In comparison with the progress seen in other areas of surgery, advances in understanding the basic neurobiology of SCI and development of therapeutic strategies have been slower to realize. This is unfortunate, given that SCI costs society in excess of $7 billion annually and bears the greater cost of human suffering related to impaired ambulation; sensation; and bowel, bladder, and sexual functions.

During the last decade, new hope emerged for patients who have suffered SCI, as intensive research brought a number of promising therapies to clinical trials. Ten randomized controlled trials examining methylprednisolone sodium succinate, tirilizad mesylate, monosialotetrahexosylganglioside, thyrotropin releasing hormone, gacyclidine, naloxone, and nimodipine have been completed. Although the primary outcomes in these trials were largely negative, a secondary analysis of the North American Spinal Cord Injury Study II demonstrated that when administered within 8 hours of injury, methylprednisolone sodium succinate was associated with modest clinical benefits, which need to be weighed against potential complications. Thyrotropin releasing hormone (Phase II trial) and monosialotetrahexosylganglioside (Phase II and III trials) also showed some promise, but we are unaware of plans for future trials with these agents. These studies have, however, yielded many insights into the conduct of clinical trials for SCI. Several current or planned clinical trials are exploring interventions such as early surgical decompression (Surgical Treatment of Acute Spinal Cord Injury Study) and electrical field stimulation, neuroprotective strategies such as riluzole and minocycline, the inactivation of myelin inhibition by blocking Nogo and Rho, and the transplantation of various cellular substrates into the injured cord. Unfortunately, some experimental and poorly characterized SCI therapies are being offered outside a formal investigational structure, which will yield findings of limited scientific value and risk harm to patients with SCI who are understandably desperate for any intervention that might improve their function. Taken together, recent advances suggest that optimism for patients and clinicians alike is justified, as there is real hope that several safe and effective therapies for SCI may become available over the next decade. (DOI: 10.3171/FOC.2008.25.11.E14)

**Key Words** • cell-replacement therapy • neuroprotection • spinal cord injury • stem cell • surgical timing • translational research

**Abbreviations used in this paper:** ALS = amyotrophic lateral sclerosis; ASIA = American Spinal Injury Association; BMSC = bone marrow stromal cell; CNS = central nervous system; CSF = cerebrospinal fluid; FDA = Food and Drug Administration; FIM = Functional Independence Measure; GM-1 = monosialotetrahexosylganglioside; MPSS = methylprednisolone sodium succinate; NASCIS = North American Spinal Cord Injury Study; OEC = olfactory ensheathing cell; PNS = peripheral nervous system; SCI = spinal cord injury; SCIM = Spinal Cord Independence Measure; STASCIS = Surgical Treatment of Acute Spinal Cord Injury Study; TRH = thyrotropin releasing hormone.
studies has been insight into the conduct of SCI clinical trials. These insights are now being paired with novel scientific advances to bring a new generation of therapies to the bedside. The challenges of the last decade have thus given way to a new-found optimism as a number of new agents are showing great promise in early stage clinical trials. Based on this research, it is anticipated that effective therapies for SCI will emerge in the next decade.

In this review we seek to familiarize clinicians with ongoing clinical trials and promising treatments, which may soon revolutionize management of acute SCI, in the context of pertinent scientific advances and recently completed trials. Care for chronic SCI is also an important and active area of research, but we will not review it here.

### Completed Prospective Randomized Controlled Trials for Acute SCI

A number of agents have been subject to intensive investigation in large multicenter prospective randomized controlled trials, including MPSS and the related compound tirilizad mesylate, GM-1, TRH, gacyclidine, naloxone, and nimodipine (Table 1). Despite promising preclinical animal data, the primary outcomes of these clinical trials were largely negative, although as will be briefly discussed later, MPSS showed some promise in the secondary analyses. These trials have been reviewed extensively elsewhere, and therefore we will recount them only briefly here as a prelude to a discussion of ongoing clinical trials and lessons learned about the

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>SCI Type, Treatment Window (hrs)</th>
<th>Treatment Arms</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASCIS I</td>
<td>1984</td>
<td>330</td>
<td>Phase III RCT</td>
<td>I, 48</td>
<td>MPSS 100 mg × 10 days; MPSS 1000 mg × 10 days</td>
<td>no difference</td>
</tr>
<tr>
<td>NASCIS II</td>
<td>1990</td>
<td>487</td>
<td>Phase III RCT</td>
<td>C/I, 12</td>
<td>MPSS (24 hr) naloxone; placebo</td>
<td>negative primary analysis; secondary analysis showed improved recovery if treated w/ MPSS w/in 8 hrs of injury; naloxone negative</td>
</tr>
<tr>
<td>Maryland GM-1</td>
<td>1991</td>
<td>34</td>
<td>Phase II RCT—pilot study</td>
<td>I, 72</td>
<td>GM-1 placebo</td>
<td>improved neurological recovery w/ GM-1 in this small pilot study</td>
</tr>
<tr>
<td>Otani et al.</td>
<td>1994</td>
<td>158</td>
<td>nonblinded RCT</td>
<td>?, 8</td>
<td>MPSS (NASCIS II 24 hr) placebo</td>
<td>significantly more steroid-treated patients had some sensory improvement; no motor differences</td>
</tr>
<tr>
<td>TRH</td>
<td>1995</td>
<td>20</td>
<td>Phase II RCT—pilot study</td>
<td>C/I, 2</td>
<td>TRH placebo</td>
<td>suggestion of improved neurological recovery w/ TRH in this small pilot study</td>
</tr>
<tr>
<td>NASCIS III</td>
<td>1997</td>
<td>499</td>
<td>Phase III RCT</td>
<td>I, 12</td>
<td>MPSS (24 hr); MPSS (48 hr); MPSS bolus then TM</td>
<td>improved neurological recovery w/ MPSS if administered early (w/in 3 hrs after SCI); TM not superior to MPSS</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>1998</td>
<td>100</td>
<td>Phase III RCT</td>
<td>C/I, 6</td>
<td>nimodipine; MPSS (24 hr); nimodipine + MPSS (24 hr) placebo</td>
<td>no difference; study likely underpowered to detect a difference</td>
</tr>
<tr>
<td>Gacyclidine</td>
<td>1999</td>
<td>280</td>
<td>Phase II RCT</td>
<td>C/I, 2</td>
<td>gacyclidine (0.005 mg/kg); gacyclidine (0.01 mg/kg); gacyclidine (0.02 mg/kg) placebo</td>
<td>negative study; trend to improved motor recovery w/ incomplete cervical injuries</td>
</tr>
<tr>
<td>Pointillart et al.</td>
<td>2000</td>
<td>106</td>
<td>blinded RCT</td>
<td>?, 8</td>
<td>MPSS (NASCIS II 24 hr) nimodipine; MPSS &amp; nimodipine placebo</td>
<td>no neurological differences between groups; trend to increased infections in groups receiving MPSS</td>
</tr>
<tr>
<td>Sygen (GM-1)</td>
<td>2001</td>
<td>797</td>
<td>Phase III RCT</td>
<td>I, 72</td>
<td>MPSS &amp; low-dose GM-1; MPSS &amp; high-dose GM-1; MPSS &amp; placebo</td>
<td>negative primary outcomes; trend to improved secondary outcomes</td>
</tr>
</tbody>
</table>

* Further trials are not planned for any of the agents presented in this table, to the knowledge of the authors. Abbreviations: C = complete; I = incomplete; RCT = randomized controlled clinical trial; TM = tirilizad mesylate; ? = unpublished or unclear data.
methodological challenges associated with evaluating novel SCI therapies.

