Stem Cell Therapy for Amyotrophic Lateral Sclerosis: Yesterday, Today and Tomorrow

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Stem Cell Therapy for Amyotrophic Lateral Sclerosis: Yesterday, Today and Tomorrow

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease, which have no any effective treatment method. There are various pathophysiological processes underlying the disease such as oxidative stress, glutamate toxicity, inflammation and loss of the giall neurotrophic support. There is no cure yet for ALS but there are many clinical trials that focused different therapeutic targets. One of the most popular treatment methods is cell transplantation. The cell-based therapies are promising for ALS patients with many evidences including beneficial effects in protection neurons and replacement of degenerated neurons. For this purpose many types of stem cells such as embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), neural stem cells (NSCs) and olfactory ensheathing stem cells (OESCs) can be used. In recent years ongoing experimental stem cell applications from all over the world seems to be a groundbreaking in medicine although, there are many challenges. As a result, cell transplantation has become a promising therapeutic option for ALS. In this article, we reviewed stem cell treatment modalities for ALS in the light of current literature.

Keywords

Stem cell; Regeneration; Amyotrophic lateral sclerosis

Introduction

Amyotrophic lateral sclerosis (ALS) is one of a group neurodegenerative disease, which have no any treatment method effectively. Although, ALS has been known for over a century, the patients are usually lost shortly after diagnosis due to respiratory failure. Today's applied stem cell therapies provide a glimmer of hope to ALS patients for the future in contrast to classical treatment methods. In this article, we review the stem cell treatment modalities for ALS in the light of the literature.

ALS, also known as Lou Gehrig's disease, was described in 1874 by Jean-Martin Charcot [1]. It is a fatal disease characterized by the degeneration of upper and lower motor neurons. Generally resulting in death due to respiratory failure an average of three years after the beginning of symptoms [2]. The disease occurs more common in adult men than women and incidence rates increase with age [3].

Pathological Mechanisms

Although ALS is easily recognizable by clinically, there are a lot of underlying pathophysiological processes. Mutations in Cu2+/Zn2+ super-oxide dismutase (SOD1) and TAR DNA binding protein-43 (TDP-43) have been regarded to relate with ALS [4,5]. Hexanucleotide repeat expansions in the 5' noncoding region of the C9ORF72 gene is another recently discovered mutation regarding familial form of ALS [6]. Another pathophysiological process is excitotoxicity. It means abnormal cell death due to enhanced activity of glutamate that the main excitatory neuromediator of central nervous system (CNS).

Nogo A is a neuromuscular junction protein that inhibits regrowth of axons. It was showed that Nogo A levels are increased in ALS patient and rat models [7]. Furthermore, it is known connection of ALS and mitochondrial damage with the presence of abnormal mitochondria aggregates in skeletal muscle and intramuscular nerve of patients with ALS [8]. Also, immunological responses and neuroinflammation, due to the contribution of toxic glia, have been known as important process of the disease [5].

Current Therapeutic Approaches to ALS

There is no cure yet for ALS. It is primarily for the treatment of symptoms, so, various supports are given to the changing needs of patients during the illness (e.g. physiotherapy, psychotherapy, tracheotomy, and gastrostomy). Riluzole is the only therapeutic drug that slowed disease progression by its antiglutamatergic properties [9].

There are many clinical trials that focused different therapeutic targets and various approaches. In recently, antagonism of Nogo-A is one of them: Ozanezumab, a humanized monoclonal antibody against Nogo-A, binds to Nogo-A and antagonizes its biological function [10,11]. Anti-sense therapy is another strategic approach after the discovery of mutations in causative genes of ALS. Anti-sense oligonucleotides (ASOs) are short, synthetic and modified nucleic acids that are able to bind to target on the mRNA. Using ASOs can lead to selective slicing of the mutant allele without viral carrier [12]. Alternative treatment are also available in experimental models of ALS, especially including several growth factors, such as insulin-like growth factor 1 (IGF-1), glial cell line-derived growth factor, brain derived growth factor, vascular endothelial growth factor and ciliary neurotrophic factor [5].

