Commentary

Edaravone in ALS

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A R T I C L E   I N F O

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Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder characterized by progressive and relatively selective degeneration of upper and lower motor neurons. Patients suffer from atrophy and paralysis of systemic voluntary muscles including respiratory muscles, leading to respiratory failure and subsequent death 3–5 years after the disease onset. Effective therapy for ALS that ameliorates its clinical course is still not known (Mitchell and Borasio, 2007).

Although ALS usually develops sporadically, 5 to 10% of cases are familial and hereditary. Twenty percent of familial ALS (FALS) are caused by mutations in the copper and zinc-dependent superoxide dismutase (SOD1) gene, which was first reported in 1993 (Rosen et al., 1993). Mutant SOD1 brought a breakthrough to this field, since mutant SOD1 transgenic mice recapitulate the clinical symptoms and pathological findings of human FALS (Gurney et al., 1994). Mutant SOD1 transgenic mouse models provided invaluable tools for testing effective drugs which extend their lifespan. Up to now, more than 20 drugs have been claimed to be effective in the therapy of mouse ALS.

A big problem, however, is arising: none of these drugs have yet to be shown to be effective as well in human sporadic ALS (SALS) patients (Benatar, 2007). Why? A couple of explanations are conceivable. First, mutant SOD1 transgenic mice may not be a good model for human sporadic ALS cases despite their apparent similarities. Indeed, mutant SOD1 associated FALS and SALS exhibit different microscopic neuropathology. The former is characterized by Lewy body-like inclusion containing mutant SOD1, whereas for the latter skein-like or round inclusions containing TDP-43. Since TDP-43 is implicated in the pathogenesis of SALS as well as in a subgroup of FALS, developing a new ALS mouse model based on TDP-43 could solve these problems in the future (Neumann et al., 2007). A second possible explanation is that the most therapies in mouse models are initiated prior to disease onset, which is impossible in human patients until presymptomatic diagnosis for ALS becomes available. Thirdly, whether drug dosage and bioavailability comparable to mouse experiments are replicated in human trials remains unclear.

An alternative explanation is the difference in the design of mouse experimental therapies and human clinical trials. Randomized controlled trials, which are designed to eliminate numerous confounding factors including observation biases, are standard in human clinical trials. In contrast, mouse experiments are generally not performed as rigorously as human trials, increasing risks of producing “false positive” results (Benatar, 2007).

Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a free radical scavenger that has been approved in Japan since 2001 as a therapeutic agent to reduce neuronal damage caused by acute ischemic stroke (Yoshida et al., 2006). Edaravone eliminates lipid peroxide and hydroxyl radicals by transferring an electron to the radical, thereby ameliorating the ischemic neuronal damage. Oxidative stress is implicated as one of the pathogenetic mechanisms for ALS (Barber et al., 2006). Moreover, a small-sized open trial of edaravone suggested that edaravone is safe and may delay the progression of functional motor disturbances in ALS patients (Yoshino and Kimura, 2006). Thus, edaravone is a promising therapeutic agent for human motor neuron diseases including ALS.

In a previous issue, Ito et al. reported an experimental therapy of a mutant SOD1 mouse model using edaravone (Ito et al., 2008). Taking the problems associated with the therapeutic experimental design in mouse experiments, they carefully optimized the dosage of edaravone so that the pharmacokinetic profile after intraperitoneal injection became comparable to that in human patients. Moreover, they started treatment only after the disease onset, similar to human ALS treatment. Furthermore, they used only female mice for analysis considering the gender difference in lifespan and randomized blind analyses were adopted for all the behavioral as well as pathological observations. This methodological rigorosity has never been considered seriously in previous experimental therapies of mutant SOD1 ALS mouse models, most of which have failed to be replicated in human patients.

Edaravone significantly slowed the motor function decline as assessed by multiple behavioral tests such as rotarod tests. However, the lifespan of edaravone-treated mice were not significantly higher.

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than those of control mice, suggesting that edaravone may improve the motor function of the ALS mice without apparent lifespan-expanding effects (Ito et al., 2008). This uncoupling in the mechanisms underlying motor function and lifespan further implies that pathways causing motor function decline are not necessarily the ones causing eventual death, usually by respiratory muscle failure. That said, it would be possible to identify drugs that can improve the quality of life in ALS patients without affecting lifespan, which seems to be an easier goal compared with identifying lifespan-extending drugs for ALS. Moreover, it was clinically important that edaravone was effective even when administered after the disease onset. On the other hand, it would be intriguing to administer edaravone to ALS mice at their presymptomatic stage to understand how the point at which edaravone is used during the course of disease affects its outcome.

It is noted that high-dose edaravone treatment leads to a decrease of mutant SOD1 accumulation in the spinal cord. Since administration of edaravone resulted in a marked decrease of 3-nitrotyrosine/tyrosine ratio, a marker of oxidative stress, suppression of oxidative stress is likely to be upstream of the inhibition of aggregate formation (Kabashi and Durham, 2006; Valentine and Hart, 2003). It has long been debated how oxidative stress is induced by SOD1 mutations (Barber et al., 2006). Reduced enzymatic activity of SOD1 and generation of peroxynitrite due to aberrant copper chemistry have been proposed as plausible mechanism explaining “gain of toxic function” of mutant SOD1 (Beckman et al., 1993; Deng et al., 1993; Robberecht et al., 1994). However, the fact that a subgroup of SOD1 mutants retains full enzymatic activity and that H46R and H48Q mutants which completely lose binding sites for copper still cause ALS suggests that mechanisms unrelated to SOD1 activity may also be involved (Borchelt et al., 1994; Valentine et al., 2005; Wang et al., 2003). It has been shown that mutant SOD1 overexpression in a neuronal cell line leads to transcriptional repression of antioxidant proteins by reducing the level of transcriptional factor NRF2 (Kirby et al., 2005). It would be intriguing to investigate whether edaravone affects the level of NRF2 when administered to ALS mice.

Another interesting unresolved question is which cells are the targets of edaravone. Recently, it has been shown that motor neuron death in mutant SOD1 ALS mouse models is non-cell autonomous (Boillée et al., 2006; Yamanaka et al., 2008). In other words, mutant SOD1-expressing astroglial or miroglial cells promote motor neuron death. In this context, edaravone may decrease the aggregates in non-neuronal glial cells, resulting in amelioration of neurodegeneration. These questions should be addressed in further analysis in the future.

A recent systematic review of randomized controlled trials of antioxidant therapies against ALS including vitamin E and acetylcysteine has shown that there is no substantial evidence to support their clinical use (Orrell et al., 2008). However, the evidence for the beneficial effects of edaravone on human ALS patients awaits the publication of the results of a phase III clinical trial of ALS, currently ongoing in Japan (http://www.als.net/research/studies/tdfAnimalStudyList.asp).

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References


