Lonjon et al., Orthopedic Muscul Sys 2012, S1
DOI: 10.4172/2161-0533.S1-002

Orthopedic & Muscular System: Current Research

Letter Open Access

Research in Acute Traumatic Spinal Cord Injuries: Progresses and Prospects

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Keywords: Spinal cord injuries; Therapeutic strategies; Cell transplantation

Acute spinal cord injury (ASCI) is a frequent pathology that mostly occurs in a brutal context and affects young people. 80 to 90% of patients with complete spinal cord injury do not show any spontaneous neurological recovery [1-3]. Quick interventions, using neuroprotective approaches that aim at limiting the extension of tissue destruction remain a first-rate strategy. In parallel, several studies focussed on making injured tissues more permissive to axonal re-growth with the aim of reconstructing functional circuits. Finally, over the last 10 years and thanks to progresses in molecular and cellular biology, cell substitution-based strategies emerged as promising and feasible therapeutic options. It appears now clear that only a global strategy involving the sequential use of several therapeutic approaches may lead to significant improvements and time is now ripe to review them briefly.

The estimated incidence of such traumatisms lies in between 10.4 and 83 cases per million of inhabitant per year [4], depending on the countries. Car accidents and falls represent respectively 35 and 33% of the cases. Natural history and clinical evolution of human acute SCI are now better known. Analyses of recent major clinical trials intended for pharmacological neuroprotection have improved our knowledge of spontaneous neurological modifications after SCI [5-7]. Most studies report significant changes in the AIS score over the first year.

About 80% of patients with an initial A score on AIS do not show any neurological change. Of the remaining 20%, 10% move to grade B and 10% to grade C. Moreover, complete quadriplegic patients appear to have a better spontaneous recovery than thoracic paraplegic patients; indeed, one third of quadriplegic patients (AIS A) move to B, C or D. Furthermore, patients initially scored B, C or D recover generally better than complete patients. Patients with severe lesions very often exhibit a partially preserved zone where sensorimotor impairment is incomplete. This region is of variable extension and sensorimotor recovery is always better and faster in this area than in unpreserved subjacent levels. Data from the EMSCI (European Multicenter Study in Spinal Cord Injury; http://emsci.org) and the "Sygen" study reported respectively 80 and 77% changes in this partially spared area over the first 3 months [6].

Because of low spontaneous recovery and lack of effective pharmacological strategies, the general interest in the use of stem cells and their derivatives has generated great hopes for spinal cord "repair". Unfortunately, premature clinical applications of cell transplantation in humans yielded disappointing results [8-10]. These transplants imply complex biological interactions between the graft and the host which deserve to be further studied, especially on the long term. Indeed, side effects of cellular transplants are not negligible. For instance, several studies in animal and humans describe an increased incidence of neuropathic pain induced by transplants [10,11]. In addition, cell transplantation by itself may cause some SCI resulting in neurological worsening [12]. Moreover, extrapolation to human of results obtained in animal require great caution; species differences should not be underscored, and thus results obtained in rodents are hardly directly applicable to human. In this respect, the use of MRI in animal studies may bring a translational tool [13,14].

The use of "large animal" models such as pigs or non-human primates are an essential step towards the evaluation of these cell transplant experiments; they will reduce the risks and avoid unnecessary future clinical trials in humans [15]. Finally, tumoral potential of these grafts on the long time should be carefully evaluated.

Cell transplant strategies are likely to be more effective in patients with incomplete SCI. Indeed, the presence of intact tissue constitutes a potential substrate for regeneration of axons. However, cell transplantation in incomplete patients requires a comprehensive evaluation for a possible spontaneous anatomical and functional improvement, in order to avoid an always possible worsening of the symptoms. Our current scientific knowledge on mid or long term potential for "repair" does not yet provide sufficient arguments that would let us consider long term and stable clinical benefit [16].

The recent discovery of neural precursor cells in the adult human spinal cord may offer an alternative to cell transplant strategies [17]. Indeed, stimulation of endogenous stem cells may induce the synthesis of permissive molecules and/or trophic agents promoting regeneration. Alternatively, one cannot exclude that appropriate stimulation of these progenitor cells could also induce their differentiation and integration in functional circuits, thus promoting spinal cord "repair". Because of possible side effects (see above) and even if in these conditions clinical benefits may be difficult to appreciate, present clinical trials are conceivable only for patients with complete spinal cord injury (AIS A).

The most appropriate lesion topography for first intention repair is the mid-thoracic region. Grafting in the cervical region could induce possible dramatic side effects. Alternatively, recovery of lumbar region lesions would be more difficult to ascertain.