**Methylprednisolone Sodium Succinate (Solu-Medrol)**

Corticosteroids have been used in neurotrauma for decades but have only recently been subject to intensive scientific scrutiny. Their neuroprotective effects include antioxidant properties, which are associated with a reduction in tumor necrosis factor–α synthesis and nuclear factor κB activity, enhancement of spinal cord blood flow, reduced calcium influx, reduced posttraumatic axonal die back, and attenuated lipid peroxidation.5,11 Following the accumulation of preclinical data6 that was generally (but not universally) supportive of a neuroprotective role for steroids in animal models of acute SCI, methylprednisolone was studied in 5 prospective acute SCI trials in humans,7 making it the most extensively studied drug in acute SCI.

Three landmark NASCIS studies examined the use of MPSS for acute SCI. The first NASCIS study, published in 1984,15 compared a high-dose with a low-dose group; placebo was judged unethical because benefit from steroid administration was presumed.5 Neurological improvement was not significantly different between the 2 groups, although a statistically significant increase in wound infection was noted in the high-dose group, as well as increased rates of gastrointestinal hemorrhage, sepsis, pulmonary embolism, delayed wound healing, and death.74 Animal studies completed subsequent to NASCIS I suggested that higher doses were required for neuroprotection.16 The NASCIS II trial17 was thus designed to examine a higher dose of MPSS compared with placebo and the opioid antagonist naloxone given within 24 hours of injury. In the overall analysis of all patients randomized within 24 hours, there was no neurological benefit in the MPSS-treated group, and hence, this trial was negative.17 However, a post hoc analysis (reportedly planned priori6) demonstrated that patients receiving the drug within 8 hours of injury benefited neurologically, notably those whose injury was initially complete (ASIA Grade A).74 As in NASCIS I, a trend toward an increased incidence of wound infection and pulmonary embolism was associated with MPSS administration.74

The NASCIS III trial14,15 was designed and powered to further explore the beneficial effects of MPSS administration within 8 hours of injury, as reported in NASCIS II. Additionally, the trial assessed functional outcome (by using the FIM), which was not previously analyzed in NASCIS trials. This study compared the 24-hour infusion used in NASCIS II to a 48-hour MPSS infusion, and it also included a treatment group that received tirilizad mesylate, a 21-aminosteroid believed to be an antioxidant without glucocorticoid effects.9 Like NASCIS II, when considering all patients recruited, this trial demonstrated no sustained benefit to MPSS with respect to motor and sensory scores in treatment groups. A post hoc analysis noted that patients receiving the MPSS bolus 3–8 hours after injury demonstrated improved neurological function at 6 weeks and 6 months (but not at 1 year) when they were given MPSS for 48 hours rather than 24 hours. This led to the recommendation that within 3 hours of injury, the 24-hour infusion would suffice but, if initiated within 3–8 hours of injury, a 48-hour MPSS regimen was better than the 24-hour regimen of the NASCIS II protocol. The 48-hour regimen represents the highest dose of MPSS prescribed for any clinical condition22 and was associated with a 2-times higher rate of severe pneumonia, a 4-times higher rate of severe sepsis, and a 6-times higher incidence of death in the 48-hour group than in the 24-hour group.74

Two other prospective SCI trials in humans involving corticosteroids have been published, including the work of Otani et al.12 and Pointillart et al.120. The former authors noted some neurological benefit from methylprednisolone administration, whereas the latter authors reported none. Nonetheless, both of these studies were small and plagued by substantial methodological problems, which limit their interpretation as either positive or negative studies.

Intense and systematic scrutiny of these data has led to tremendous controversy around the use of MPSS for acute SCI.28,75,76,108 Two predominant concerns have arisen. First, the benefits noted have not only been modest, but in both NASCIS II and III they were only detected in the secondary analysis of a fraction of the enrolled population. Second, high rates of adverse events were consistently associated with MPSS administration. The scrutiny surrounding the execution and interpretation of the NASCIS trials culminating in the American Association of Neurological Surgeons/Congress of Neurological Surgeons systematic review of this literature in 2002, which concluded that “treatment with methylprednisolone for either 24 or 48 hours is recommended as an option in the treatment of patients with acute spinal cord injuries that should be undertaken only with the knowledge that the evidence suggesting harmful side effects is more consistent than any suggestion of clinical benefit.”71

Although many continue to administer steroids, the rationale for this administration has changed. A survey published in 2006 revealed that the majority of respondents continue to administer methylprednisolone, but they are motivated predominantly by fear of litigation.41 The view of the senior author (M.G.F.) is that MPSS administration remains justified for acute SCI (within 8 hours) in non-diabetic and non-immunocompromised patients given the severity of SCI deficits and current lack of alternatives.44

**The Ganglioside GM-1 (Sygen)**

Gangliosides are complex glycolipids abundant in the membranes of nervous tissue. Exogenous administration of GM-1, a ganglioside also known as Sygen, was found to promote neural repair and functional recovery in a number of animal models.9 In 1991, the prospective randomized Maryland GM-1 study of 37 patients reported that GM-1 treatment resulted in statistically significant improvement in ASIA motor score compared with placebo.90 Efficacy was noted as late as 48 hours after injury, and its predominant effect on lower-extremity function suggested an effect on axons traversing the injury.1 This led to the largest prospective randomized clinical trial in acute SCI to date, the Sygen Multi-Center Acute Spinal...
Cord Injury Study, which enrolled > 750 patients from 28 institutions over 5 years. This study failed to dem-
strate a significant difference in its primary outcome
measure—a 2-point improvement on the modified Benzel
walking scale. This was, in retrospect, an ambitious end
point, considering the number of patients enrolled in the
trial with complete ASIA Grade A injuries who attained
less benefit than patients with incomplete injuries. The
patients treated with GM-1 did demonstrate more rapid
neurological recovery as well as a trend to improved bow-
el/bladder function and sacral sensation. It has also been
postulated that greater efficacy with GM-1 may have been
seen had it been given earlier after injury. Because the
patients enrolled in this study were obligated to receive
MPSS first, GM-1 was not administered, on average, until
55 hours after injury. We are unaware of any plans for
future trials with this agent, although this data set con-
tinues to produce invaluable insights into study design,
which will be discussed later.

