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Review

Spinal cord clinical trials and the role for bioengineering

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ABSTRACT

There is considerable need for bringing effective therapies for spinal cord injury (SCI) to the clinic. Excellent medical and surgical management has mitigated poor prognoses after SCI; however, few advances have been made to return lost function. Bioengineering approaches have shown great promise in preclinical rodent models, yet there remains a large translational gap to carry these forward in human trials. Herein, we provide a framework of human clinical trials, an overview of past trials for SCI, as well as bioengineered approaches that include: directly applied pharmacologics, cellular transplantation, biomaterials and functional neurorehabilitation. Success of novel therapies will require the correct application of comprehensive preclinical studies with well-designed and expertly conducted human clinical trials. While biologics and bioengineered strategies are widely considered to represent the high potential benefits for those who have sustained a spinal injury, few such therapies have been thoroughly tested with appreciable efficacy for use in human SCI. With these considerations, we propose that bioengineered strategies are poised to enter clinical trials.

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Abbreviations: ASIA, American Spinal Injury Association; AIS, ASIA Impairment Scale; ESC, embryonic stem cell; FES, functional electrical stimulation; FIM, functional independence measure; MPSS, methylprednisolone sodium succinate; NACTN, North American Clinical Trials Network; NASCIS, National Acute Spinal Cord Injury Study; NCT, National Clinical Trials database; NPC, neural precursor cell; OEC, olfactory ensheathing cell; OPC, oligodendrocyte progenitor cell; RCT, randomized controlled trial; SCI, spinal cord injury; SCIM, spinal cord independence measure; UCB, umbilical cord blood.

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1. Introduction

Knowledge of the pathophysiology and mechanisms underlying spinal cord injury (SCI) has increased greatly in recent decades due to prolific preclinical research. Advances in the basic understanding of SCI have allowed significant exploration into various therapeutic strategies for the treatment of spinal injuries (see recent systematic reviews [70,71,116]). Surgical and medical management of SCI has also seen significant advances [34], greatly increasing the survival of spinal injured persons, which will likely inform the application of novel regenerative medicines. Despite these advances and the success of several putative treatments in rodent models of SCI, a considerable translational gap remains [69]. Few recently developed biologics and bioengineered strategies are poised to cross the translational gap and enter the clinic. There has been a recent emergence of novel clinical trials in SCI, such as cell transplantation therapy, albeit with considerable difficulties.

This review aims to provide a meaningful overview of the current status of human trials for SCI, the bioengineered therapeutics poised for human application, and the proper framework needed to close the interceding translational gap. Considerations for future clinical trials will also be addressed, as informed by the recent tribulations of cancelled clinical trials. For comprehensive discussions on preclinical animal data and human clinical trials for SCI, please refer to corresponding articles within this issue and reviews elsewhere [71,113,116].

1.1. Targeting therapy

Spinal injuries involve a primary physical injury and a secondary subsequent physiological cascade that disrupts motor, sensory and autonomic functions [30,114]. These secondary sequelae can include cardiac output, vascular tone, and respiratory functions, which pose a high risk of morbidity and mortality [103]. Understanding the mechanisms of injury is crucial for developing therapeutic interventions and avoiding potential adverse consequences.

Endogenous repair and regenerative mechanisms are employed during the secondary phase of injury to minimize the extent of the lesion, to clear cellular debris, to reorganize the blood supply through angiogenesis, to form protective barriers (scarring) through astrogliosis, reunite local synaptic connections (anatomical plasticity) and to remodel damaged neural circuits (connective plasticity) [98]. These endogenous processes offer exploitable targets for therapy, and can be thought of in terms of their reparative process, or the temporal injury progression through: immediate (minutes to hours), acute (hours to days), subacute (days to weeks), and chronic (months to years) phases of SCI. Putative therapy should address one or more of these injury phases, with corresponding therapeutic targets of: (1) minimizing acute cell loss, (2) promoting sustained neuroprotection, (3) permissive tissue modification, and/or (4) functional neuroplasticity and regeneration (see Fig. 1).

1.2. Treating spinal injury: history and clinical challenges

Medical and surgical management of patients incurring spinal injuries has advanced greatly. Presentation with traumatic spinal injury long remained a condition *not to be treated*; however, surgical management improved around the Second World War, with the development of posterior stabilization and surgical decompression [55].

While peri-injury management has proven increasingly difficult, early surgical decompression, aggressive medical management and comprehensive imaging have advanced the standards of care [34]. While much preclinical data exists, the majority of which is in thoracic rodent models, there is great discrepancy in the clinical community about what preclinical data is required to take potential therapy into human trials [69]. There are examples of large prospective, controlled multicenter studies that have shown some neurological benefit, however, such as early surgical decompression and potential for corticosteroids with STASCIS [36] and NASCIS trials, respectively [6]. Recent clinical trials have evaluated corticosteroids, directly applied biologics and cell-based therapy in SCI. These trials have engendered much controversy, however, the issues raised are as much related to the current landscape of clinical trials in SCI as the therapy themselves.

2. Conducting human trials for SCI

2.1. Framework of human studies

Clear and thorough guidelines have been recently formed for conducting human trials involving patients with SCI. This framework has been defined by large collaborative efforts on the basis of clinical trial design [72], outcome measures [108] and suitable patient populations [32,118]. The premature suspension or cancellation of the first clinical trials involving directed cell transplantation therapy for SCI (see below) has underscored the importance of these considerations before moving into arduous and costly studies [83,97].

The Ottawa Statement and Declaration of Helsinki propose clear and well-regarded guidelines on the registration, operation, and reporting of global human clinical trials [105]. Despite some deliberations, the proposed guidelines have been largely accepted by the NIH, CIHR, WHO, and others internationally [26,68]. Most countries having begun legislation in this new phase of medical research with human participants, such as the Fair Access to Clinical Trials Act, a pending legislation before the U.S. Congress first proposed in 2005. Registration of clinical trials is a key issue, best posed by the International Clinical Trials Registry Platform (ICTRP), and a priori necessary by the International Committee of Medical Journal Editors (ICMJE) for publication [25]. Conversely, uncontrolled trials (i.e. without concurrent untreated/comparison group) and patient studies are not governed by these regulations or legislation and may operate outside such standards. Industry and public institutes have slowly conformed to these standards and transparencies [68,95]; however, data reported in the registry is often incomplete, changed, or inaccurate [56]. Registry and reporting is necessary to recovery from the mistrust caused by recent clinical trials scandals [15,105], and move forward with public and governmental support.