Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that mostly affects the neurons responsible for movement. ALS also affects other neurons related to cognition and emotional affect. Neurons related to movements include upper motor neurons, which have cell bodies in the motor cortex, and lower motor neurons, which have cell bodies in the brainstem and spinal cord. Upper motor neurons make synaptic contact with lower motor neurons, which in turn have synapses at muscle fibers. Progressive loss of upper motor neurons leads to slow performance of movements and spastic speech, whereas loss of lower motor neurons causes muscle weakness and ultimately death from respiratory failure.

ALS is proving to be a more complex disorder than originally believed with loss of other neurons in many affected individuals. Approximately half of patients with ALS have elements of frontotemporal lobe dementia (FTLD) associated with loss of neurons in the frontal and temporal lobes. The most common form of FTLD is the behavioral variant, characterized by social withdrawal, general apathy, difficulties with making decisions, and word-finding difficulties. Loss of other neurons, the location of which is the brainstem or spinal cord and not precisely known, associated with sigma-1 receptors reduces emotional control leading to inappropriate laughing or crying known as emotional lability or pseudobulbar affect, which is present in approximately 30% of patients with ALS.

**Pathophysiology and Targets for Treatment**

Although the pathologic processes leading to neuronal death in ALS are not known, several mechanisms involved in maintenance and function of neurons have been considered for roles in the disease process and investigated as potential therapeutic targets. This has been the rationale for a large number of clinical trials that had the goal of slowing the rate of progression of ALS. Most trials have been for drugs to slow degeneration of motor neurons, and a few trials have addressed pseudobulbar affect. No clinical trials have addressed FTLD to date. There are 2 drugs that have gained approval by the Food and Drug Administration (FDA) for slowing progression and 1 for reducing pseudobulbar affect.

**Available Treatments**

**Riluzole**

Riluzole was the first drug approved by the FDA for ALS. The proposed drug mechanism is reduction of the presynaptic release of glutamate, which is the neurotransmitter that activates upper and lower motor neurons. This putative mechanism is based on the concept that relative excess of glutamate may cause excitotoxicity of upper and lower motor neurons contributing to neuronal death, which is supported by the fact that patients with ALS have increased glutamate levels in the spinal fluid. There were 2 trials of riluzole, 1 with 155 subjects and the other a pivotal trial with 956 subjects. Both used tracheostomy-free survival as the primary endpoint measure and forced vital capacity, summed isometric muscle strength, and global impression scale as secondary endpoint measures. Both studies showed statistically significant results for the primary endpoint measure, which led to FDA approval.

In the pivotal trial for riluzole, subjects had to be <5 years from symptom onset and have forced vital capacity (FVC) that was ≥60% of the expected value, which is a validated predictor of disease stage for ALS. Subjects were randomized to 1 of 4 groups: placebo or 1 of 3 doses of riluzole, 50 mg, 100 mg, or 200 mg, in 2 divided daily doses. There was a statistically significant greater survival rate at 12 months, although not at 18 months, and although the effect increased with dose, there were more side effects at the higher dose. Survival data for the placebo arm included 242 subjects with 122 (50.4%) surviving free of tracheostomy 12
months, while the 100 mg arm included 242 subjects with 134 (56.8%) alive at 12 months, resulting in a 6.4% survival advantage. Extrapolation of survival data to the time axis indicated a 2- to 3-month longer survival among those taking riluzole (Figure 1). The FDA approved the 100 mg dose. There were no significant effects on the secondary outcome measures. Although the drug was met with mixed enthusiasm, it has been designated standard-of-care treatment for patients with ALS by the American Academy of Neurology and the European Federation of Neurological Diseases.

**Edaravone**

Edaravone is a disease-modifying drug approved by the FDA for ALS in 2017. The proposed mechanism of action is reduction of free radical excitotoxicity, and the drug was initially developed to treat cell death resulting from stroke. For patients with ALS, the drug is given intravenously in a loading dose of 60 mg per day for 14 consecutive days, followed by a maintenance dose of 10 days monthly. Two trials compared edaravone to placebo using improvement on the ALS functional rating scale-revised (ALSFRS-R) as the primary endpoint measure. The ALSFRS-R assesses a patient’s functional abilities in 4 domains: bulbar, fine motor function, gross motor function, and breathing. Secondary endpoint measures for the edaravone trial included change in FVC, grip strength, and the modified Norris scale, which measures bulbar and limb function.

In the first trial for edaravone, subjects were recruited within 3 years of symptom onset, had an overall change in the ALSFRS-R of −1 to −4 points over a 12-week observation period before randomization, and an FVC ≥70% of the expected value. There was no effect of edaravone compared to placebo. A post hoc analysis suggested that a subset of patients with a more rapid rate of progression benefitted from treatment with edaravone.

A second trial of edaravone was carried out with a restricted subset of patients, who showed some degree of impairment in each of the ALSFRS-R domains, an FVC ≥80% of expected value, entry within 2 years of symptom onset, and a further decline of −1 to −4 ALSFRS-R points during a 12-week observation period. For this subset of patients, edaravone slowed the rate of disease progression, as measured by a decrease in ALSFRS-R score, by 33% at 6 months compared to the rate of disease progression for patients in the placebo group. Extrapolation of the rate of progression of the edaravone arm to the rate of progression of the placebo arm indicated that at 6 months, those on the drug were at the same range of ALSFRS-R values that the placebo group was at 4 months (Figure 2). There was no effect of the drug on FVC or grip strength. It is notable that >90% of subjects in both arms were also taking riluzole. A 6-month extension of subjects taking edaravone in this study continued to have a decreased rate of progression; however, there was no corresponding placebo arm for comparison because subjects in the placebo group were taking edaravone during the 6-month extension study.