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Received November 17, 2011; **Accepted** January 04, 2012; **Published** January 10, 2012

Citation: Lonjon N, Privat A, Bauchet L, Perrin FE (2012) Research in Acute Traumatic Spinal Cord Injuries: Progresses and Prospects. Orthopedic Muscul Sys S1:002. doi:10.4172/2161-0533.S1-002

Assessments (neurological, functional, psychological and quality of life scales) as well as the use of ASIA, FIM and SCIM classifications are of paramount importance. Due to the moderate clinical benefit expected and to the number of required patients for such analysis, clinical studies must be conducted on a large multicentric scale.

Delay for applying cell transplantation therapy should be ideally comprised between 1 to 6 weeks after traumatism. Grafting too early may interfere with spinal shock whereas presence of fibrotic tissues in chronic phase may be detrimental to the grafting potential. Debates on the origin of the cell to be used remain open. Even if autologous transplants may reduce many problems this strategy requires obtaining a sufficient number of cells to be grafted in a time window compatible with a possible favourable outcome. In that time frame the use of non-autologous cells such as embryonic stem cells may be the only alternative. However, current progresses with iPS cells may ultimately bring an optimal tool [18].

The importance of cell transplantation in the context of therapeutic applications of restorative CNS traumatism is undeniable. Most likely, the transplanted cells will provide trophic support and not replace damaged nerve cells. However, many obstacles still limit the therapeutic use of cell transplantations for spinal cord injured patients. It is indeed necessary not only to deepen our understanding of the sequence of cellular and molecular events after spinal cord injury, but also to control the proliferation, differentiation and fate of transplanted cells in host tissues.

Thus, nowdays only clinical measures are taken to limit the risk of worsening spinal cord lesions. To prevent secondary displacement, clinical recommendations impose to immobilize the rachis as early as possible with a rigid restraint. Ventilatory disorders have to be treated immediately at the scene of the accident and mean arterial pressure maintained at ≥80 mm Hg. The spinal cord injured patient should then be directed to an adapted medical unit (competent intensive care and surgical units with appropriate technical equipment such as MRI). Because of the absence of conclusive proofs from randomized studies, the delay and impact of spinal decompression surgery remain controversial. However, research on animal models provid strong experimental evidences of the benefit on neurologic recovery of early surgical decompression [19,20]. Clinical trials on the impact of surgery have low levels of evidence (2 or 3). Surgery is nevertheless a validated practice, and its realization in the first 24 hours is recommended [21]. Even if there is no agreement on the therapeutic window in which surgical interventions may be most beneficial; in absence of major contre-indication, most of the clinical teams perform surgery within the first forty-eight hours after traumatism. This delay is shortened to the first eight hours in case of neurological worsening or in case of cervical dislocation.

Perspective

Over the last twenty-five years, basic research made significant progresses in the understanding of the pathophysiology of SCI. To date, these efforts did not result in clinical improvements [22]. A major spinal cord research organization, the International Spinal Research Trust: IRST, www.spinal-research.org/) has recently defined key objectives for international research and resources to commit to achieve them [23]. Similarly, basic rules for clinical trials have been set up by the international organization ICCP [24].

Despite all efforts made so far, and given the limited efficacy of neuroprotective strategies in clinical trials, it remains first necessary to better understand the pathophysiological mechanisms leading to cell death after acute trauma. It is also indeed mandatory to understand the role of different processes contributing to final injury, such as the composition and consequences of glial scar formation, consequences of microvascular lesions, role of the inflammatory response, extension of cell death and factors inducing cyst formation.

Progresses are awaited in two directions: first, a comprehensive analysis of the natural history of the progression of the lesion, for which the in-time follow-up with RMN, both imaging and spectroscopy, is an appropriate tool for translational studies. Second, basic research should also focus on developing our knowledge of events occurring at molecular level. For instance, it is not only important to better understand the role of already identified factors (inhibitory or promoting) that may play a role in regeneration but also to identify other actors (and their mechanisms of action) which can promote and guide axonal re-growth and synaptogenesis [17].

Cell transplantation, associated or not with genetic engineering, appears as a field of great expectations, with an impressive development over the last decade [25]. The enthusiasm must be however, modulated by serious restrictions, including ethical considerations [26]. A major issue, in that perspective, is to decide whether transplanted cells will serve as substitutes for destroyed neurons and /or glial cells, of whether they will contribute through trophic factors to the regeneration of local circuits [27]. In that respect, an example of choice is that of the reactivation of the central pattern generator of locomotion (CPG) which can be restored either by the transplantation of serotoninergic neurons [28] or by the boosting of the regeneration of intrinsic serotonergic neurons through the trophic influence of transplanted foetal stem cells [12].

In any case, future definition of clinical trials in spinal cord injury will have to bring together pertinent preclinical data with matching groups of patients.

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This article was originally published in a special issue, **Spine Injury** handled by Editor(s). Dr. Xu Chao Jin, Wenzhou medical college, China