

TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS USING STEM CELL THERAPY



Introduction

Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressing degenerative disease that selectively attacks motor neurons in the cortex, in the brain stem and in the spinal cord, and leads to muscle weakness, muscle atrophy, fasciculations, spasticity, paralysis and eventually to death within 3–5 years after the appearance of the clinical symptoms. It is generally known, that the annual death rate due to ALS is 2 deaths per 100.000 people (200 people in the Czech Republic alone, and 140.000 people worldwide). ALS most commonly strikes people between 40 and 60 years of age, but younger and older people may also suffer from this disease. Men are affected more often

than women. ALS occurs in both sporadic (90 %) and familial forms (10 %). The exact mechanism leading to motor neuron degeneration is not known, but it is believed that the pathogenesis of the disease involves a complex series of various mechanisms. Despite improved understanding of the mechanisms underlying ALS, treatment remains essentially only supportive and focused on symptomatic relief. Over the past few years, stem cell research has expanded greatly as a tool for developing new therapies to treat incurable diseases among which ALS also belongs. Stem cell therapy has proved promising on several animal models of ALS and human clinical studies.

Cellular therapy – new challenge in the treatment of ALS

The limited effect of the pharmacological treatment (Rilutek) has led some researchers to investigate the therapeutic potential of stem cell transplantation. Considering the need for a more complex approach, much attention has been placed on cellular therapy as a promising new treatment strategy for ALS. Optimal source for the neurotransplantation seem to be some types of stem cells, particularly the so-called mesenchymal stem cells. These stem cells can repair damaged and degenerated tissue by replacing dying population of cells, or they can rescue cells in the degenerating brain or spinal cord by producing of cytokines (interleukins) and/or neurotrophic factors that slow down degenerative processes.

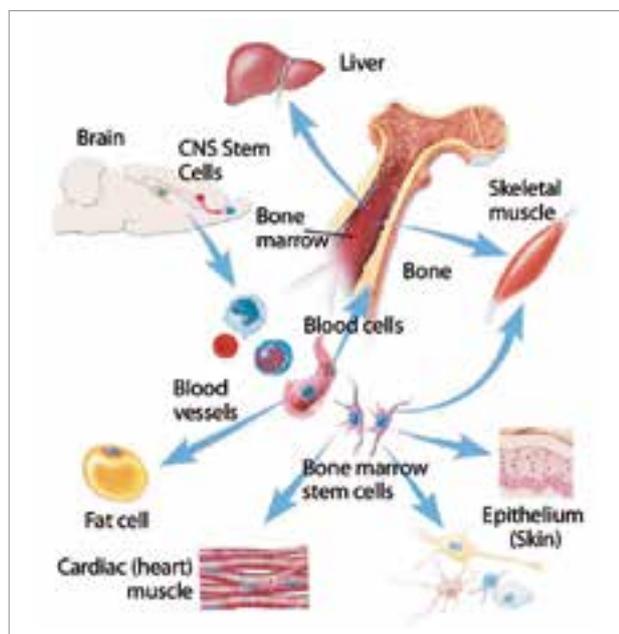


*"We want to, we have to and we will treat even the most incurable patients" says professor **Eva Sykova, M.D., Ph.D., D.Sc., Director of the Institute of Experimental Medicine AS CR, EU Centre of Excellence (IEM AS CR), with hope in her eyes about the future treatment of ALS patients using mesenchymal stem cells.***

Mesenchymal stem cells

Mesenchymal stem cells (MSC) are heterogeneous populations of stem cells that can be isolated from a variety of tissues such as bone marrow, adipose tissue, umbilical cord tissue or blood, etc. They have the ability to change (differentiate) into a wide range of cell types, such as bone cells, cartilage, tendon, muscle cells and adipose tissue, as well as neurons (nerve cells), cardiomyocytes (heart cells) or insulin-producing cells. The mesenchymal stem cells produce specific growth factors (neurotrophic factor BDNF-brain-derived neurotrophic factor, neural growth factor-NGF or insulin growth factor 1-IGF-1) and cytokines (a group of signaling proteins that are significantly involved

in the immune response), which support the expansion and the differentiation of hematopoietic cells. They can be easily isolated and expanded in culture with no risk of malignant transformation. The administration into the body is accompanied only with very mild side effects and induces only a low immune response, and thus they are destined for frequent clinical use. It is therefore apparent that MSC have unique immunological and biological properties, inter alia they also exhibit anti-proliferative (inhibits the growth of certain cells), immunomodulatory and anti-inflammatory effects. **Mesenchymal stem cells are therefore good candidates for use in the regenerative medicine and the cell therapy.**



