

# Disease-Modifying Treatment of Amyotrophic Lateral Sclerosis

Jordan Schultz, PharmD, MSCS, BCACP

**A**myotrophic lateral sclerosis (ALS) is a spectrum of neurodegenerative syndromes.<sup>1,2</sup> Classical, or Charcot, ALS affects approximately two-thirds of patients and is characterized by deterioration of upper and lower motor neurons (UMNs and LMNs, respectively) of the spine, resulting in muscle spasticity, weakness, and wasting. Other motor system diseases include progressive bulbar palsy (PBP), affecting about a quarter of patients, progressive muscular atrophy (PMA), and primary lateral sclerosis (PLS).

ALS is homogeneously spread throughout the world, with some areas of the western Pacific Rim experiencing locally increased incidence, such as specific people of Guam, Japan, and New Guinea.<sup>1</sup> Men are slightly more likely to be affected than women (1.5:1), with a typical age of onset of 62 years.<sup>3</sup> Just 5% of cases are diagnosed in patients younger than 30 years. Familial ALS is associated with earlier onset. Bulbar onset is more common in women and older patients (43% are aged more than 70 years).

The natural course of the disease varies substantially between patients.<sup>4</sup> ALS can progress at varying speeds, which may affect the timing of therapy and medical interventions. Approximately half of patients die within 30 months of symptom onset, whereas approximately 20% of patients survive between 5 and 10 years. Negative prognostic factors include bulbar and respiratory site of disease onset, executive dysfunction, and decline in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) prior to first evaluation.<sup>5</sup>

Multidisciplinary symptomatic and palliative care remains the cornerstone of ALS management.<sup>4</sup> The management of the symptoms associated with ALS can be challenging. Patients with ALS may need physical, medical, and psychological interventions throughout the course of their disease. No cure exists for ALS and only 2 disease-modifying treatments have been approved in the United States: riluzole and edaravone. This article discusses the state of pharmacologic management of ALS, agents currently in development, and strategies for managing symptoms in patients with ALS.

## ABSTRACT

Currently, there is no cure for amyotrophic lateral sclerosis (ALS) and the foundation of ALS management revolves around symptomatic and palliative care. Early diagnosis offers the best prognosis for a longer, quality life while living with the disease. Many medications are used to relieve symptoms but there are only 2 pharmacologic agents indicated for the management of ALS. For 2 decades, riluzole had been the mainstay of disease-modifying therapy, but in 2017, edaravone became the second agent approved in the management of patients with ALS. The mechanism of either agent is not well known. Riluzole is thought to reduce damage to motor neurons through an inhibitory effect on glutamate release, while edaravone is thought to act as a neuroprotective agent that prevents oxidative stress damage as a free radical scavenger. With the lack of treatment options, it is imperative for healthcare professionals to understand the nuances of using these 2 agents to optimize therapy and quality of life for patients with ALS.

*Am J Manag Care.* 2018;24:S327-S335

For author information and disclosures, see end of text.

## Riluzole

Riluzole was approved in the United States in 1995 and the European Union in 1996.<sup>6</sup> Riluzole extended the median time to tracheostomy or death of patients with ALS by 2 to 3 months in clinical trials.<sup>7</sup> Riluzole is recommended for all patients with ALS; however, there are few data to indicate if it is effective in patients who had onset more than 5 years prior.<sup>8</sup> Miller et al identified that riluzole provided a small beneficial effect on both bulbar and limb function, but not on muscle strength.<sup>9</sup> Recently, Fang et al identified that riluzole may be most effective in the advanced respiratory stage of ALS in concert with findings by Seibold et al and Brooks et al.<sup>10-12</sup>

### Proposed Mechanism of Action

Glutamate excitotoxicity has been proposed to contribute to ALS pathogenesis.<sup>13,14</sup> Glutamate is the predominant excitatory neurotransmitter in the central nervous system. Six different receptors bind glutamate to initiate an action potential. Of these, the N-methyl-d-aspartic acid (NMDA) receptor and the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor lacking the GluR2 subunit allow the influx of calcium ions upon binding glutamate. Calcium ions entering the cell are sequestered in the endoplasmic reticulum (ER). Glutamate excitotoxicity occurs when glutamate in the local environment of these channels remains high, leading to excessive ion channel activity, calcium influx, damage to the ER, and neuronal death. The AMPA receptor lacking the GluR2 subunit is implicated in excitotoxic neuronal degeneration.