**Thyrotropin Releasing Hormone**

In addition to the hormonal functions well known
to physicians, TRH has been shown to antagonize sec-
ondary injury mediators such as excitotoxic amino acids,
peptidoleukotrienes, endogenous opioids, and platelet-
activating factor, likely underlying its dose-dependent
functional improvement in rats following experimental
SCI. In 1995 the only clinical trial ever conducted with
TRH in acute SCI was published. This randomized,
double-blind, placebo-controlled trial included complete
and incomplete injuries and compared TRH with place-
bo. Based on a secondary analysis of a smaller cohort of
patients, those with incomplete SCI (but not those with
complete SCI) achieved statistically significant function-
al improvements on the NASCIS and Sunnybrook scales.
This result must be interpreted with caution, however, as
the trial was plagued by attrition; because only 20 pa-
tients were ultimately analyzed, this result may represent
Type I error. No further clinical SCI studies to investigate
TRH have been initiated.

**Gacyclidine (GK-11)**

Glutamate is the main excitatory neurotransmitter
in the CNS, but its excess following CNS injury leads
to excitotoxicity, which now has a well-established role
in secondary injury. Antagonism of glutamate receptors
has proven a challenging therapeutic approach, however.
Previous trials of antiglutamatergic agents have been un-
successful because of significant cognitive side effects,
including agitation, sedation, hallucinations, and memory
deficits, even with competitive antagonists such as Selfo-
tel. Interestingly, a noncompetitive N-methyl-D-aspar-
tate receptor antagonist, gacyclidine, showed promise as
a neuroprotective agent.

Gacyclidine or GK-11 (Beaufour-Ipsen Pharma) has shown
evidence of improved function, histology, and
electrophysiology in a rat model, in addition to substan-
tially better tolerability than other N-methyl-D-aspartate
antagonists. A double-blind Phase II human trial that
was completed in France randomized more than 200 pa-
tients to receive 3 escalating doses of gacyclidine.
Early benefit was seen in the treatment groups, but this was not
maintained at 1 year. At 1 year postinjury, however, those
with incomplete cervical injuries receiving high doses of
gacyclidine exhibited a nonsignificant trend toward im-
proved motor function. Despite the fact that this nega-
tive result likely stems from insufficient statistical power,
this agent is no longer being pursued for SCI. Its use is,
however, being explored in traumatic brain injury and
organophosphate poisoning and tinnitus (patent number
20060205789).

**Nimodipine**

Intracellular calcium levels are tightly regulated, as
high concentrations can activate calpains and other de-
structive enzymes within the cell that lead to apoptosis.
Excitotoxic glutamate release is also calcium-dependent.
Nimodipine is an L-type calcium channel blocker that may
antagonize these processes. Indeed, its potential (albeit modest) benefit in subarachnoid hemorrhage is be-
lieved to result from neuroprotective effects rather than
a smooth-muscle relaxing effect on blood vessels. The
latter effect can, however, cause hypotension and spinal
cord ischemia in the context of injury. When hypotension
is avoided, animal studies of nimodipine have demon-
strated improvement in spinal cord function. A human
trial for SCI was completed in France in 1996. This trial
comprised 100 patients in 4 treatment arms: nimodipine,
MPSS (NASCIS II protocol), both agents, and placebo.
Benefit over placebo was not demonstrated in any treat-
ment group, although it is quite likely that this study was
also underpowered to reveal a therapeutic effect.

**Opioid Antagonism**

Dynorphin A, an endogenous opioid, is released fol-
lowing SCI and has neurotoxic effects; it also reduces
spinal cord blood flow by nonopioid mechanisms. Con-
cordantly, opioid antagonism following SCI has led to
improved electrophysiology and reduction in edema, as
well as decreased levels of excitotoxic amino acids. In
the 1980s the opioid antagonist naloxone was examined in a Phase I SCI trial in humans. The results suggested benefit, but imbalance between experimental groups make this result difficult to interpret. A more definitive examination of this agent was performed in the NASCIS II trial where, unlike MPSS, naloxone unfortunately showed no neuroprotective bene-
fit.

**Toward the Next Generation of Trials**

**Lessons From Completed Trials**

Although the completed trials in SCI failed to bring a robustly neuroprotective compound to the clinic, much
has been learned from these studies. The high quality of the trials and the intense scrutiny of their design and
interpretation of outcome measures are playing a criti-
cal role in shaping the next generation of trials. In par-
0
Advances in spinal cord injury therapeutics

Table 2: Summarized recommendations for the conduct of SCI clinical trials

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials of treatments that are most efficacious when given soon after injury will require larger patient numbers than those effective at later time points.</td>
<td>1</td>
</tr>
<tr>
<td>Trials involving motor incomplete SCI patients, or trials in which an accurate assessment of ASIA impairment scale grade cannot be made before the start of the trial, will require large patient numbers &amp;/or better objective assessment methods.</td>
<td>1</td>
</tr>
<tr>
<td>The ASIA impairment scale forms the standard basis for measuring neurological outcomes.</td>
<td>3</td>
</tr>
<tr>
<td>An improvement in the measurable performance of a meaningful function or behavior is necessary for any therapeutic intervention to be universally accepted as clinically beneficial.</td>
<td>2</td>
</tr>
<tr>
<td>The SCIM assessment may be a more specific &amp; accurate outcome tool for detecting clinical end points in SCI than the FIM.</td>
<td>3</td>
</tr>
<tr>
<td>Clinical trials for SCI should include blinded assessments.</td>
<td>5</td>
</tr>
<tr>
<td>The most rigorous &amp; valid SCI clinical trial would be a prospective double-blind RCT using appropriate placebo controls. However, in specific situations, it is recognized that other trial procedures may have to be considered.</td>
<td>5</td>
</tr>
<tr>
<td>The use of external controls in SCI clinical trials is strongly discouraged.</td>
<td>2</td>
</tr>
<tr>
<td>Experimental therapies should have proven benefit in &gt;1 animal model before translation to humans.</td>
<td>4</td>
</tr>
<tr>
<td>Consideration should be given to using novel trial designs such as adaptive randomization &amp; Bayesian statistics.</td>
<td>4</td>
</tr>
<tr>
<td>Clinical trials require follow-up of appropriate duration: 6–12 mos for neuroprotection trials, 12–24 mos for regenerative therapies.</td>
<td>4</td>
</tr>
<tr>
<td>Clinical management should follow recently published guidelines regarding acute &amp; chronic SCI management.</td>
<td>4</td>
</tr>
</tbody>
</table>

