is applied to the dura of the spinal cord postinjury. Based on documentation of preclinical efficacy, a phase I/IIa trial was undertaken during which 1 of 2 Cethrin dosages was applied to the dura during surgery in 48 patients with complete injuries.[6] No serious complications were attributed to Cethrin at 1-year follow-up. Furthermore, among patients receiving doses of 1 and 3 mg, those with cervical injuries showed improvement on the American Spinal Injury Association motor score (mean of 27 points for patients in the 1 mg group and 21 points for patients in the 3 mg group). Such improvements compare favourably to the 10 points of motor recovery reported for similar patients in historical case series.

Anti-Nogo
Nogo-A is a protein that has been shown to block axonal growth in the human CNS.[37] Anti-Nogo is a monoclonal antibody engineered to target Nogo-A and promote neural regeneration.[38] This drug is currently in the early stages of clinical investigation.

What is the current status of cellular transplantation as a treatment option?

The transplantation of stem cells and autologous non–stem cells has been intensively studied in preclinical injury models. Various cellular subtypes have been used for this purpose, seeking optimal balance of the one or more key mechanisms through which each is theorized to act (release of growth-promoting trophic factors, environmental modification [i.e., reduction of scar or inflammation] and cellular replacement). In preclinical studies, cellular transplantation, either alone or in combination with other therapies, has been associated with enhanced neurobehavioural recovery, with no single cellular subtype showing superiority.[39] Although prematurely used to treat patients with spinal injuries in several countries, no study has established efficacy for the transplantation of any cellular line. However, in the existing early phase trials, major

adverse events related to transplantation have been rare. When interpreting the results of clincal studies involving transplantation of cellular subtypes (Table 2),[40-48] it is important to consider that, independent of treatment, most patients will undergo some natural neurologic recovery that will plateau 4–6 months after injury. For noncontrolled studies in which patients receive transplants before this plateau, it is impossible to discern whether improvements are related to treatment or simply to the patient's natural recovery potential. For this reason, results must be interpreted with caution.

Table 2: Summary of types of cells and the results of associated published or ongoing clinical research into their use for the treatment of spinal cord injury

Type of cell	Clinical studies published or underway	Patient population and time of cell administration	Results
Bone marrow–derived stem cells	Geffner et al. 2008[40] Autologous cells given via intraspinal injection, IV or topically	8 patients: 4 with acute injury (5 d–6 mo), 4 with chronic injury (5–21 yr)	No major adverse events; improvements in quality of life as measured by Barthel scale* and bladder function (quantitative results not reported)
	Yoon 2007[41] Autologous cells with GM-CSF injected at site of lesion	35 patients: 17 acute (< 2 wk), 6 subacute (2–8 wk), 12 chronic (> 8 wk)	No major adverse events in patients given implants; at least 1-grade improvement in AIS† in 30.4% of patients v. 0% in historical cohort
	Sykova 2006[42] Autologous cells given IA or IV	20 patients: 7 acute (10–30 d), 13 chronic (2–17 mo)	No major adverse events; 5/7 acute patients and 1/13 chronic patients underwent neurologic improvement
	Deda 2008[43] Autologous cells via intraspinal injection	9 patients with chronic complete injury	All patients improved by at least 1 AIS grade; no complications reported
Olfactory ensheathing cells	Mackay-Sim 2008[44] Autologous cells injected intraspinally	6 patients with chronic (> 6 mo) complete thoracic injury	No adverse events; no functional improvement; 1 patient had sensory improvement
	Lima 2010[45] Olfactory mucosa containing cells injected intraspinally	20 patients with chronic (18–89 mo) complete injury	1 case of aseptic meningitis; at least 1-grade improvement in AIS 55% of patients
Schwann cells	Saberi 2008[46] Autologous cells obtained from sural nerve and injected intraspinally	Interim safety report of 4/33 patients with chronic (28–80 mo) thoracic injury	No major adverse events; transient paresthesia and muscle spasms noted in all 4 patients
Activated autologous macrophages	Knoller 2005[47] Cells injected intraspinally immediately caudal to lesion	8 patients with acute (< 14 d) complete injury	No major adverse events related to implantation; at least 2-grade improvement in AIS in 3 patients (38%)
	Lammertse 2012[48] Cells injected intraspinally immediately caudal to lesion	43 patients (26 treatment, 17 control) with acute (< 14 d) complete injury	At least 1-grade improvement in AIS in 7 patients in treatment group (27%) and 10 patients in control group (59%); 1 case of postoperative spinal instability, 1 case of postoperative atelectasis attributed to treatment
Human embryonic stem cells	Geron Corp., Menlo Park, CA Cells injected intraspinally	Target enrolment of 8 patients with acute (7–14 d) complete thoracic injury	Trial stopped before completion after implantation in 4 patients
Tissue-derived adult neural stem cells	Curt (ongoing) Allogeneic cells injected intraspinally	Target enrolment of 12 patients with chronic (> 6 wk) thoracic injury	Currently enrolling, no data reported

