

## Mesenchymal Stem Cells As A Therapeutic Option For Patients With ALS

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### Abstract

It has been postulated that mesenchymal stem cells could play a role in treatment of patients with amyotrophic lateral sclerosis. Variety of mechanism behind MSC action has been proposed including immunomodulation and delivery of trophic factors. The scientific rationale in preclinical studies is being proved along with first clinical uses. Recent advances in stem cell research rises new hope for patients with ALS.

**Keywords:** Mesenchymal stem cells; Amyotrophic lateral sclerosis; Pathophysiology

### Background

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with poorly understood pathophysiology. Death of upper and lower motor neuron results in weakness and paralysis of skeletal muscles including respiratory musculature. Disease typically begins with muscle weakness and atrophy or progressive bulbar palsy and leads to respiratory distress and death about 5 years from the diagnosis. About 1-2 new cases per 100000 per year are diagnosed, about 10% is familial and connected with superoxide dismutase 1 (SOD1) mutation.

Despite scientific development, there is no successful treatment for ALS, riluzol only prolongs survival for about 10-20% [1]. Stem cell treatment might be a disease-modifying strategy for ALS patients. Mesenchymal stem cells (MSC) have been defined by International Society for Cellular Therapy, they are known to be weakly or non-immunogenic and thus applicable in an allogeneic setting [2]. Wharton's jelly-derived MSC (WJ-MSC) seem to be a preferable source because of easiness and safety of the harvesting procedure as well as a rich number of cells contained in the umbilical cord. WJ-MSC have high immunomodulatory capabilities as well as good proliferation and differentiation potential. Their characteristics close to embryo-derived stem cells but with lower risk of potential tumorigenesis [3].

### Mechanism of action

The mechanism behind ALS are not entirely known. Studies on animal models have been undertaken to deepen understanding of the disease and explore potential mechanisms of treatment with MSC. The hypothesis include indirect effects such as the delivery of growth factors in situ, modulation of glial cells secretome, up-regulating regulatory T-cell activity. Preclinical studies showed that MSC express 12 neural genes and 11 transcription factors, and are able to differentiate into neural and glial cells in an appropriate media [4].

Sun et al. [5] study on ALS animal model proved that MSC plays a role in neuroprotection of motor neurons, astrocytes, microglia, and modulates their response to apoptosis. Modulation of response to inflammation by down-regulating expression of TNF $\alpha$  and IL-6 and iNOS was observed as well. According to Uccelli et al. [6] study, paracrine mechanisms are more probable than local production of growth factors since MSC intravenous infusion into mouse ALS model lead to amelioration of motor neuron function, slowdown of weight loss and survival improvement, despite low engraftment rates. The results of co-culture of MSC with peripheral blood mononuclear cells

derived from ALS patients, showed up-regulation of anti-inflammatory cytokines levels including IL-4, IL-10 and TGF- $\beta$ , and increased regulatory T-cell/total lymphocyte ratio [7].

### Preclinical studies

It has been confirmed during *ex vivo* experiment that WJ-MSC maintain their immunomodulatory properties upon a long-term culture and preserve genetic stability through expansion up to 15 passages without chromosomal changes and malignant transformation both *in vitro* and after MSC injection into nude mice with follow-up of 4 weeks [8]. Some investigators in preclinical studies gave insight into possible MSC mechanisms in treating ALS. Marconi et al. [9] study explored effect of systemic injection of autologous adipose tissue-derived MSC into mouse model of ALS. Stem cell administration slowed down the deterioration of motor neuron function by 4-6 weeks. The study revealed higher number of lumbar motor neurons on the neuropathologic examination as well as higher level of both glial-derived neurotrophic (GDNF) and basic fibroblast growth factors (bFGF). Since MSC are able to produce bFGF, but not GDNF, the investigators hypothesize that MSC in ALS treatment acts through enhancement of neuroprotection by producing soluble factors that modulate biological functions of local glial cells. Boido et al. [10] administered human MSC into cisterna lumbalis of ALS mouse model and observed prevention of IL-10 and vascular endothelial growth factor down-regulation and increased IL-13 production. Another study showed promising results after multiple intravenous infusions of amniotic-derived MSC into ALS mouse model [11]. An intravenous delivery of bone marrow-derived MSC (BM-MSC) on animal model was found to be effective in ameliorating disease course and alternating cytokine profile [12].