*The following references apply to this table and Table 4:

as the reference trials in the translational SCI field. For example, analysis of the large Sygen database has been valuable for defining the variance in spontaneous neurological recovery among patients deemed to have the same injury severity.43

Subsequently, a number of authors have published recommendations for the scientific and ethical conduct of future trials, including Tator39 (select recommendations are provided in Table 2), Cesaro,24 and Sagen127 with the latter 2 addressing cell replacement therapies. A parallel effort has come from the International Campaign for Cures of Spinal Cord Injury Paralysis, which published 4 documents in 200743,85,130,143 designed to improve SCI clinical trials (a summary of these recommendations is provided in Table 2). These documents provide recommendations related to the following: 1) statistical power needed for clinical trials in relation to injury severity and timing of administration of the experimental therapy; 2) appropriate clinical trial outcome measures; 3) inclusion/exclusion criteria and ethics; and 4) clinical trial design. These recommendations will be extremely helpful for the SCI community in its further clinical evaluation of novel therapies.

It is a paradox that despite this enlightenment, more experimental therapies in SCI than ever before are being pursued in an environment of questionable scientific rigor and ethics. In particular, recent years have seen many patients travel appreciable distances at great personal cost and risk to seek cell or tissue transplantation therapies, which are at best unproven and at worst very dangerous.37 Additionally, information surrounding the conduct and results of many current SCI clinical trials is not in the public domain,39 in contravention of the current effort to promote registration of trials embodied by the Ottawa Statement.86 It will be important for future trials to adhere to these recommendations.

Largely in response to this issue, the International Campaign for Cures of Spinal Cord Injury Paralysis has produced an additional document designed for patients considering enrollment in an SCI clinical trial.134 This excellent resource aims to educate patients about the clinical trials process and encourages them to participate in studies of high scientific and ethical quality. These new publications thus provide patients and clinicians with important tools that will be essential to the conduct of future trials.

New Clinical Tools

In recent years, clinical guidelines have been published for the management of acute and chronic SCI.60,114 Adherence to these guidelines in future trials should decrease variability and increase the chance of detecting clinical effects. Standardized care would also make comparison of trial results more facile.
A number of new clinical assessment tools have also been devised. The ASIA Impairment Scale, alternatively known as the International Standard for Neurological Classification of Spinal Cord Injury, was first published in 1982 and now forms the international standard for postinjury evaluation of neurological function. The simplified form of the ASIA Impairment Scale bears the same form as the earlier Frankel scale and maintains backward compatibility with it. The Modified Benzel Classification system, used in the GM-1 trial, may be used in future trials as it addresses some of the perceived deficits of the ASIA Impairment Scale: it subdivides ASIA Grade D

### Table 3: Summary of recently published and ongoing, well-documented, unpublished experimental trials for acute and subacute SCI*

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Intervention</th>
<th>Lead Center/Organization</th>
<th>Date of Initiation</th>
<th>Proposed No. of Patients</th>
<th>Complete, Published Phases</th>
<th>Current Study Type</th>
<th>Registration Information†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>recently published studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OEF stimulation device implantation</td>
<td>Indiana U Medical Center, Australia</td>
<td>?</td>
<td>20</td>
<td>Phase I/II</td>
<td></td>
<td>Phases I, randomized, multi-center controlled trial</td>
<td>NR</td>
</tr>
<tr>
<td>Australian OEC trial</td>
<td>OEC transplantation</td>
<td></td>
<td>pre-2005</td>
<td>6</td>
<td>Phase I, single-blinded w/ control</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>PROCORD (enrollment suspended)</td>
<td>activated autologous macrophages</td>
<td>Proneuron</td>
<td>2005</td>
<td>61, suspended at 50</td>
<td>Phase I</td>
<td>Phase II, randomized, multi-center controlled trial</td>
<td>NR</td>
</tr>
<tr>
<td>Prague BMSC transplantation</td>
<td>BMSC transplantation</td>
<td>Prague</td>
<td>?</td>
<td>20</td>
<td>?</td>
<td>?</td>
<td>NR</td>
</tr>
<tr>
<td>Korean BMSC transplantation</td>
<td>BMSC transplantation</td>
<td>Inha U Hospital</td>
<td>2001</td>
<td>35</td>
<td>Phase I/II non-randomized</td>
<td>?</td>
<td>NR</td>
</tr>
<tr>
<td><strong>ongoing, unpublished studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STASCIS timing of surgical decompression</td>
<td>U of Toronto, Thomas Jefferson U, Spine Trauma Study Group, U of Maryland</td>
<td>May 2007</td>
<td>450</td>
<td>NA</td>
<td>nonrandomized prospective observational</td>
<td>Phase II</td>
<td>NCT00475748</td>
</tr>
<tr>
<td>early &amp; late surgery for traumatic central cord syndrome</td>
<td>surgical decompression</td>
<td>U of Maryland</td>
<td>May 2007</td>
<td>30</td>
<td>?</td>
<td>Phase II</td>
<td>NR</td>
</tr>
<tr>
<td>systemic hypothermia</td>
<td>hypothermia (cooled to 33°C at 0.5°C/hr, maintained for 48 hrs)</td>
<td>Miami</td>
<td>January 2007</td>
<td>100</td>
<td>NA</td>
<td>Phase I/II</td>
<td>NR</td>
</tr>
<tr>
<td>minocycline</td>
<td>250 mg IV bid x 7 days</td>
<td>Calgary</td>
<td>?</td>
<td>?</td>
<td>Phase I</td>
<td>Phase II</td>
<td>NR</td>
</tr>
<tr>
<td>riluzole</td>
<td>Na+ channel blockade, anti-glutamatergic 50 mg PO bid</td>
<td>U of Toronto, North American Clinical Trials Network</td>
<td>late 2007</td>
<td>36</td>
<td>NA</td>
<td>Phase I</td>
<td>NR</td>
</tr>
<tr>
<td>ATI-355 Nogo-blockade</td>
<td></td>
<td>Novartis</td>
<td>May 2006</td>
<td>16</td>
<td>NA</td>
<td>Phase I</td>
<td>NCT00406016</td>
</tr>
<tr>
<td>Cethrin</td>
<td>Rho inhibition</td>
<td>BioAxone Therapeutics/ Aseres Pharmaceutical</td>
<td>February 2005</td>
<td>47</td>
<td>NA</td>
<td>Phase I</td>
<td>NCT00500812</td>
</tr>
<tr>
<td>CSF drainage</td>
<td>CSF drainage</td>
<td>U of British Columbia</td>
<td>March 2008</td>
<td>22 enrolled to date</td>
<td>NA</td>
<td>Phase I</td>
<td>NCT00135278</td>
</tr>
</tbody>
</table>