Clinical trials with riluzole were undertaken on the basis that riluzole may modulate glutamatergic transmission. However, trials with other targeted inhibitors of glutamatergic transmission (eg,

ceftriaxone, memantine, and talampanel) have failed.<sup>6</sup> Further, the accumulated data suggest that physiologically achievable levels of riluzole have only limited effects on glutamate receptors.<sup>6</sup> Instead, it is becoming apparent that riluzole has many other actions on neurotransmitter function, including:

- Modulation of persistent Na<sup>+</sup> channel current
- Potentiation of calcium-dependent K<sup>+</sup> current
- Inhibition of neurotransmitter release
- Inhibition of fast Na<sup>+</sup> current
- Inhibition of voltage-gated Ca<sup>2+</sup> current
- Other possible effects on neurotransmission

### Landmark Studies

Despite a poor understanding of the exact mechanism of action of riluzole in ALS, the drug received marketing authorization by the FDA based on the results of 2 trials.<sup>7,8,15</sup> These studies were placebo-controlled, double-blind, international trials that included 1114 patients with probable or definite ALS for less than 5 years and a forced vital capacity (FVC) of greater than or equal to 60%. Patients received placebo or 50, 100, or 200 mg riluzole daily, split between morning and evening doses (**Figure 1**).<sup>6,13</sup> The patients were evenly matched between groups, based on age; disease duration; body weight; respiratory, neurological, and muscle function; and clinician- and patient-assessed subjective status.

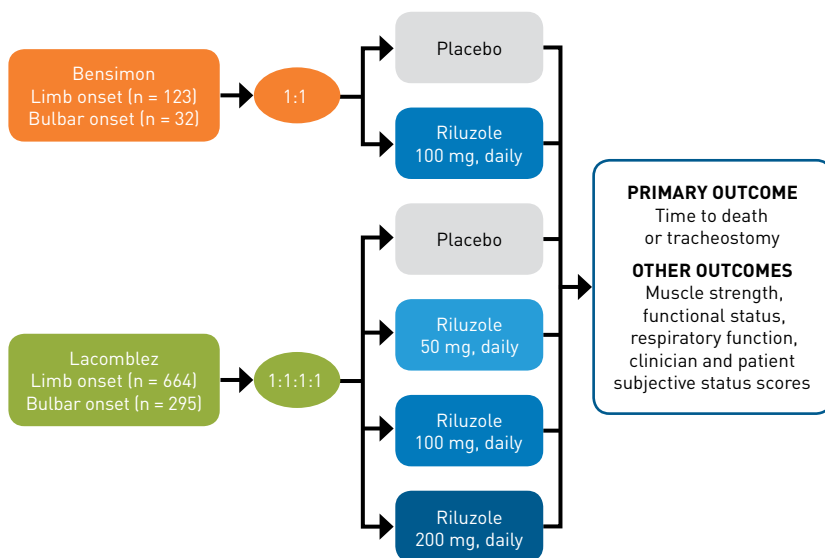
In the smaller study by Bensimon et al, the median time to death or tracheostomy was 83 days longer for patients receiving riluzole compared with placebo.<sup>7</sup> There was an early increase in survival in patients receiving riluzole compared with placebo; however, by 15 months, the curves had almost merged. The survival differences

were not statistically significant as determined by the planned statistical analysis, but a post hoc analysis demonstrated significant differences in survival between the riluzole and placebo groups.<sup>8</sup>