### Clinical setting

The first use of MSC in a clinical setting of ALS was reported by Mazzini et al. [13]. The study was done on 9 patients who received

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Received March 9, 2016 Accepted April 21, 2016 Published April 27, 2016

**Citation:** Boruczkowski D, Gładysz D, Grudniak M, Kosterna K, Pawelec K (2016) Mesenchymal Stem Cells As A Therapeutic Option For Patients With ALS. Gen Med (Los Angel) 4: 235. doi:10.4172/2327-5146.1000235

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autologous BM-MSc via intra spinal delivery in an unstandardized dose and number of injections. There were no serious adverse effects and no clinical improvement. Four patients complained of pain in the intercostal area, 5 patients reported dysesthesia in lower limbs. Symptoms subsided up to 6 weeks after MSC administration. The investigators concluded that MSC administration in ALS patients appears to be safe and well-tolerated [13]. The same patients were evaluated 3 years after MSC therapy. A slowdown of the decline of the forced vital capacity was observed in 4 patients [14]. The same therapeutic approach was repeated on 10 patients with ALS. Similar adverse effects were described [15]. The long-term follow up of above-described patients equaled nearly 9 years. No slowing down of ALS clinical course was observed, however no disease acceleration or new tissue formation was reported [16].

A study conducted by Prabhakar et al. [17] evaluated influence of autologous BM-MSc over ALS disease course. Ten patients underwent lumbar puncture with stem cell administration and no adverse effects were observed. The authors concluded that MSC administration led to disease stabilization in 1 year period of follow-up since no significant deterioration in ALS Functional Rating Scale was noted.

Karussis et al. [18] intravenously or intrathecally infused autologous BM-MSc in 19 ALS patients, in a few cases stem cells were labelled with superparamagnetic iron oxides. Adverse effects were non-serious and self-limiting, and included: fever, headache, lower limb pain, dyspnea. No late adverse effects were noted during follow-up of 6-25 months. The course of the disease remained stable or lightly improved in most of the cases. MRI study on patients who received labelled cells showed that MSC infused in the lumbar area were detected in the occipital horns of the ventricles, subarachnoid space and spinal cord. Immunological analysis proved that first immunomodulatory effects were detectable just 4 hours after MSC administration and consisted of down-regulation of lymphocyte proliferative responses and up-regulation of CD4+CD25+ regulatory T cells [18].

Another study administered autologous mesenchymal stem cells intravenously and intrathecally. Stem cells infused through lumbar puncture were committed to neuronal differentiation. Disease progression was observed in study and control group, however its dynamics was significantly slower in patients who received stem cell therapy [19].

Oh et al. [20] conducted an open label phase I clinical trial with intrathecal injections of autologous BM-MSc. Seven out of 8 patients received 2 doses with time interval of about 1 month. No serious adverse effects were noted within 12 months of follow-up. The course of the disease seemed to be slower after therapy in comparison to previous decline. A retrospective analysis of 57 ALS patients, including 20 controls and 37 patients treated with autologous bone marrow mononuclear cells, showed survival benefit of stem cell therapy [21]. Another approach was demonstrated by Deda et al. [22] and Blanquer et al. [23]. The first above-mentioned study delivered bone marrow-derived hematopoietic progenitor cells to 13 patients via total laminectomy and under general anesthesia [22]. The second one administered neurosurgically BM-MNC to patients with bulbar-onset ALS and noted slower disease progression [23].

## Summary

Application of stem cells as an actual therapy for ALS patients is still in debate. It is a promising method, however current results are difficult to evaluate due to vast heterogeneity of patients and therapeutic schemes as well as lack of long-term follow-up. A growing number of clinical trials undertake this issue to assess answers about MSC efficacy

and safety. WJ-MSc seem to be an interesting source for therapeutic use.

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