Mesenchymal stem cells (MSCs) were first well-defined in 2001 and since then, a multitude of preclinical experiments and clinical studies have verified their safety in various indications and modes of application. **Thanks to their great plasticity, their biological properties and their ability to modulate the host immune system, the MSC seem to be very attractive source for the treatment of ALS.** MSCs have been repeatedly tested with success on rodent models to treat diseases such as CNS trauma and ALS. After the transplantation MSC can freely migrate to the brain and spinal cord. MSC transplantation in animal models has shown increased survival of neurons and oligodendrocytes (glial cells responsible for myelin formation) and has prevented the pathological changes leading to the development of ALS. Finally, MSCs can promote the proliferation (newly formed cells) and maturation of local neural precursor cells, leading to their differentiation into mature neurons and oligodendrocytes.

“MADE IN” Bioinova: Suspensions of Human Autologous MSCs

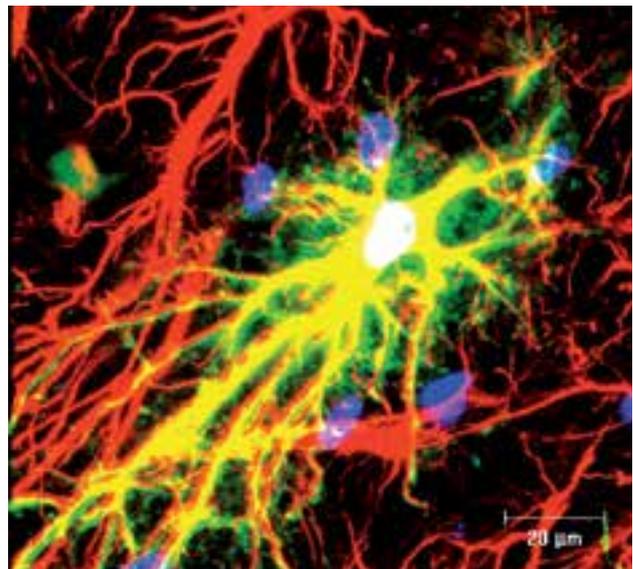
Experimental treatment carried in the Teaching Hospital Motol in Prague, Czech Republic uses mesenchymal stem cells harvested from the bone marrow, which, as we have mentioned above, are capable of differentiating (maturing) and transform into a number of different cell types. In this clinical trial, mesenchymal stem cells are taken from the participant's bone marrow, cultured into healthy cells (pre-determined number of cells) capable of delivering neurotrophic factors (molecules that support motor neurons, the nerve cells that die in ALS) and then re-administered to the participants from whom they were taken. The aim here is to verify the safety of administrated substances into the human body and thereby induce a reduction and a slowdown of the development of neurodegenerative diseases (by delivery of trophic factors that support dysfunctional neurons and inhibit cell death).

The main substance consists of cultivated (expanded to 3rd passage of multiplication) human autologous mesenchymal stem cells collected from bone marrow blood at a concentration below 0.1 %. The medicinal product is a suspension composed of these cells (as the active component) and diluent. The expansion process (multiplication), which utilizes plastic adhesion as a selection criterium, purifies this active component.

The method and amount of administration: Single intrathecal infusion (administered into the spinal canal) composed of approx. 1.5 ml of a suspension of cultivated autologous mesenchymal stem cells.



This product was developed in Bioinova, in cooperation with the IEM AS CR. The product is based on our research of appropriate storage conditions for human MSCs with regard to their viability. The development of the manufacturing process was focused on finding and validating a sufficient primary packaging (cryo-test-tubes) with respect to the ease of application and mechanical stability. The seal tightness was validated. The product is manufactured in the clean rooms of Bioinova following Good Manufacturing Practice (GMP). This novel investigational medical product, its pre-clinical testing and its intended clinical utilization are well-positioned in the context of current (cellular) research for advanced therapies. Neurodegenerative diseases such as ALS have recently become the target of stem cell-based therapeutic approaches that hold considerable promise as potential means of improving or supporting the repair and regeneration of damaged or lost tissues.



