

Stem Cells may Beat Riluzole in Treatment of Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic lateral sclerosis, commonly known as Lou Gehrig's disease, or simply ALS, is a neurodegenerative disease that slowly kills its victims within a few years after diagnosis. This is a complex disease in which every motor neuron in the body is killed over a relatively short time period - within 3 years or so, thus killing the victim. This disease can be classified into three main categories based on the neurological levels affected - bulbar onset, cervical onset, and lumbar onset (Mitchell and Borasio). Bulbar onset can further be divided into two subcategories - upper motor neuron (UMN) bulbar onset, and lower motor neuron (LMN) bulbar onset. The former involves loss of speech due to spastic dysarthria and the latter involves wasting of tongue tissue accompanied with flaccid dysarthria and dysphagia (Kiernan et al.). Bulbar onset occurs first about one third of the time (Gordon). Cervical onset involves loss of function in upper limbs and can include both upper motor neurons and lower motor neurons. In contrast, lumbar onset involves weakening of lower limbs, including feet (Mitchell and Borasio). Rilutek was first FDA approved to treat ALS almost a decade ago. Since then, several studies have shown that Rilutek may not be so effective at prolonging life in patients with ALS. In recent years, stem cells have become a subject of great debate among the scientific community due to their implications in curing diseases like ALS. Stem cells have been shown in clinical trials to prolong life in patients in ALS even more than Rilutek has. They have also shown to control glutamate uptake in transgenic mice with the SOD1 gene, which is promising for new treatments in ALS patients. Although Rilutek has also shown to control glutamate uptake, stem cells may have a better effect.

Keywords: ALS; Glutamate excitotoxicity; Stem cells; Astrocytes; Riluzole

Review

Amyotrophic lateral sclerosis, commonly known as Lou Gehrig's disease, or simply ALS, is a neurodegenerative disease that slowly kills its victims within a few years after diagnosis. This is a complex disease in which every motor neuron in the body is killed over a relatively short time period - within 3 years or so, thus killing the victim. This disease can be classified into three main categories based on the neurological levels affected - bulbar onset, cervical onset, and lumbar onset [1]. Bulbar onset can further be divided into two subcategories - upper motor neuron (UMN) bulbar onset, and lower motor neuron (LMN) bulbar onset. The former involves loss of speech due to spastic dysarthria and the latter involves wasting of tongue tissue accompanied with flaccid dysarthria and dysphagia [2]. Bulbar onset occurs first about one third of the time [3]. Cervical onset involves loss of function in upper limbs and can include both upper motor neurons and lower motor neurons. In contrast, lumbar onset involves weakening of lower limbs, including feet [1].

In addition to the previous forms of ALS, there is also another form known as Familial ALS. Familial ALS is an autosomal disease, and can be either dominant or recessive, and accounts for almost 5% of all cases. It is thought that the autosomal dominant form is linked to the SOD1 gene in humans, also known as hSOD1. It has been shown that mice with this mutated gene develop a motor neuron disease that is similar to ALS, causing death [4]. Astrocytes are thought to be a large player in motor neuron death as shown by some mouse models with the SOD1 mutant gene.

The manifestation of ALS has been a long-standing debate since the discovery of the disease. Glutamate-induced excitotoxicity is thought to play a role in the pathogenesis of this disease [2]. Because of repetitive firing by glutamate receptors, neuronal damage and death can be induced by glutamate-mediated excitotoxicity [5]. The mechanism by which motor degeneration is mediated via glutamate-mediated excitotoxicity is not well known [2]. Motor neurons are supported in large part by astrocytes. In normal motor neurons, astrocytes help to recover synaptic glutamate rather fast via EAA2T, a glial glutamate transporter. This rapid removal is accomplished when astrocytes insert finger-like processes loaded with EAA2T into glutamate synapses, which removes synaptic glutamate after it has been released from the presynaptic terminal [5]. In theory, the loss of astroglial glutamate transporters may lead to an increase of glutamate concentrations at motor neuron synapses, causing glutamate receptor-mediated excitotoxicity [4].

In healthy individuals, astrocytes take up glutamate and a shunting cycle further regulates it by breaking it down into glutamine, repackaging it, sending it to the presynaptic neuron, then converting it back to glutamate. This is so common that about 80% of glutamate is processed by transporters on the membranes of astrocytes [6]. There are two astrocytic glutamate transporters, GLAST and GLT-1. The former is dominant in the cerebellum, whereas the latter is dominant in the forebrain. These transporters clear glutamate using a Na⁺-electrochemical gradient maintained by Na⁺/K⁺ ATPase, and the ATPase is coupled to glutamate transporters [7]. Not only do astrocytes seem to play a large role in a variety of neuronal functions, but they also have a special ability to shrink in size via aquaporin channels that may allow them to reduce the leakage of neurotransmitters, in particular, glutamate [6].

Several studies have attempted to explain the role that glutamate, glutamate transporters, and astrocytes play in the development of ALS. Rothstein et al. [8] performed a study high-affinity sodium-dependent glutamate transport in individuals diagnosed with ALS, individuals with no health issues, and individuals with other neurological disorders separate from ALS. The results showed that there was a 66% decrease in glutamate uptake in the cervical spinal cord, a 47% decrease in glutamate uptake in the motor cortex, and a 38% decrease of glutamate uptake in the somatosensory cortex of individuals with ALS compared to those individuals with no neurological diseases. Another study conducted by Dunlop et al. [9] to assess glutamate uptake capacity in transgenic SOD^{G93A} rats. Diseased rats exhibited a decrease in glutamate transport activity in spinal cord synaptosomes, with a 43% reduction at the end stage. The researchers also performed immunohistochemical analysis, which revealed a marked decrease in the glutamate transporter, GLT-1. They did not find this decrease in any other areas of the brain.