* To the authors’ knowledge, all therapies presented here are currently being investigated in clinical trials, or further trials are planned. Abbreviations: bid = twice daily administration; IV = intravenous; NA = not applicable; NR = not registered; OEF = oscillating electrical field; PO = by mouth; U = University.
† At http://www.clinicaltrials.gov.
TABLE 4: Human therapy considered experimental, with uncertain methodology or status*

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Intervention</th>
<th>Location</th>
<th>No. of Treated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>?</td>
<td>pulsed electrical stimulation</td>
<td>Beijing</td>
<td>100+</td>
</tr>
<tr>
<td>minocycline/tacrolimus</td>
<td>coadministration</td>
<td>Riyadh</td>
<td>?</td>
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<tr>
<td>Russian OEC transplantation</td>
<td>OEC transplantation</td>
<td>Russia</td>
<td>many</td>
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<tr>
<td>Huang OEC transplantation</td>
<td>? fetal OEC transplantation</td>
<td>Beijing</td>
<td>300+</td>
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<tr>
<td>China BMSC transplantation</td>
<td>BMSC transplantation</td>
<td>?</td>
<td>90</td>
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<tr>
<td>Russian BMSC transplantation</td>
<td>fetal BMSC/peripheral blood cell transplantation</td>
<td>2 centers</td>
<td>15</td>
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<tr>
<td>Schwann cells</td>
<td>cellular transplantation</td>
<td>2 groups in China</td>
<td>?</td>
</tr>
</tbody>
</table>

* Most studies presented here have been reported only by Tator.†

Advances in spinal cord injury therapeutics

into 3 different grades to reduce ceiling effect and additionally assesses walking and sphincter function. Some believe that this scale is not valid, however, as it cannot be applied immediately following injury when a patient is unable to ambulate.139

The SCI-specific quality of life measures will undoubtedly receive increased emphasis in future trials. Although the FIM has been perhaps most widely used in the SCI literature thus far, it is likely that the SCIM, published in 2001,22 will be increasingly applied as it has demonstrated more sensitivity to functional changes in patients who have suffered SCI than the FIM.22 The SCIM assesses self-care, respiration, sphincter management, and mobility and has been revised to increase inter-observer reproducibility.23 Also emerging are scales that assess walking following SCI. The Walking Index for Spinal Cord Injury (the GRASSP outcome measure).

Clinical Trial Networks

Because of the relatively low incidence of SCI, clinical trial networks will undoubtedly play a key role in recruiting patients into clinical trials of novel therapies.

Ongoing Clinical Trials

More than 70 clinical trials for SCI are registered online at http://www.clinicaltrials.gov; however, the majority of these relate to interventions for chronic SCI and will not be reviewed here. Here we describe registered intervention trials involving patients with acute and subacute SCI as well as others we have identified and of which we have some knowledge (Tables 3 and 4).

Surgical Trials and Nonpharmacological Interventions

Surgical Treatment of Acute Spinal Cord Injury Study

It is surprising that in our modern age a question as fundamental as whether early decompression for acute human SCI is or is not beneficial for neurological recovery remains incompletely answered.45 While a significant body of animal research has demonstrated neurological benefit to early decompression of the injured spinal cord, some clinicians prefer to delay decompression in patients with multiple trauma in light of the medical instability often seen in the acute postinjury phase.45,46,140

In an effort to address this question with evidence of the highest possible quality, the STASCIS was initiated in 2003 by Drs. Fehlings and Vaccaro of the University of Toronto and Thomas Jefferson University (Philadelphia, PA), respectively. This trial was designed to be randomized; however, resistance to randomizing to an intentionally delayed decompression led to restructuring as a prospective observational study. This study has an accrual target of 450 patients with traumatic cervical SCIs ranging in age from 16 to 70 years. A 2-year follow-up period postinjury is planned. Preliminary analysis suggests a benefit to early decompression based on an operational definition of “early” being < 24 hours.

As a result of this and a belief that there may be benefit from “ultra-early” decompression, the University of Toronto has established the practice of performing decompression (by traction or open surgery) immediately following initial imaging in patients with isolated cervical SCI (whenever feasible within 12 hours of injury). The greatest barriers to achieving early decompression in the SCI population are likely based on delays in transfer and challenges with accessing imaging and operating room facilities. Implementation of the STASCIS protocol will require major efforts to influence public policy.

Early Versus Late Decompression of Central Cord Syndrome

Central cord syndrome is uniquely challenging with respect to determining the optimal timing of interven-
tion; most patients present without spinal instability and experience substantial spontaneous neurological improvement. Although attempts have been made to identify factors that influence the neurological outcome after central cord syndrome \(^2\) and to specifically address whether early surgery is beneficial, \(^27\,59\,103\) a prospective trial is needed. Fortunately, investigators at the University of Maryland have registered a Phase II, single-center randomized clinical trial examining the timing of decompression in central cord syndrome. This trial seeks to randomize 30 patients to decompression within 5 days or after 6 weeks of injury. The study will compare ASIA, FIM, and SCIM scores; degree of canal compromise; spinal cord compression; and syrinx size. A 1-year follow-up has been planned. Unfortunately, it appears that this trial is being plagued by resistance to randomization as the STASCIS was, and therefore the future of this trial is currently uncertain.

**Oscillating Field Stimulation**

Neurites grow toward the negative pole (cathode) in an electrical field. \(^{68,79}\) Researchers at the Indiana University Medical Center have developed an implantable oscillating field stimulator, which is capable of creating an electrical field along the rostrocaudal axis of the spinal cord, and they hope to capitalize on this finding. Because neurite outgrowth is stimulated only toward the negative pole, the device oscillates, changing polarity every 15 minutes to promote axonal growth in both directions. This device underwent trial in 10 patients with complete SCI from C-5 to T-10 who also received methylprednisolone per the NASCIS III protocol. The oscillating field stimulator was implanted within 18 days and removed at 15 weeks postinjury. In that study, reported in 2005, \(^{131}\) patients were assessed for 1 year after the procedure by using the ASIA grade, visual analog scale pain score, and somatosensory evoked potentials. The mean improvement in light touch was 25.5 points (\(p = 0.02\)), the mean improvement in pinprick sensation was 20.4 points (\(p = 0.02\)), and the mean improvement in motor status was 6.3 points (\(p = 0.02\)). Based on comparison with patients in the NASCIS III trial, efficacy is suggested; however, as these are historical controls from a distinct trial protocol, the neurological improvement must be interpreted with caution. Of note, the complications observed in this trial were low (1 wound infection and 1 device failure), and the FDA has reportedly approved enrollment of additional patients in this study. Cyberkinetics Neurotechnology Systems, Inc. (Foxborough, Massachusetts) has purchased the intellectual property for this technology, and we look forward to additional data from the investigators.

