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A GUIDE FOR PATIENTS

LITERATURE

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❖ Amyotrophic lateral sclerosis (ALS)

➢ ALS Pathogenesis and Therapeutic Approaches: The Role of Mesenchymal Stem Cells and Extracellular Vesicles

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative
A disease characterized by progressive muscle paralysis determined by the degeneration of motoneurons in the motor cortex brainstem and spinal cord. The ALS pathogenetic mechanisms are still unclear, despite the wealth of studies demonstrating the involvement of
Several altered signaling pathways, such as mitochondrial dysfunction, glutamate excitotoxicity, oxidative stress, and neuroinflammation. To date, the proposed therapeutic strategies are targeted to one or a few of these alterations, resulting in only a minimal effect on the disease course and survival of ALS patients. The involvement of different mechanisms in ALS pathogenesis underlines the need for a therapeutic approach targeted to multiple aspects. Mesenchymal stem cells (MSC) can support motoneurons and surrounding cells

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➢ Mechanisms underlying the protective effects of mesenchymal stem cell-based therapy

Mesenchymal stem cells (MSCs) have been extensively investigated for the treatment of various diseases. The therapeutic potential of MSCs is attributed to complex cellular and molecular mechanisms of action including differentiation into multiple cell lineages and regulation of immune responses via immunomodulation. The plasticity of MSCs in immunomodulation allow these cells to exert different immune effects depending on different diseases. Understanding the biology of MSCs and their role in treatment is critical to determine their potential for various therapeutic applications and for the development of MSC-based regenerative medicine.

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➢ Mesenchymal Stromal Cell Therapies for Neurodegenerative Diseases

Mesenchymal stromal cells are multipotent cells that are being used to treat a variety of medical conditions. Over the past decade, there has been considerable excitement about using MSCs to treat neurodegenerative diseases, which are diseases that are typically fatal and without other robust therapies. In this review, we discuss the proposed MSC mechanisms of action in neurodegenerative diseases, which include growth factor secretion, exosome secretion, and attenuation of neuroinflammation.

We then provide a summary of preclinical and early clinical work on MSC therapies in amyotrophic lateral sclerosis, multiple system atrophy, Parkinson's disease, and Alzheimer's disease. Continued rigorous and controlled studies of MSC therapies will be critical to establish efficacy and protect patients from possible untoward side effects.

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➢ NurOwn, phase 2, randomized, clinical trial in patients with ALS

To determine the safety and efficacy of mesenchymal stem cell (MSC)-neurotrophic factor (NTF) cells (NurOwn®, autologous bone marrow-derived MSCs, induced to secrete NTFs) delivered by combined intrathecal and intramuscular administration to participants with amyotrophic lateral sclerosis (ALS) in a phase 2 randomized controlled trial.

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➢ Therapeutic Potential of Mesenchymal Stromal Cells and MSC Conditioned Medium in Amyotrophic Lateral Sclerosis (ALS)

Administration of mesenchymal stromal cells (MSC) improves functional outcomes in the SOD1G93A mouse model of the degenerative motor neuron disorder amyotrophic lateral sclerosis (ALS) and in models of other neurological disorders. We have now investigated the effect of the interaction between MSC and motor neurons (derived from both non-transgenic and mutant SOD1G93A transgenic mice), NSC-34 cells, and glial cells (astrocytes, microglia) (derived again from both non-transgenic and mutant SOD1G93A ALS transgenic mice) *in vitro*. In primary motor neurons, NSC-34 cells, and astrocytes, MSC conditioned medium (MSC CM) attenuated staurosporine (STS) – induced apoptosis in a concentration-dependent manner. Studying MSC CM-induced expression of neurotrophic factors in astrocytes and NSC-34 cells

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➢ Phase I Trial of Repeated Intrathecal Autologous Bone Marrow-Derived Mesenchymal Stromal Cells in Amyotrophic Lateral Sclerosis

Stem cell therapy is an emerging alternative therapeutic or disease-modifying strategy for amyotrophic lateral sclerosis (ALS).