Besides the existing therapies, stem cell researches are promising for ALS patients with many evidences including beneficial effects in protection neurons and replacement of degenerated neurons.

Stem Cell Therapies for ALS

Stem cells are undifferentiated cells that have the capability to continuously divide and differentiate into various kinds of cells and tissues. Many classifications of stem cells exist, regarding on the differentiation potential; totipotent cell has the capability to create an organism, pluripotent cells can be converted into all cell types, and multipotent cells can be converted into cell types in their own tissues [13]. According to the sources from which they obtained; as embryonic, fetal and adult stem cells [14]. Multiple cell types are employed as a source for cell-mediated therapies; embryonic stem
cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs) and neural stem cells (NSCs).

Mesenchymal Stem Cells (MSCs)

MSCs have been known after isolation from bone marrow (BM) by Friedenstein [15]. MSCs are multipotent stromal cells that can be isolated from various connective tissues but mostly isolated from BM and adipose tissue [16]. MSCs can provide the possibility of autologous transplantation, so it also avoids triggering of immune mechanisms as well as the ethical and practical issues of embryonic and fetal-derived stem cells [17].

In recent years many researches have been conducted, some of them are considered as "a milestone". In 2003, Mazzini et al. has placed the autologous bone marrow-derived MSCs into the spinal cord at TH7-TH9 level for 7 patients to determine safety and tolerability of direct transplantation of MSCs [18]. They have reported that direct injection of autologous MSCs into the spinal cord in ALS patients is a safe method which does not show significant acute or chronic toxicity with nine-year follow-up results [19]. Further, they did not determine any tumor formation and abnormal cell growth by neuroradiologic analysis [17]. The studies in animal models of ALS have been increasing after Mazzini's findings. Zhao et al. performed a study to investigate the therapeutic potential of human MSC (hMSC) in the mouse model of ALS in 2007 [20]. They observed that significantly delayed disease onset, increased lifespan and delayed disease progression compared with untreated mice [20]. Another trial in 2008, Vercelli et al. have transplanted hMSCs into the lumbar spinal cord of asymptomatic SOD1 mice and they identified that hMSCs were found in the spinal cord 10 weeks after transplantation and astrogliosis, microglial activation were reduced and motoneuron counts were higher [21]. In another study, Boucheri et al. have injected MSCs by intratechial way to symptomatic hSOD1 rats and observed that MSCs differentiated into astrocytes at the site of degeneration and decreased motor neuron loss in the lumbar spinal cord [22].

With increasing trials, researches began to search various aspects of the field. Kim et al. in 2010 performed a dose-dependent study, they transplanted different doses (1×10^5, 2×10^5, and 1×10^6 cells) of ALS-hMSCs into the cisterna magna of SOD1 mice and observed that a cell dose of 1×10^5 cells significantly more prolonged life span and delayed the decline of motor performance than other doses [23].

By exploring the therapeutic benefits of growth factors to protect dying motor neurons in ALS, glial cell line-derived neurotrophic factor (GDNF) has been one promising growth factor that has proven to be a protective factor of motor neurons [24,25]. Also, other neurotrophic factors, such as insulin-like growth factor (IGF-I), vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) have been begun to use as protective factors of motor neurons in many models of ALS. Suzuki et al. mentioned as "trojan horses" about hMSCs in their study, which was, performed intramuscular transplantation with hMSCs engineered to secrete GDNF to deliver growth factors to the terminals of motor neurons and to the skeletal muscles in rat model [25]. After it have been shown hMSCs modified to release GDNF decrease disease progression rat models, studies have accelerated in this field. Krakora et al. prepared hMSC engineered to secrete GDNF (hMSC-GDNF), vascular endothelial growth factor (hMSC-VEGF), insulin-like growth factor-I (hMSC-IGF-I), or brain-derived neurotrophic factor (hMSC-BDNF), and they determined that hMSC-GDNF and hMSC-VEGF prolonged survival and slowed the loss of motor function, but hMSC-IGF-I and hMSC-BDNF did not have any effect [26].