A similar trial involving pulsed electrical stimulation has been conducted in 100 patients in Beijing by investigators Xu and Liu, as reported by Tator. \(^{139}\) The results of this work are uncertain, however.

**Cerebrospinal Fluid Drainage**

In thoracoabdominal aortic aneurysm surgery, CSF drainage has been found to significantly reduce the incidence of ischemic paraplegia. \(^{59}\) This suggests that lowering intrathecal pressure improves spinal cord perfusion pressure, attenuating ischemia and providing neuroprotection. Investigators at the University of British Columbia have initiated a safety and feasibility study to evaluate CSF drainage as a neuroprotective strategy after acute SCI (clinicaltrials.gov identifier NCT00135278). This study involves CSF drainage through a lumbar intrathecal line. Twenty-two patients have been enrolled to date, and there have been no adverse events attributed to the drainage of CSF (for example, neurological deterioration, meningitis, or headache/nausea/vomiting). Neurological recovery is a secondary measure in this pilot study, although the planned enrollment will not be sufficient to make strong statements about the influence of CSF drainage on neurological outcome.

**Hypothermia**

Hypothermia has long been explored for its putative neuroprotective effects despite risks that include coagulopathy, sepsis, and cardiac dysrhythmia. In addition to reducing metabolic rate, hypothermia also appears to reduce extracellular glutamate, vasogenic edema, apoptosis, neutrophil and macrophage invasion and activation, and oxidative stress. \(^{42,57,61,72,77,78,97,111,154}\) Indeed, therapeutic hypothermia has become a treatment guideline for patients resuscitated from an out-of-hospital cardiac arrest. \(^{110}\) In traumatic brain injury, a number of trials have demonstrated inconsistent effects. \(^{65,86}\) In animal models of traumatic spinal cord injury, both regional and systemic hypothermia have been studied and have demonstrated mixed results. \(^{65,86}\) Until recently, only regional hypothermia has been described in acute human SCI; however, researchers from the Miami Project to Cure Paralysis have begun to explore the role of systemic hypothermia in SCI. In 2007 they initiated a clinical trial which involves rapid cooling with chilled intravenous saline to decrease the core body temperature to ~34°C in comparison with historical controls. We anxiously await the results of this trial.

**Pharmacological Trials**

**Minocycline**

Minocycline is a synthetic tetracycline derivative commonly used in the treatment of dermatological conditions such as acne and rosacea. It has also demonstrated neuroprotective effects in animal models of stroke, Parkinson disease, Huntington disease, ALS, and multiple sclerosis. \(^{150}\) A number of independent laboratories have reported that minocycline attenuates secondary injury and enhances functional recovery in various animal models of SCI \(^{93,136,141,147}\) Its mechanism of action in SCI appears to be mediated in part by the inhibition of microglial activation, \(^{48,67,92,122,152}\) in addition to antiapoptotic properties; \(^{48,142,153}\) the latter may stem from a reduction in levels of pro-neural growth factor and inhibition of cytochrome c release. These promising preclinical results have led to 2 clinical trials, which are now ongoing. The first, led by researchers at the University of Calgary, is a prospective randomized placebo controlled Phase I/II

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G. W. J. Hawryluk et al.
Advances in spinal cord injury therapeutics

human trial of intravenous minocycline in which patients are randomized within 12 hours of their injury. The investigators recently reported that trial enrollment will be halted in November 2008 with a subsequent decision on whether a Phase III study is warranted. We eagerly await further information about this trial.

Less is known about the second study, being conducted by investigators at Riyadh Armed Forces Hospital, Saudi Arabia. This trial is reportedly assessing the effectiveness of minocycline when administered in combination with the immunosuppressant tacrolimus (FK506), which inhibits the enzyme calcineurin.109

Riluzole

Riluzole or Rilutek (Sanofi-Aventis) is a benzothiazole anticonvulsant which has been licensed for patients with ALS for ~10 years,8 perhaps prolonging their lives by 2–3 months.104 Its neuroprotective effects appear to result from blockade of voltage-sensitive sodium channels whose persistent activation following injury has been associated with degeneration of neural tissue,129 as well as antagonism of presynaptic calcium-dependent glutamate release.106 Of interest in SCI, it demonstrates synergy with MPSS,197 and animal models of SCI have demonstrated neuroprotective effects when administered as late as 10 days after injury.109,129 Recent in vitro studies additionally have suggested that riluzole may promote outgrowth of sensory neurons.135 Hepatotoxicity may be an important side effect of this therapy; however, this treatment has been well-tolerated in the ALS population, and the changes in liver enzymes are reversible after stopping this medication.91

Based on these promising experimental results and an established track record in ALS, it is anticipated that a human multicenter SCI trial will begin in mid-2008, enrolling patients (with a target of 36) with ASIA Grade A, B, or C and injuries between neurological levels C-4 and T-10. Patients will be enrolled within 12 hours of injury and given the same daily dose as that given to ALS patients. A 10-day course will be given as glutamate, and sodium-mediated secondary injury is maximal during this period.115,129 A 1-year follow-up is planned, with the primary safety end point assessed at 3 months and neurological assessment at 6 months, including ASIA grade, SCIM, and Brief Pain Inventory. Coadministration of MPSS will be permitted.

Targeting Myelin-Associated Inhibitors of Regeneration

Work by David and Aguayo30 performed many years ago at the Montreal Neurological Institute demonstrated the very important finding that central neurons have the capacity to regenerate across peripheral nerve grafts. The conclusion of this work was that components of the CNS environment must inhibit axonal regrowth after injury and that CNS neurons do have the capacity to regenerate their disrupted axons. A number of inhibitory proteins present largely in myelin have subsequently been identified, Nogo being the first.71,109 Work is underway to interrupt the inhibitory effect that these molecules have on axonal regrowth following injury. Two such agents that have reached clinical trials are ATI-355 and Cethrin.