In the larger study by Lacomblez et al, the median time to death or tracheostomy was increased by 60 days (**Figure 2**).<sup>14,15</sup> No initial increase in survival was seen in this study. As before, the survival differences were not statistically significant as determined by the planned statistical analysis, but a post hoc analysis demonstrated a significant effect of riluzole.<sup>8</sup>

After adjustment for prognostic factors, there was a significant overall drug effect at 12 and 18 months (**Figure 3**).<sup>15</sup> At 18 months, the 50 mg, 100 mg, and 200 mg riluzole doses decreased the risk of death or tracheostomy compared with the placebo by 24% ( $P = .04$ ), 35% ( $P = .002$ ), and 39% ( $P = .0004$ ), respectively.

**FIGURE 1.** Riluzole Study Trial Designs<sup>6,13</sup>



Contrary to the study by Bensimon et al, Lacomblez et al did not observe difference in the treatment effect between groups based on different sites of disease onset (bulbar versus limb).<sup>7,15</sup> Further, while riluzole improved survival (defined as time to death or tracheostomy) in both studies, preservation of muscle strength and neurological function was not seen in either study, despite improved bulbar and limb functional scores being found in the Cochrane meta-analysis of these clinical trials.<sup>9</sup> However, asthenia and muscle relaxation are known effects of riluzole in healthy volunteers, and may mask neuroprotective effects in patients with ALS.<sup>15</sup>

**Adverse Effects and Monitoring**

Riluzole is relatively well tolerated. In a pooled analysis of safety data from patients receiving placebo (n = 320) or 100 mg/day riluzole (n = 313), the most common adverse effects (AEs) in the riluzole group ( $\geq 5\%$  of patients and more frequently than in the placebo group) were asthenia, nausea, dizziness, decreased lung function, and abdominal pain.<sup>8</sup> In many cases, the incidence of AEs with riluzole was only marginally higher than with placebo. The most common AEs leading to discontinuation in the riluzole group were nausea, abdominal pain, constipation, and elevated alanine aminotransferase (ALT).

*Hepatotoxicity*

Elevations in ALT were common. Approximately 50%, 8%, and 2% of the combined patients from both trials receiving riluzole experienced elevation of ALT level above normal, above 3 times the upper limit of normal (ULN), and above 5 times ULN, respectively.<sup>8</sup> Maximum ALT levels typically occurred within 3 months after initiating riluzole. Patients should be monitored for hepatotoxicity monthly for the first 3 months, and periodically afterwards. Riluzole should be discontinued in patients whose ALT is greater than 5 times the ULN, or displaying other signs of hepatotoxicity (eg, elevated bilirubin).

*Neutropenia*

Riluzole has immune-suppressive effects and can cause severe neutropenia (absolute neutrophil count <500/mm) within the first 2 months of treatment.<sup>8</sup> Patients should be aware of the potential for febrile illnesses and report these occurrences promptly.

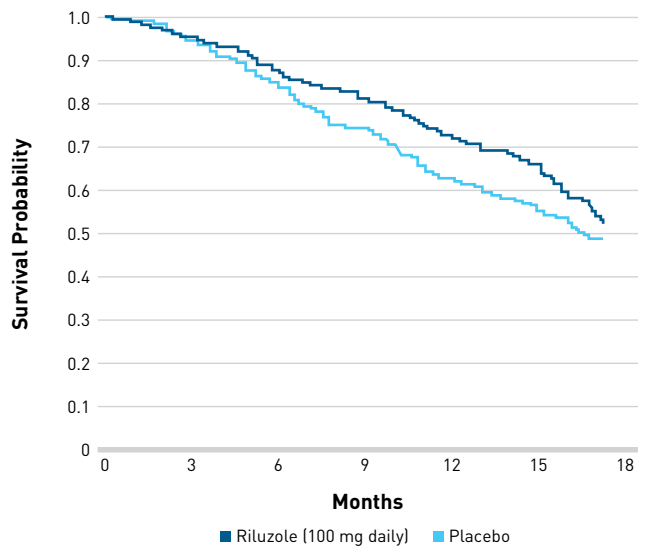
*Pneumonitis*

Interstitial lung disease, including hypersensitivity pneumonitis, may occur in patients receiving riluzole.<sup>8</sup> Riluzole should be discontinued if interstitial lung disease develops.