About us

BIOINOVA Ltd., a certified manufacturer of medicinal products for clinical trials, came into being in 2008 as a spin-off company of the Institute of Experimental Medicine AS CR with the aim of increasing the efficiency and innovative potential of knowledge transfer from research institutions into clinical practice through their connection to the business and application spheres. Bioinova has a production capacity for aseptic processes (class A/B) and an international team of qualified professionals who specialize in preparing manufacturing processes, clinical trials and registration procedures for somatic cell therapy products. Since 2010, Bioinova has had permission from the State Institute of Drug Control for the aseptic production of pharmaceutical products based on mesenchymal stem cells for phase I, II and III clinical trials. The certificate is valid in all EU countries. Production takes place in class A/B clean rooms in accordance with the rules of Good Manufacturing Practice (GMP) laid down in Directive 2003/94/EC. Bioinova is located in the **Innovative Biomedical Centre of the Institute of Experimental Medicine AS CR**. Bioinova is a respected company and a trusted supplier of cellular materials for clinical trials and medical practice.



The "ROLE" of Bioinova

Effective treatments for ALS – as a devastating disease – have eluded researchers for many years. **In 2013 alone, there were 117 active projects worldwide to fight against ALS – according to the international institution ALS Association the total amount of money spent during this period was nearly \$20.000.000**, which proves the global severity of the disease. The Bioinova Company, in collaboration with scientific teams of Institute of Experimental Medicine ASCR, makes every effort to find effective, efficient and affordable treatment, based on the application of the suspension of autologous mesenchymal stem cells. Now, there is encouraging new evidence that a high dose of cells and the direct delivery of MSCs together with various growth factors leads to a marked improvement in the prognosis and life span of experimental rats in an animal model of ALS (preclinical safety study in rats NOV/2011 – FEB/2012). This data suggests that intrathecal injection with an optimized cell number could be a potential route for stem cell therapy in ALS patients. This led Bioinova, as the study sponsor, to propose a clinical trial using MSCs for the treatment of amyotrophic lateral sclerosis using autologous MSC from the bone marrow. This clinical study is already running – in phase IIa. of development (JAN/2012 – DEC/2016). The title of the study is: A Prospective, Non-randomized, Open Label Study to Assess the Safety and Efficacy of Autologous Multipotent Mesenchymal Stem Cells in the Treatment of Amyotrophic Lateral Sclerosis. Participants will receive one dose of autologous mesenchymal stem cells, but we plan to use repeated transplants as well. Following the administration of the cells, the subjects will be followed up for 18 months.

The vision of Bioinova is to develop and implement its own innovative products in the field of cell therapy and tissue engineering, and place them in the global healthcare market.

Why you should trust us

Scientists from the IEM AS CR and the team at Bioinova have made great progress in understanding basic stem-cell biology and are working intensely to find ways to translate that knowledge into practical therapies for patients. Although there is still much work to be done, the collaborative model for scientific discovery is lending momentum and direction to the lofty goal of developing stem-cell therapies for treating people with ALS.



Bioinova, as a subsidiary company of the Institute of Experimental Medicine ASCR, has taken to previous research of the Institute on ALS and gradually expanded further knowledge of the research. From 2002 the IEM AS CR has treated more than 45 patients with spinal cord injury with autologous bone marrow mesenchymal stem cells and found that the application of these cells is well tolerated and safe. Bioinova with its studies on an animal model of ALS confirmed these results and expanded its scope also on human patients suffering from this disease. According to the animal model this procedure is able to delay the decline in motor function and to increase the overall survival of symptomatic animals. It is expected that the same effect will be found in humans.

YES, WE WANT TO GO AND MOVE ON! WILL YOU HELP US TOO?



On the basis of the latest scientific knowledge, it can be said that stem cells have opened new perspectives for the treatment of neurodegenerative diseases as well as for the potential cure of ALS patients. It is evident that MSCs have neuroprotective and immunomodulatory effects and are with its unique biological properties destined to be used as an advanced therapy medicinal product. Therefore, we would like to initiate a new clinical trial with newly defined aim of achieving the highest goal – using biological activities of mesenchymal stem cells and in response to the already achieved clinical results to find a new, safe and effective treatment for patients suffering from ALS.

Therefore, please accept our challenge and engage into the scientific research. The results of the studies are an important step, and they enable the practical application of research findings in clinical practice!



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