ATI-355

In the late 1980s, pioneering work by Caroni et al.19,21 demonstrated that oligodendrocytes and their myelin membranes are major inhibitors of axonal growth within the CNS. Caroni and Schwab20 biochemically separated 35- and 250-kD inhibitory fractions within CNS myelin (NI-35 and NI-250) and developed a monoclonal antibody, IN-1, that could block their inhibitory properties in vitro. Subsequent in vivo application of IN-1 in rodents resulted in substantial axonal sprouting and some long distance corticospinal axonal regeneration within the adult mammalian CNS.128 Importantly, this antibody treatment was associated with improved performance on a variety of functional tests, including open field locomotion, rope climbing, and food pellet reaching.17,50 The IN-1 antibody was then instrumental in the characterization and protein sequencing of its target antigen,153 which led to the cloning of what is now known as Nogo.26,35,123

The humanized anti-Nogo antibody has been shown to promote axonal sprouting and functional recovery following SCI in numerous animal models, including primates.51,52 In May 2006 a human Phase I clinical trial was initiated by Novartis in Europe to assess the safety, feasibility, and pharmacokinetics of this antibody in patients with complete SCI between C-5 and T-12, who are 4–14 days postinjury. The agent is being administered via continuous intrathecal infusion, and patients are being enrolled in 4 increasing dose regimens, with the highest dose being delivered over 28 days. The FDA has expressed concerns with the external nature of the infusion pump, and hence the clinical evaluation has been limited to Europe and Canada. In addition, neutropenia was recently reported as a severe adverse event associated with this therapy, and it will be interesting to see how this impacts the trial.

Cethrin

McKerracher and Higuchi102 have developed a therapy that exploits the fact that all known myelin and extracellular matrix inhibitors identified thus far signal via activation of the guanosine triphosphatase Rho. When activated, Rho binds to Rho kinase (ROCK), noted to be a key regulator of axonal growth cone dynamics and cellular apoptosis. Their work involves a toxin produced by Clostridium botulinum, C3 transferase, which is a specific inhibitor of Rho. Interruption of this final common pathway thus has the potential to be more potent than efforts to antagonize any single myelin inhibitor. This agent facilitated axonal growth and promoted functional recovery in a mouse model of SCI.12 The early neurological improvement observed in the C3-treated animals suggested an additional neuroprotective effect. Supporting this, Dubreuil et al.98 subsequently demonstrated a reduction in p75-dependent apoptosis in association with their therapy.

To improve cellular permeability, McKerracher’s group created a recombinant version incorporating a transport sequence. The resulting protein, referred to as...
which is currently poorly understood. Other complications can be complicated by genesis or exacerbation of neuropathic pain,70,101

dence suggests that some transplantation regimens may be contraindicated before human trials are undertaken. For instance, evidence pertaining this approach; cell transplantation into injured human spinal cords is being conducted in numerous centers outside North America. Many believe that these approaches require greater optimization and understanding before human trials are undertaken. For instance, evidence suggests that some transplantation regimens may be complicated by genesis or exacerbation of neuropathic pain,70,101 which is currently poorly understood. Other serious complications have been described such as in a patient who developed tumorlike overgrowth following a procedure performed in Russia, as reported by neurosurgeons from the University of British Columbia. Even if these strategies are associated with benefit free from harm, lack of appropriate trial methodology will greatly limit any conclusions that can be drawn from this work. Nonetheless, many patients continue to travel great distances at enormous financial cost to undergo such experimental transplantation procedures despite the inherent risk and questionable gains.

Cellular Transplantation Therapies

Because limited substrate for neural repair is a significant obstacle following SCI, cell replacement strategies are believed to be among the most promising new strategies for treating SCI. A multitude of cell types have been tried, including neural precursor cells, olfactory ensheathing cells, bone marrow–derived stromal cells, and others. The goals of these strategies differ among researchers with some aiming to produce new neurons that will integrate into functional circuits; groups such as our own have sought and achieved oligodendrocyte differentiation and remyelination.81 Despite diverse strategies, functional benefit has been consistently seen, though the magnitude of this benefit has been uniformly modest and important controversies exist regarding the purported mechanism of action of various cell types.

Unfortunately, in the field of cell transplantation, excitement and enthusiasm have exceeded the science supporting this approach; cell transplantation into injured human spinal cords is being conducted in numerous centers outside North America. Many believe that these approaches require greater optimization and understanding before human trials are undertaken. For instance, evidence suggests that some transplantation regimens may be complicated by genesis or exacerbation of neuropathic pain,70,101 which is currently poorly understood. Other serious complications have been described such as in a patient who developed tumorlike overgrowth following a procedure performed in Russia, as reported by neurosurgeons from the University of British Columbia. Even if these strategies are associated with benefit free from harm, lack of appropriate trial methodology will greatly limit any conclusions that can be drawn from this work. Nonetheless, many patients continue to travel great distances at enormous financial cost to undergo such experimental transplantation procedures despite the inherent risk and questionable gains.

Activated Autologous Macrophages (PROCORD)

Activated autologous macrophages were the first cellular substrate to be transplanted into patients with SCI in a carefully designed, rigorous clinical trial. This strategy is based on the notion that differences in the ability of axons within the CNS and PNS to regenerate are related to differences in the macrophage response within the 2 environments. For instance, in contrast to the CNS, macrophages in the PNS are abundant, rapidly clear myelin debris, and also secrete nerve growth factor.117 In the 1990s, pioneering work in an animal model of SCI by Schwartz’s group (reported by Rapalino and colleagues125) demonstrated that autologous macrophages activated ex vivo by peripheral myelin could promote functional recovery when injected into the injured spinal cord. Additionally, transplanted, autologous macrophages were associated with enhanced synthesis of beneficial trophic factors interleukin-1β and brain-derived neurotrophic factor while decreasing the synthesis of tumor necrosis factor–α, which is known to have neurotoxic effects. This technology was then commercialized by Proneuron Biotechnologies, Inc., and a clinical trial for human SCI was launched in Israel. In the initial trial 8 patients with complete SCI were enrolled, and they underwent transplantation within 14 days of injury.83 The results were published in 2005, and the investigators reported that 3 of the 8 patients with ASIA Grade A recovered to ASIA Grade C, and no major adverse events related to the cell transplant were encountered. This encouraging result led to the subsequent multicenter Phase II ProCord trial in Israel and the US. Unfortunately this trial was suspended prematurely in the spring of 2006 for financial reasons, and there are currently no plans to continue this study. Fortunately, 1-year data on safety and neurological recovery in the 50 patients enrolled will be published in 2008 (D. Lamsert, personal communication).