Neural Stem Cells (NSCs) and Progenitor Cells

NSCs are self-renewing, multipotent cells that characterized by their capability to mainly differentiate into neurons, astrocytes, and oligodendrocytes [27]. Firstly, Temple described multipotent, self-renewing progenitor and stem cells in the subventricular zone in 1989 and Reynolds and Weiss isolated neural progenitor and stem cells from the adult striatal tissue in 1992, from mice brain tissue [28,29].

The role of NSCs during neurodegenerative diseases such as ALS is being evaluated by several research groups around the world. In 2006, Xu et al. have showed in a mouse ALS model that transplantation of NSCs, which isolated from fetal spinal cord was effective in delaying disease progression [30]. After it has been proved that spinal grafting of NSCs into the lumbar spinal cord of SOD1 rats leads to a moderate therapeutically effect and extension of lifespan by experimental studies. In a recent study, Heffner et al. have performed a study that aimed to analyze the degree of therapeutically effect of NSCs once transplanted into the lumbar spinal cord, so, they derived hNSCs from an 8-week gestation fetus and transplanted into lumbar spinal cord of SOD1 rats. Finally they observed that the neurological function of transplanted animals was well preserved, but disease onset and lifespan of transplanted animals was not different from the untreated controls [31]. However, in another study by Xu et al. transplanted hNSCs into the lumbar (L4-L5) and cervical (C4-C5) cord of SOD1 rats, and they have observed that disease onset in dually grafted animals was delayed by 10 days and disease duration in NSC-grafted animals was longer by 7 days compared to control animals [32]. Findings of multiple levels of spinal cord transplantation shows us that in the future we may need various treatment protocols, as in the study of Milteccic et al. transplanted NSCs labeled with green fluorescent protein via intravenous injection in rat models and 7 days later 13% of injected cells were found in the motor cortex, hippocampus and spinal cord [33].

Other approach is bipotent neural progenitor cells (NPCs) that studied human fetal cortex-derived neural cells that are cultured as 3-dimensional aggregates termed “neurospheres” in the presence of mitogens and these cells differentiate into astrocytes and neurons but not oligodendrocytes [17,34]. There is recently various studies about hNPCs that can secrete neurotrophic factors after recognition of glial cell-derived neurotrophic factor (GDNF) enhance survival of motor neurons in 1994 [35]. Watabe et al. examined neuroprotective effect of human GDNF encoded by an adenovirus vector on the death of lesion adult rat spinal motoneuron and observed prevention of loss of motor neuron [36]. Other neurotrophic factors have been also tried, Hwang et al. showed that intrathecal transplantation of immortalized hNSCs expressing human vascular endothelial growth factor (VEGF) gene delayed disease onset and enhanced the survival of the SOD1 mouse model of ALS [37].

These results suggest that neurotrophic factors especially with genetically modified human NSCs have regenerative and supportive properties for neurons and showed treatment potential might be more valuable in the treatment of ALS for future.

Embryonic Stem Cells (ESCs) and Induced Pluripotent Stem Cells (iPSCs)

Pluripotent stem cells are able to differentiate into all cell types.
ESCs are derived from the inner cell mass of an embryo at blastocyst stage [38]. Since Thomson et al. developed a technique to isolate embryonic stem cells in 1998 [39], ESCs drawn researchers’ attention because of their plasticity and potentially unlimited capacity for self-renewal. However, the improvements of ESCs applications are impeded with some religious and ethical concerns for e.g. destruction of human embryos. For that reason, iPSCs have opened up another new territory for cell-based therapies [40].

Shinya Yamanaka is pioneer of iPSC technology that can be generated pluripotent stem cells directly from adult cells. Yamanaka and colleagues have showed in 2006 that the introduction of four specific genes (Oct4, Sox2, c-Myc and Klf4) could convert somatic cells into pluripotent stem cells [41,42]. After all of these in 2008, Dimos et al. have performed first demonstration of the use of iPSC methodology in ALS [43]. The authors demonstrated that human fibroblasts could be differentiating into motor neurons expressing appropriate motor neuron markers including HB9 and ISLET [44]. Furthermore, iPSC-derived cells technology has been hampered a lack of access to motor neuron. Thus, autologous somatic cell replacement therapy becomes possible for studying the mechanisms of disease pathogenesis and drug discovery [45,46].

