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WORKSHOP REPORT - CELL THERAPY FOR AMYOTROPHIC LATERAL SCLEROSIS

Intraspinal stem cell transplantation for amyotrophic lateral sclerosis: Ready for efficacy clinical trials?

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Abstract

Intraspinal stem cell (SC) transplantation represents a new therapeutic approach for amyotrophic lateral sclerosis (ALS) clinical trials. There are considerable difficulties in designing future efficacy trials, some related to the field of ALS and some that are specific to SCs or the mode of delivery. In October 2015, the most controversial points on SC transplantation were addressed during an international workshop intended to bring together international SC and ALS researchers in a public discussion on a topic for which expertise is limited. During the meeting, a discussion was started on the basic structure of the ideal clinical trial testing the efficacy and safety of SC transplantation. The current document includes a number of consensus points reflecting the design of phase II/III clinical trials.

Key Words: *ALS, clinical trials, stem cells, transplantation*

Introduction

Our knowledge on the molecular basis of amyotrophic lateral sclerosis (ALS) has significantly progressed over the past few years; however, such discoveries have not yet translated into new therapeutics. A critical analysis of the failure of clinical trials of proposed disease-modifying drugs in the past half-century shows potential methodological reasons that account for these negative results [1]. With the advancement of stem cell (SC) technology, clinical trials have been proposed as a novel therapeutic approach. However, when we consider the use of SCs for treatment, the level of complexity of designing SC clinical trials is further increased by the extreme physiological heterogeneity of these cells, limited knowledge about optimal dosing schedule, uncertainty about the proper way of delivery, need of immunosuppression, high trial costs and ethical concerns. Clinical trials for Parkinson disease that used primary fetal tissue have

*Please see Appendix.

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demonstrated, although with controversial results, that fetal neural SCs could be suitable for neurodegenerative diseases [2]. Recent *in vivo* studies have shown that transplanted neural stem/precursor cells display good survival and integration capacity into the damaged brain parenchyma while also eliciting putative therapeutic effects in different pathological conditions [3,4]. In these studies, in addition to integration and differentiation into neurons, astrocytes and oligodendrocytes, transplanted neural stem cells (NSCs) exerted their beneficial effects through an immunomodulatory action involving both innate and adaptive (local versus systemic) immune responses (e.g., microglial and astroglial scar reduction, T-lymphocyte inhibition), as well as secretion of trophic factors and cross correction of missing enzymatic activities.

Intraparenchymal injection has been the method of choice for most clinical studies. Local injections of SCs have the obvious advantage of placing the cells close to their therapeutic target and favor the diffusion of trophic and immunomodulatory factors to both the latter and the surrounding glia, thereby enhancing the likelihood of accomplishing therapeutic effects. Preclinical studies in ALS animal models have clearly demonstrated that SC transplantation in critical regions of the spinal cord involved in crucial functions such as respiratory capacity or the control of limb movements offer the most significant clinical benefit [5,6]. Chronic inflammation plays an important role in ALS. A most important therapeutic potential of SCs relies on their ability to regulate inflammation and to empower resident cells to facilitate tissue repair through endogenous stem cell activation or environment modulation. Both neural precursor cells [7] and mesenchymal stem cells (MSCs) [8] promote "bystander" immunomodulation because they can release soluble molecules and express immuno-relevant receptors that are able to modify the inflammatory environment. MSCs were found to attenuate neuroinflammation in SOD1G93A transgenic mice [9,10].

The first U.S. Food and Drug Administration and Italian Institute of Health–approved cell therapy trials for ALS, based on the transplantation of human neural progenitors cells (hNPC), were completed without significant side effects [11,12]. However, substantial challenges must be addressed and resolved to advance the use of SC transplantation in efficacy trials for ALS. We discuss the most controversial points addressed during an international workshop intended to bring together international SC and ALS researchers in a public discussion of a topic on which expertise is limited. During the meeting, a discussion was started on the basic structure of the ideal clinical trial testing the efficacy and safety of intraspinal SC transplantation. The current document includes a number of consensus points reflecting the design of phase II/III clinical trials.

What have we learned from the first generation of clinical trials of intraspinal stem cell transplantation?

Few studies have addressed the safety of intraspinal SC transplantation in small phase I/II clinical trials [11–15]. The most consistent results of the first phase I clinical trials indicate that ALS patients tolerate the surgical procedure and that the intraparenchymal delivery of the cells into the spinal cord is safe in expert hands. Surgery was uncomplicated in most patients, and few side effects were reported. In all published trials, the most common negative event was transient pain in the surgery site. The atrophic spinal cord of ALS patients is capable of tolerating up to at least 3 mL of cell suspension and 20 sites of injection at all segments (cervical, thoracic, and lumbar) [13,14]. Both bone marrow SCs (MSCs and hematopoietic SCs) and fetal NSCs have shown no abnormal growth or tumor formation even in the long term up to 9 years for bone marrow SCs and 2 years for NSCs [12]. In all clinical trials, the risk of teratogenicity have been reduced with the administration of pluripotent SCs or by differentiating SCs *in vitro* into postmitotic phenotypes before administration [13]. *Post mortem* analysis showed the integrity and survival of the grafted cells up to 2.5 years post-transplantation [15,16]. Secondary proliferative lesions have been reported after SC transplantation in the context of SC tourism [17]. All published studies demonstrated no acceleration in the course of the disease due to the treatment. These results are not definitive but provide clear signals that cellular grafting is feasible and relatively safe in ALS patients and support moving towards efficacy trials.

Translation into phase II/III clinical trials: barriers and challenges

Patients selection

In phase I clinical trials, the primary aim is to assess safety using a risk escalation paradigm [18]. Invasive procedures, in fact, can generally be justified in patients with significant disability to be later extended to less severely affected patients. In phase II/III clinical trials, more restrictive inclusion/exclusion criteria should be adopted to reduce the heterogeneity of disease progression. Similar to pharmacological trials, the maximum disease duration for the inclusion is proposed to be 2 years from symptom onset with a maximum age of 65 years (range: 18–65 years). Younger patients might benefit more than older patients as also evidenced in Parkinson disease [19]. The cells, in fact, should survive and integrate well in the adult brain and spinal cord; however, the supportive host environment starts to decline in aged individuals. Moreover