Schwann Cells

Schwann cells, the myelinating cells of the PNS, may represent an environment permissive of regeneration similar to the peripheral nerve grafts used by Richardson and colleagues.126 Another potential benefit of these cells is the ability to harvest them from an autologous source, such as the sural nerve. The work of Bunge15 at the Miami Project has explored this possibility since the early 1990s. A limitation of this technique, however, appears to be that regenerating CNS axons readily grow into the permissive environment that these cells provide; however, they are not prone to growing out of them and back into the hostile CNS environment. Nonetheless, a formal clinical trial in Schwann cell transplantation for SCI is being planned at the Miami Project, which, if initiated, would represent the realization of nearly a generation of pioneering scientific work in SCI for the investigators. It should also be noted that 2 groups in China have reportedly performed transplantation of peripheral nerve–derived Schwann cells into the injured human spinal cord,139 but this work has not been formally reported.
Advances in spinal cord injury therapeutics

Olfactory Ensheathing Cells

Olfactory ensheathing cells are specialized glia of the olfactory system, which may address the PNS to CNS barrier inherent to Schwann cells. The OECs’ escort regenerating axons of olfactory receptor neurons from the PNS to the CNS of the olfactory bulb. A host of promising preclinical data culminated in a report of OEC transplantation promoting axonal regeneration and functional recovery in a model of complete spinal cord transection.124 Amid these encouraging findings, however, significant controversies exist about the myelinating potential of OECs. Evidence suggests that remyelination may instead be mediated by the contaminating Schwann cells, which also bear the p75 marker.56 Nonetheless, interest remains high in this autologous transplantation strategy, and a number of centers are currently implanting OECs or tissue acquired from the olfactory region consisting of OECs and other cells in patients with SCI.

In an uncontrolled Portuguese pilot study,96 7 patients with ASIA Grade A injuries were reportedly treated with autologous olfactory mucosal implants at 6 months–6.5 years postinjury. Apparently, all patients had improvement in ASIA motor grades, and 2 progressed from ASIA Grade A to C. Additionally, 2 patients reported return of sensation in their bladders, and 1 regained voluntary anal sphincter contraction. One patient had a decline in ASIA sensory grade related to the procedure, and several patients experienced temporary pain in the trunk or lower limbs that was relieved by gabapentin and resolved after 2–3 months. However, this work has not been subjected to independent analysis, and it is unclear what to conclude from this preliminary work.

An Australian center conducted a single-blinded trial of “purified” autologous olfactory ensheathing cells in 3 patients with complete thoracic SCI within 6–32 months of injury. A comparison was made to matched but untransplanted controls.47 Before and after surgery the patients were assessed using MR imaging, medical, neurological, and psychosocial assessments, as well as ASIA and FIM scoring. One-year follow-up data revealed no motor improvement, but also absence of surgical complications or neurological worsening.47 The investigators intend to observe these patients for 3 years.

A group in China, led by Huang, is believed to have the world’s largest experience with a cell transplantation approach for SCI, having transplanted olfactory tissue from aborted fetuses into the spinal cords of > 300 patients.37 Given this experience, it is unfortunate that there is a lack of scientific methodology being applied to the selection of patients, acquisition and characterization of the transplanted tissue, and outcome evaluation, although neurological recovery is being measured according to ASIA standards in recent patients. Of note, although 1 case of rapid neurological recovery has been reported following the Huang procedure,79 surgeons in Miami found no benefit in patients assessed at their center before and after the therapy.37 It should also be noted that in Russia, Bryukhovetskiy is performing many OEC transplantations in patients with chronic SCIs as late as a decade postinjury, but little else is known about this experimental initiative.159

Bone Marrow Stromal Cells

Bone marrow stromal cells demonstrate a surprising ability to migrate to the site of CNS injury following intravascular or intrathecal administration, albeit at a low rate. Importantly, they can also be transplanted in autologous fashion like Schwann cells and OECs. A number of groups are currently transplanting BMSCs into the injured spinal cords of humans and are reporting benefit. These claims of neurological efficacy need to be interpreted very cautiously as these trials are small and generally conducted without controls or blinded observers.

A Korean group has reported the results of autologous human BMSC transplantation combined with administration of granulocyte macrophage-colony stimulating factor in a Phase I/II open-label, nonrandomized study.116,151 This trial involved 35 patients with ASIA Grade A who underwent transplantation within 14 days (17 patients), between 14 days and 8 weeks (6 patients), or at > 8 weeks (12 patients) after injury compared with 13 control patients treated with decompression and fusion only. At the time of publication, the mean follow-up was 10.4 months after injury, and neurological function was reportedly improved in 30.4% of the acute and subacute groups, but no significant improvement was observed in the chronic group. No serious adverse clinical events were noted.

Investigators in Prague have also pursued a human BMSC trial.137,139 Their trial involved 20 patients with complete SCI who underwent transplantation 10–467 days postinjury. Follow-up examinations were completed by 2 independent neurologists using the ASIA scale, and motor and somatosensory evoked potentials. Improvement in motor and/or sensory functions was noted in 5 of 7 acute, and 1 of 13 chronic patients leading the authors to suggest a therapeutic window of 3–4 weeks following injury. In 11 patients observed for > 2 years, no complications were observed.

According to Tator,139 90 patients have received similar transplants in China, and in Russia, 2 groups are using these cells in humans. In 2003, one of the Russian groups reported that of the 15 patients with ASIA Grade A in whom they transplanted fetal nervous and hematopoietic tissues, 6 improved to ASIA Grade C, and 5 improved to Grade B.123 In addition, groups in Brazil and Russia are transplanting stem cells obtained from peripheral blood, but little is known about this work.159

Human Embryonic Stem Cells

Researchers at the University of California, Irvine, led by Dr. Hans Keirstead, have reported promising results in a rat SCI model with the transplantation of human embryonic stem cells. These cells differentiate into oligodendrocyte progenitors and achieve remyelination of spared, demyelinated spinal cord axons.82,92 They have developed a technique to ensure high purity of their cell isolates, as well as techniques for culturing these cells without the need for feeder cells which could theoretically lead to viral contamination, or nonhuman polysaccharide epitopes on the surface of transplanted cells.145 These have been critical steps in making these cells suitable for human transplantation.
Indeed, the biopharmaceutical corporation Geron is attempting to bring this cell type into human clinical trials. A Phase I trial had been proposed as early as 2006.\textsuperscript{145} Geron had hoped to initiate this clinical trial in 2008; however, the FDA recently placed this trial on clinical hold for reasons that are not known at the time of this writing. Formal release of this information will be of great importance to the field as the FDA’s response to this proposed trial will set precedents of monumental importance to future cell replacement therapies in humans.\textsuperscript{145}

Conclusions

With lessons from recently completed trials in hand, over a dozen new clinical trials are underway. The possibility that at least one of these treatments will be effective for SCI is high. Furthermore, many more promising therapies are currently in preclinical studies with the promise of entering clinical trials in the near future. There is thus clear reason for researchers, clinicians, and patients to be optimistic. It is unfortunate that despite the lessons of the past, many experimental therapies and are being tested or used in an unsatisfactory fashion. Hopefully, the promotion of recently published guidelines will increase what can be learned from the patients who participate in such trials.

Disclaimer

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Neurosurg, Focus / Volume 25 / November 2008


G. W. J. Hawryluk et al.
Advances in spinal cord injury therapeutics


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