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The aim of this open-label phase I clinical trial was to evaluate the safety of two repeated intrathecal injections of autologous bone marrow (BM)-derived mesenchymal stromal cells (MSCs) in ALS patients. Eight patients with definite or probable ALS were enrolled. After a 3-month lead-in period, autologous MSCs were isolated two times from the BM at an interval of 26 days and were then expanded in vitro for 28 days and suspended in autologous cerebrospinal fluid. Of the 8 patients, 7 received 2 intrathecal injections of autologous MSCs (1×10^6 cells per kg) 26 days apart

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➢ Mesenchymal Stem Cells: A Potential Therapeutic Approach for Amyotrophic Lateral Sclerosis?

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the degeneration of both upper and lower motor neurons. Patients show both motor and extra-motor symptoms. A cure is not available at this time, and the disease leads to death within 3–5 years, mainly due to respiratory failure. Stem cell therapy is arising as a new promising approach for the treatment of neurodegenerative disorders. In particular, mesenchymal stem cells (MSCs) seem the most suitable type of stem cells, thanks to their demonstrated beneficial effects in different experimental models, to the easy availability, and to the lack of ethical problems.

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➢ Neuroprotective Potential of Cell-Based Therapies in ALS: From Bench to Bedside

Motor neuron (MN) degeneration is a main feature of amyotrophic lateral sclerosis (ALS), a neurological disorder with a progressive course. The diagnosis of ALS is essentially a clinical one. The most common symptoms include a gradual neurological deterioration that reflect the impairment and subsequent loss of muscle functions. Up-to-date ALS has no therapy that would prevent or cure a disease. Modern therapeutic strategies comprise of neuroprotective treatment focused on antiglutamatergic, antioxidant, antiapoptotic, and anti-inflammatory molecules.

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➢ Stem cell therapy in amyotrophic lateral sclerosis: A methodological approach in humans

Introduction: Recently it has been shown in animal models of amyotrophic lateral sclerosis (ALS) that stem cells significantly slow the progression of the disease and prolong survival. We have evaluated the feasibility and safety of a method of intraspinal cord implantation of autologous mesenchymal stem cells (MSCs) in a few well-monitored patients with ALS.

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➢ Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), formerly known as Lou Gehrig's disease, is a neurological disorder that affects motor neurons, the nerve cells in the brain and spinal cord that control voluntary muscle movement and breathing.

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➢ The multifaceted role of kinases in amyotrophic lateral sclerosis: genetic, pathological and therapeutic implications

By reviewing recent findings on kinase function in ALS, Guo *et al*. show that kinases are implicated in ALS disease progression on three levels: a) genes encoding kinases are causal or risk genes in ALS; b) kinases interact with proteins encoded by ALS genes; and c) kinases participate in major ALS disease mechanisms.

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➢ The role of excitotoxicity in the pathogenesis of amyotrophic lateral sclerosis

Unfortunately and despite all efforts, amyotrophic lateral sclerosis (ALS)

remains an incurable neurodegenerative disorder characterized by the progressive and selective death of motor neurons.

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➢ SOD1 misplacing and mitochondrial dysfunction in Amyotrophic lateral sclerosis pathogenesis

Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease presenting as sporadic (sALS) or familial (fALS) forms. Even if the list of the genes underlining ALS greatly expanded, defects in superoxide dismutase 1 (*SOD1*), encoding the copper/zinc SOD1

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➢ Calcium Dyshomeostasis and Lysosomal Ca^{2+} Dysfunction in Amyotrophic Lateral Sclerosis

Recent findings in the understanding of amyotrophic lateral sclerosis (ALS) revealed that alteration in calcium (Ca^{2+}) homeostasis may largely contribute to motor neuron demise. A large part of these alterations is due to dysfunctional Ca^{2+}-storing organelles, including the endoplasmic reticulum (ER) and mitochondria.

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➢ The role of excitotoxicity in the pathogenesis of amyotrophic lateral sclerosis

Introduction: Recently it has been shown in animal models of amyotrophic lateral sclerosis (ALS) that stem cells significantly slow the progression of the disease and prolong survival. We have evaluated the feasibility and safety of a method of intraspinal cord implantation of autologous mesenchymal stem cells (MSCs) in a few well-monitored patients with ALS.

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info@stemcellcareindia.com

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