**Dextromethorphan/Quinidine Combination Therapy for Pseudobulbar Affect**

Dextromethorphan/quinidine combination therapy is approved by the FDA for treatment of pseudobulbar affect in patients with ALS. Dextromethorphan is the active drug, and quinidine inhibits breakdown of dextromethorphan. The pathology of pseudobulbar affect is not known, and the effect of dextromethorphan is believed to be through
agonist action of the sigma-1 receptor in the endoplasmic reticulum that modulates calcium signaling. There were 2 randomized trials showing significant reduction in pseudobulbar affect symptoms in patients with ALS as measured by a validated scale.\textsuperscript{13-15} Interestingly, there was anecdotal observation of improvement in bulbar function (speech and swallowing), leading to a phase 2 clinical trial measuring the effect of dextromethorphan/quinidine combination therapy, which significantly improved bulbar function.\textsuperscript{16}

**Treatment Issues and Patient Counseling**

Although both riluzole and edaravone had statistically significant effects on primary endpoint measures in phase 3 trials, because the measures were different, it is difficult to compare drug efficacy. The subjects enrolled in the trials for the 2 drugs also differed. For the riluzole trial, the inclusion criteria were broad (<5 years from symptom onset and FVC $\geq 60\%$), and the ALSFRS-R scale was not available. For the first edaravone trial, the inclusion criteria were sufficiently broad that the lack of efficacy was attributed to a group of subjects with a very slow rate of progression, and the pivotal trial restricted subjects to those with involvement of all 4 domains covered in the ALSFRS-R, onset of symptoms <2 years, and FVC $\geq 80\%$. It has been estimated that at the time of diagnosis and start of medications, <10% of patients with ALS will fulfill those criteria.\textsuperscript{17} The death rate in the riluzole trial at 18 months was very much higher than that in the edaravone trial at 12 months (Table). It is not clear why survival rates are lower, and one answer is that patients taking riluzole were further along in their course, and the drug’s success is more realistic across the spectrum of patients with ALS. Another answer is that patients with ALS are better cared for in multidisciplinary clinics,\textsuperscript{18,19} which were less common in the 1990s, although it is not known how many subjects in the edaravone study received multidisciplinary care. Inconsistent patterns of significance for secondary outcome measures further complicate attempts at comparison.

Although a survey of ALS neurologists before the edaravone trial estimated that a 20% slowing in the rate of progression indexed to the ALSFRS-R would be a “meaningful” change for a patient, no patients with ALS were asked what would be a meaningful decrease in progression.\textsuperscript{20} In a recent study of patients with ALS, their caregivers’ perceptions of change in the rate of decline of the ALSFRS-R score showed a nonlinear perceived change over time and variable interpretation of changes in ALSFRS-R domains (loss of bulbar and fine motor control were more important than loss in other domains). There was no correlation between various quality-of-life measures and changes in ALSFRS-R score.\textsuperscript{21} The edaravone trial supports a 33% slowing on the ALSFRS-R scale at 6 months. It is unrealistic to expect the drug to stop progression completely, and it is not clear if a patient will perceive any but the most marked slowing of symptoms in the setting of continued decline.

The approval of edaravone has led to patient counseling issues for the neurologist related to the drug’s degree of efficacy, owing to restricting it to specific groups of patients based on the differences between the first and pivotal trials subject criteria, patient time, and physical effort expended, complications of route of administration, and cost.\textsuperscript{22} Similar issues of efficacy and cost were raised when riluzole was first approved, but these are magnified with edaravone. Some neurologists are not enthusiastic about either drug. However, balancing this is the ethical issue of not offering an approved drug to a patient with ALS, as these 2 drugs are the only ones known to modify the course of the disease. A related issue is whether both drugs should be taken concurrently. The FDA did not restrict edaravone to a specific group of patients with ALS, but insurance companies are beginning to require that patients meet the entry criteria in the pivotal trial and show a slowing in the rate of progression at 6 months before approving continued financial support for the drug. Restrictions of the drug are difficult to explain to patients who do not meet the criteria.

<table>
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<tr>
<th>Treatment</th>
<th>Enrolled</th>
<th>6-month survivors</th>
<th>12-month survivors</th>
<th>18-month survivors</th>
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<tr>
<td>Riluzole 100 mg</td>
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<td></td>
<td>134</td>
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<tr>
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<tr>
<td>Edaravone 60 mg months 7-12\textsuperscript{b}</td>
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<tr>
<td>Edaravone placebo</td>
<td>68</td>
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\textsuperscript{a}Nonsurvivors include those who died, had a tracheostomy, or left the trial due to reduced respiratory function.\textsuperscript{b}Values for the edaravone trials are extrapolations.
Cost and administration of the drugs are also important issues for patients. When riluzole was first available, costs were in the hundreds of dollars per month; edaravone as a brand name drug costs more than $100,000 per month. There are also major differences in routes of administration, oral for riluzole and intravenous for edaravone, frequently requiring placement of a central venous catheter, which adds to the cost. Further, there is a major time commitment with edaravone, requiring 14 infusions the first month and 10 every month thereafter, for a total of 124 hour-long infusions the first year as well as travel and setup time.

Summary

ALS remains a challenging disease. The armamentarium of drugs to treat and manage symptoms is slowly growing, but the effects of riluzole and edaravone on modifying the course of progression remain largely subclinical in magnitude.

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