Different cells are ongoing trial, olfactory ensheathing cells (OESCs), are a type of macroglia of the olfactory nerve found in the nervous system. In 2008 Morita et al. developed a cell transplantation method via fourth cerebral ventricle in mice. OESCs was used as a stem cell source with MSCs in this study and they showed that OEC transplantation revealed no adverse effects but some significant differences in clinical evaluation were found between OEC-treated and non-transplanted animals [47]. OESCs have also demonstrated positive effects on ALS progression by Li et al. including evidence of myelination, increased motor neuron numbers, and increase in survival following intraspinal transplantation in SOD1 rats [48-52]. There are also clinical trials except preclinical trials. Clinical trials with different cell sources have been summarized in Table 1.

### Prospects for the Future

As we look for the future, although various studies mentioned above are very new, but all of these are showing how stem cell treatment is promising. If we comment in the future what would be developments in this field, we need to look on the current issues of stem cell treatment. Interestingly, we could not see well-designed treatment strategies targeting the upper motor neurons except trial of Martinez et al. which blood-derived stem cells were transplanted into the frontal cortex of ALS patients to target the upper motor neurons [17,53]. The different routes of administration stem cells was tested in the studies described above, intravenous, intraspinal or intraventricular injection are currently under development, establishing standardized practices for the delivery of cellular therapies to ensure reproducible injection volumes and targeting accuracy will assist in the design and interpretation of future clinical trials [54]. Underlying the pathogenesis of ALS is not known exactly. Especially, developments in the field of genetic engineering and reprogramming along with iPSC therapies will bring new aspects for future.

In conclusion, current treatments can not provide effective solutions to regenerate neurons, at the same time can not prevent loss of neurons in ALS. So, a result from different preclinical studies has caused quite a stir with hope to treatment. Todays, stem cell therapies are in infancy age, there are many challenges for e.g. suitable type of stem cell, immune reactions, and some ethical issues but in the very near future we can say hopefully that stem cell therapies can be applied effectively.

### Disclosure or Disclaimer

The authors declare no potential conflicts of interest.

### References


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**Table 1**: Summary of clinical trials of stem cell therapies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cell Type</th>
<th>Delivery Method</th>
<th>Trial details / Patient No.</th>
<th>Outcomes</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazzini et al. [18]</td>
<td>MSC</td>
<td>Intraspinal</td>
<td>T7-T9 injections / 10 patients</td>
<td>No toxicity, approach is safe and feasible</td>
<td>Italy</td>
</tr>
<tr>
<td>Huang et al. [49]</td>
<td>OESC</td>
<td>Intracranial</td>
<td>10 OESC 20 control patients</td>
<td>Beneficial effects on disease progression</td>
<td>China</td>
</tr>
<tr>
<td>Karussis et al. [50]</td>
<td>MSC</td>
<td>Intrathecal or combined intravenous</td>
<td>10 Intrathecal 9 combined</td>
<td>Approach is safe and feasible Immunomodulatory effects observed</td>
<td>Israel</td>
</tr>
<tr>
<td>Baek et al. [51]</td>
<td>MSC</td>
<td>Intraventricular</td>
<td>1 patient</td>
<td>Clinical, laboratory, and radiographic evaluation of the patient revealed no serious adverse effects</td>
<td>South Korea</td>
</tr>
<tr>
<td>Glass et al. [52]</td>
<td>NPC</td>
<td>Intraspinal</td>
<td>L2-L4 injections 12 patients</td>
<td>No disease progression approach is safe and feasible</td>
<td>U.S.</td>
</tr>
<tr>
<td>Martinez et al. [53]</td>
<td>MSC</td>
<td>Motor cortex</td>
<td>10 MSC 10 control patients</td>
<td>Well-tolerated approach is safe and feasible</td>
<td>Mexico</td>
</tr>
</tbody>
</table>


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