ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Amyotrophic Lateral Sclerosis (ALS)

INTRODUCTION

ALS is a relentless and incurable disease that involves the death of motor neurons in the brain and spinal cord that control voluntary movement, eventually leading to complete paralysis. While progression can range from rapid to slow, the average time course from disease onset to death is about three years. One of the most difficult parts of the disease arises when the motor neurons that control breathing are affected and the patient needs to decide whether to use the support of an artificial breathing machine. Many chose not to. A genetic cause contributes to about 10-15% of ALS cases, for which therapies to silence the gene product are being explored using antisense oligonucleotides and viral methods. Most patients, however, have a sporadic form of the disease. To date, there are no drugs that can help any of these patients. One area that has received a lot of attention is cell-based therapies for ALS.

RATIONALE FOR USING CELL-BASED THERAPIES FOR ALS

The most obvious cellular approach is to generate new motor neurons from stem cells to replace the ones lost in ALS. It is possible to make new motor neurons from a patient's own stem cells, and these can survive transplantation into the brain and spinal cord. The problem with this approach, is that placing these cells throughout the length of the spinal cord, brainstem and cortex is currently not possible nor can we get these cells to connect to their original targets. An alternative approach is to protect diseased motor neurons using stem or progenitor cells that can be isolated from various adult tissues, for instance the bone marrow or fetal brain. Stem or neural progenitor cells can differentiate into a glial phenotype and, once transplanted into the brain or spinal cord, may take up deleterious factors from the milieu, reduce disease-related inflammation and release potent growth factors that nourish dying motor neurons. A final approach is intravenous infusion of autologouse T-regulatory (Treg) lymphocytes, which may reduce ALS-related inflammation.

WHERE ARE WE WITH CELL BASED THERAPIES AND CLINICAL TRIALS FOR ALS?

There are no clinical trials aimed at replacing the motor neurons that are lost in ALS for the reasons given above. However, there are a few completed and ongoing trials using stem cells to modulate disease progression in ALS. These have generally used bone marrow-derived mesenchymal stem cells (MSCs) that are typically expanded in culture and then transplanted into the cerebral spinal fluid (CSF). There are currently over 40 trials either completed or started using MSCs to treat ALS in this way (ClinicalTrials.gov). In some cases, there have been some signals of effect, but these are mainly Phase I safety studies and as such any claims for efficacy need to be viewed with great caution. In a recent Phase II study, the company Brainstorm harvested and differentiated adult MSCs that secrete neurotrophic factors, and reported some positive results (ClinicalTrials.gov: NCT02017912). This has led to an ongoing larger Phase III trial by Brainstorm (ClinicalTrials.gov: NCT03280056). The treatment is repeated at three bi-monthly intervals as the cells only remain viable for a few months. These cells could help reduce inflammation through modulation of cytokines and the release several neurotrophic factors including glial cell line-derived neurotrophic factor (GDNF). The results of this Phase III trial will help to determine if this type of treatment is definitively efficacious. Another Phase 1/2a trial is assessing genetically engineering neural progenitor cells that stably release GDNF. These cells are transplanted into the spinal cord of ALS patients (ClinicalTrials.gov: NCT02943850). The cells are only given once and are meant to survive and release GDNF for the lifetime of the patient. Investigators running both of these trials plan to present results in late 2019 or early 2020. Finally a small Phase I trial

using autologous Tregs has shown safety and preliminary positive effects, but this needs to be expanded to more patients and a Phase II study (ClinicalTrials.gov: NCT03241784).

MAJOR CENTERS WORKING ON THE CLINICAL APPLICATION OF STEM CELLS FOR ALS

Many centers globally are involved with MSC trials for ALS. The ongoing stem cell trials in the USA are being done by Brainstorm, which includes many clinical sites across the USA, and by the Cedars-Sinai Medical Center. One of the important criteria for credible and responsible clinical trials for ALS is compliance with regulatory authorities, such as the FDA. There are also many clinics offering "stem cell therapies" that are not being performed with approrpaite regulatory permission or oversight. For a source of information about how to avoid such clinics please visit the ISSCR website https://www.closerlookatstemcells.org/patient-resources/

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