Nagai et al. [10] performed a study to assess the role that astrocytes may have in motor neuron death in the mutant SOD1 gene. Glial monolayers from transgenic mice with SOD^{G93A}, SOD^{G37R}, SOD^{G85R}, and SOD^{WT} genes and from non-transgenic mice were cultured and showed that expression of SOD1 in astrocytes affected morphology and survival of primary motor neurons and embryonic stem cell-derived motor neurons. They found that cell types other than astrocytes expressing the SOD1 gene did not induce motor neuron death, indicating that the death of motor neurons is astrocyte-specific. Rojas et al. [11] conducted another study to evaluate the role of astrocytes in mice expressing the SOD1 mutant gene. They found that wild-type spinal cord cells exposed to astrocytes expressing this gene release toxic factors that kill motor neurons via a pathway involved in nitroxidative stress.

It is clear that glutamate and damaged astrocytes play a role in the pathogenesis of ALS. The only FDA approved drug for the treatment of ALS to date is riluzole, known by the brand name Rilutek. It works by inhibiting presynaptic glutamate release [3]. Bensimon et al. [12] conducted a double blind, place-controlled study to evaluate the effects of riluzole on disease progression in ALS patients exhibiting bulbar-onset. Patients in the treatment group were given 100 mg per day of riluzole for 12 months. At the end of the study, 74% of the patients treated with riluzole were still alive compared to only 58% of patients alive in the placebo group. It is important to note, however, that after 21 months of treatment, the reduction in mortality rate in the treatment group dropped from 38.6% to only 19.4%, suggesting that as ALS progresses, the efficacy of riluzole decreases by a significant amount.

Although riluzole has been clinically shown to slow the progression of ALS, several new studies have suggested that riluzole may not be a very effective treatment for ALS as once thought, and that the need for new treatments is evident. In a study conducted by Dunlop et al. [9], G93A transgenic rats treated with riluzole in later stages of ALS showed significant decreases in glutamate uptake activity, indicating that, as ALS progresses, the efficacy of riluzole becomes significantly reduced. Another study conducted by Hzecka et al. [13] evaluated the percentage of plasma glutamate in patients with ALS after 3 months of treatment with riluzole, and found no significant change in plasma glutamate levels, further indicating that riluzole may not be as much of an effective treatment for ALS as previously thought.

In recent years, several clinical studies have been performed to test the efficacy of new drug treatments for ALS. These treatments have

sought to extend the life of patients of ALS, more so than the currently approved Rilutek already does. Perhaps the most important of these clinical trials are those studies involving the use of stem cells to treat ALS. Stem cells have the ability to differentiate into any cell type within the body and come in various types such as embryonic stem cells (ESCs), human umbilical cord blood derived-cells (hUCBCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs) and neural stem cells (NSCs) [14]. Prabhakar et al. [15] conducted a study on ten patients diagnosed with ALS that underwent bone marrow harvesting to assess the effect that transplantation of mesenchymal stem cells had on slowing the progression of the disease. The results showed that after a one year follow-up, 80% of the patients remained alive, which is 6% greater than the survival seen in the study conducted by Bensimon et al. [12] using riluzole as treatment, suggesting that stem cell therapy is more effective than riluzole at prolonging life in ALS patients.

Neural stem cells in particular have shown significant promise for the treatment of ALS by protecting against glutamate-induced excitotoxicity. These stem cells are self-renewing embryo cells that can differentiate into different parts of the nervous system, including astrocytes and neurons [16]. In some clinical trials, neural stem cells have been shown to migrate areas of damaged neurons, regardless of the area of transplantation [17]. Jeronina et al. [16] conducted a study to evaluate the neuroprotective effect that neural stem cells have on glutamate-induced excitotoxicity in spinal cords of rat pups with ALS. The results showed that 63% more motor neurons were present with the presence of neural stem cells in motor neurons exposed to THA when compared to the number of motor neurons present when THA was applied alone. Gu et al. [18] conducted a study to evaluate the effects of human adipose-derived stem cells had on glutamate uptake of GLT1 in SOD1^{G93A}-bearing astrocytes in transgenic mice containing the human SOD1 gene. Their results showed that downregulation of GLT1 uptake was significantly attenuated by soluble factors from human adipose-derived stem cells compared with nontransgenic mice.

Rilutek was first FDA approved to treat ALS almost a decade ago. Since then, several studies have shown that Rilutek may not be so effective at prolonging life in patients with ALS. In recent years, stem cells have become a subject of great debate among the scientific community due to their implications in curing diseases like ALS. Stem cells have been shown in clinical trials to prolong life in patients in ALS even more than Rilutek has. They have also shown to control glutamate uptake in transgenic mice with the SOD1 gene, which is promising for new treatments in ALS patients. Although Rilutek has also shown to control glutamate uptake, stem cells may have a better effect. Nonetheless, it is clear that new treatments needs to be developed for ALS, and the push to get stem cell research funded is needed if there is to be any hope in curing this life-threatening disease.

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