Note: AIS = American Spinal Injury Association Injury Scale, GM-CSF = granulocyte macrophage colony-stimulating factor, IA = intraarterial, IV = intravenous.
*Ordinal scale between 1 and 10. A high score suggests a high likelihood of living at home and functioning independently.
†Scale with 5 levels ranging from grade A (most severe) to E (perfect neurologic status).

Overall, cellular transplantation is purely an investigational therapy, which should currently only be undertaken in the context of clinical trials.

Future directions

Box 2 provides a fictional case in which the results of this review are applied in clinical practice. Recent laboratory work has identified other promising therapies yet to appear on the clinical landscape. Chondroitinase ABC is a bacterial-derived enzyme that has shown beneficial effects in rodent injury models by degrading elements of the glial scar preventing post-traumatic axonal growth.[49] When combined with magnesium, the hydrophilic polymer polyethylene glycol has shown neuroprotective properties in animal models by preserving neuronal membrane integrity.[50] Both of these treatments appear poised for eventual translation to the clinic.

More recently, several groups have begun to investigate the role of nanomedicine in promoting neuroprotection and neuroregeneration after injury.[51] Cerium oxide and gold nanoparticles have shown positive results both in vitro and in vivo. Finally, apart from pharmacologic therapies, researchers are in the early phases of investigating neuromodulatory approaches such as epidural spinal cord stimulation to aid rehabilitation efforts during the chronic phases after injury.[52] Although only described in the form of case reports, such approaches appear promising and may someday augment the benefits contributed by acute therapeutics to maximize patients' long-term potential for recovery.

> **Box 2: Applying the results of this review in clinical practice (fictional case)**
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> A 25-year-old unrestrained male driver presents to the emergency department 30 minutes after a high-speed motor vehicle accident. His mean arterial pressure is 65 mmHg. Neurological examination shows a lack of motor or sensory function below C5. Subsequent computed tomography and magnetic resonance imaging show a fracture and dislocation of the cervical spine causing compression of the spinal cord. No other major injuries are identified.
>
> Immediate attention should be placed on optimizing oxygenation and hemodynamic status, as well as on ensuring immobilization of the craniospinal axis. A mean arterial pressure of 85–90 mmHg should be achieved and maintained for the first week after injury using volume resuscitation, augmented with vasopressors as needed. Consultation with the spine surgery service should occur as early as possible to evaluate the patient's suitability for immediate decompression and stabilization surgery. Although the patient presents within 8 hours after his injury, methylprednisolone is not standard therapy; rather, it could lead to additional complications. The patient should be admitted to an intensive care unit with continuous cardiac, hemodynamic and respiratory monitoring for the first 1–2 weeks after his injury. Although several additional treatments such as pharmacologic agents, systemic hypothermia and cellular transplantation appear promising in early phase trials, none are currently recommended for routine clinical use.

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