Therapeutic Development in Amyotrophic Lateral Sclerosis

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ABSTRACT

Purpose: Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease in adults. It is almost invariably lethal within a few years after the onset of symptoms. No effective treatment is currently available beyond supportive care and riluzole, a putative glutamate release blocker linked to modestly prolonged survival. This review provides a general overview of preclinical and clinical advances during recent years and summarizes the literature regarding emerging therapeutic approaches, focusing on their molecular targets.

Methods: A systematic literature review of PubMed was performed, identifying key clinical trials involving molecular therapies for ALS. In addition, the ALS Therapy Development Institute website was carefully analyzed, and a selection of ALS clinical trials registered at ClinicalTrials.gov has been included.

Findings: In the last several years, strategies have been developed to understand both the genetic and molecular mechanisms of ALS. Several therapeutic targets have been actively pursued, including kinases, inflammation inhibitors, silencing of key genes, and modulation or replacement of specific cell populations. The majority of ongoing clinical trials are investigating the safety profiles and tolerability of pharmacologic, gene, and cellular therapies, and have begun to assess their effects on ALS progression.

Implications: Currently, no therapeutic effort seems to be efficient, but recent findings in ALS could help accelerate the discovery of an effective treatment for this disease. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮)

Key words: amyotrophic lateral sclerosis, clinical trials, molecular targets, motor neuron disease, small molecules.

INTRODUCTION

The most common adult form of motor neuron disease is amyotrophic lateral sclerosis (ALS), which leads to paralysis and death caused by respiratory failure 3 to 5 years after the onset of symptoms due to the progressive degeneration of motor neurons in the spinal cord, brainstem, and cortex.[1] Although the majority of ALS cases are sporadic (sALS), with no family history, 10% are familial and are caused by mutations in the superoxide dismutase 1 (SOD1), TARDBP, and FUS genes. Recent studies have identified expanded repeats in a noncoding region of chromosome 9 open reading frame 72 (C9orf72) as the most frequent genetic cause of ALS.[2] Rare mutations in other genes (eg, ANG, VAPB, DAO, OPTN, VCP, and UBQLN2) have also been reported. It has been observed that the pathologic mechanisms of this pathology involve mitochondrial dysfunction, protein aggregation, excitotoxicity, and oxidative stress,[3] with consequent loss of neuromuscular junction (NMJ) integrity, retrograde axonal degeneration, and motor neuronal cell death.

These discoveries support the idea that complex and multiple mechanisms can induce motor neuron degeneration, with significant implications for the development of new therapeutic strategies. In fact, no effective treatments are currently available. Riluzole is the only approved compound for ALS; it has been linked to increased survival, but has no effect on the degradation of muscular function.

The understanding of mechanisms of motor neuron degeneration in ALS is in an early stage of knowledge. The study of multiple targets for therapeutic treatments in neurons and other cell types can contribute

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to identification of adequate approaches for ALS pathogenesis and progression.

The aim of this review is to summarize preclinical and clinical studies, drawing attention to the main molecular targets that are being investigated or for which testing in ALS patients is planned (Figure).

METHODS

A systematic literature review until September 2014 was carried out on PubMed using the following keywords: *clinical trials, small molecules, molecular targets, motor neuron disease*, and *amyotrophic lateral sclerosis*. The search criteria are restricted to English-language articles and are based on clinical and preclinical studies divided according to their molecular targets. All articles found were systematically analyzed and taken into consideration when preparing the review. In addition, the ALS Therapy Development Institute website was carefully analyzed and a selection of ALS clinical studies registered at ClinicalTrials.gov—an official platform and catalog for registering a clinical trial—have been consulted and selected studies have been included in the article.

RESULTS

Protection of Mitochondria: Dexpramipexole and Rasagiline

Increasing evidence indicates that mitochondrial dysfunction and oxidative stress play a central role in the etiopathogenesis of many neurodegenerative disorders, including ALS.[4] The energy requirements of neurons are very high, so inefficient energy production caused by mitochondria perturbations can trigger neurons to die because these cells have an elevated susceptibility to aging and stress. Two drugs, dexpramipexole and rasagiline, have been proposed to protect motor neurons in ALS patients by reducing levels of oxidative stress.

Dexpramipexole, like riluzole, belongs to the benzothiazanate family and it represents an optimized development of pramipexole, which also had neuroprotective properties, but strong dopaminergic agonist effects.

Preclinical studies showed a reduction of neuronal death after dexpramipexole (KNS-760704) administration when energy demand exceeds supply by inhibiting aberrant mitochondrial leak conductance. It has been demonstrated the maintenance or increase in the production of adenosine triphosphate, the decrease of oxygen consumption and the stabilization of the metabolic profile of damaged cells. In addition, it has shown protective effects against the toxicity of proteasome inhibition.[5] Dexpramipexole is currently used for Parkinson's disease. To test the efficacy of this putative mitochondrial modulator in individuals affected by ALS, Biogen Idec proceeded with clinical trials in partnership with academic investigators. Dexpramipexole was well tolerated in a Phase II safety study (ClinicalTrials.gov identifier: NCT00647296), and it showed a dose-dependent trend toward slowing functional decline and improving survival.

Based on these promising data, tolerability and efficacy of dexpramipexole were assessed in a double-blind and placebo-controlled multicenter Phase III clinical trial (EMPOWER, ClinicalTrials.gov identifier: NCT01281189).

Investigators enrolled approximately 1000 patients who were randomly assigned to be treated with 150 mg twice daily of dexpramipexole or placebo and were followed for a period of at least 12 months. On the basis of changes in time to death and ALS Functional Rating Scale-Revised (ALSFRS-R) total scores and combined assessment of function and survival scores, the main goal was to measure the joint rank of functional outcomes adjusted for mortality up to 12 months. After this period, there was no difference in combined assessment of function and survival score, ALSFRS-R total score, and time to death between dexpramipexole-treated and placebo-treated patients. However, 8% of dexpramipexole-treated patients developed neutropenia, compared with only 2% of placebo-treated participants.[6] Although dexpramipexole performed better than many of its predecessors with regard to tolerability in the Phase II trial, the Phase III study did not meet its primary end point, no efficacy was seen in the individual components of function or survival and it did not improve symptoms or disease progression in ALS patients, so Biogen Idec discontinued development of dexpramipexole for ALS. Phase II trials should have dose selection as a goal, not efficacy, and the EMPOWER investigators based their choice of dose on results obtained from the small number of patients enrolled in Phase II.

The negative Phase III results suggest that the Phase II clinical trials for ALS might need to be redesigned. However, EMPOWER investigators intend to move forward in the development of dexpramipexole for ALS.[7]