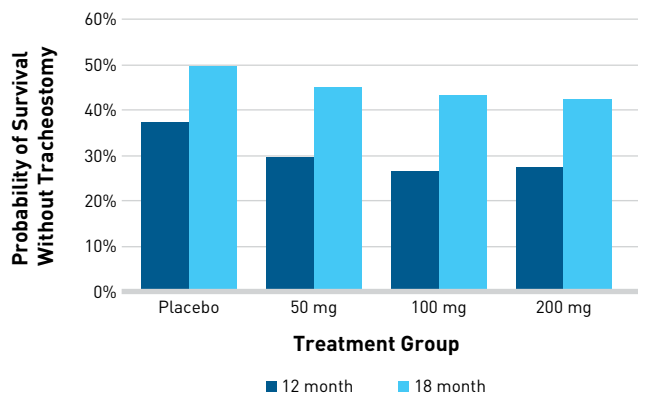
*Pharmacokinetic considerations*

Riluzole is metabolized extensively in the liver, primarily by CYP1A2.<sup>8,16</sup> The use of CYP1A2 inhibitors and inducers should be undertaken cautiously. Compared with healthy volunteers, mild and moderate

**FIGURE 2.** Kaplan-Meier Curve From the Study by Lacomblez et al<sup>8</sup>



**FIGURE 3.** Probability of Survival Without Tracheostomy<sup>13</sup>



chronic hepatic impairment reduces clearance (increases the area under the curve [AUC]) of riluzole by approximately 1.7-fold and 3-fold. Other factors that reduce riluzole clearance include Japanese descent (~50%), female gender (~45%), and smokers (~20%). On the other hand, a high-fat meal and smoking increases clearance (reduces AUC) by approximately 20% each.

**Recommendations for Use**

Riluzole should be recommended for all patients with ALS, provided there are no contraindications to its use. Riluzole is recommended by the European Federation of Neurological Societies (EFNS), American Academy of Neurology (AAN), and other neurological guidelines.<sup>17,18</sup> Riluzole is recommended for patients with ALS of less than 5 years' duration and FVC greater than 60%. However, many experts suggest

that riluzole has potential benefit for the prevention of aspiration in those patients with symptoms more than 5 years, FVC less than 60%, and tracheostomy.<sup>17</sup>

Based on the landmark studies, and 2 other controlled studies, riluzole prolongs survival by approximately 2 to 3 months. However, other uncontrolled studies, having longer follow-up periods, suggest that survival may be prolonged by up to 21 months.<sup>17</sup>

The typical dose of riluzole is 100 mg/day, orally divided in 2 separate doses of 50 mg.<sup>8</sup> This dose was deemed a good balance between efficacy and risk of AEs.<sup>15</sup> At lower doses, treatment discontinuation was primarily due to lack of efficacy, while at higher doses, it was due to toxicity. Oral availability is approximately 60%.

### Summary of Riluzole

- Mechanism of action: inhibits glutamate excitotoxicity; other undefined neuroprotective actions<sup>13,14</sup>
- Efficacy: prolongs median time to death or tracheostomy by 2 to 3 months<sup>7</sup>
- Safety: relatively well tolerated; most common AEs are asthenia, nausea, dizziness, decreased lung function, and abdominal pain; some patients may experience hepatotoxicity, neutropenia, or interstitial lung disease<sup>8</sup>
- Dosing: 100 mg/day; racial, gender, and individual metabolic variations may lead to differences in AUC and enhanced toxicity<sup>8</sup>
- Other considerations: susceptible to variable pharmacokinetics due to presystemic and systemic metabolism<sup>8,16</sup>

### Edaravone

Edaravone is an antioxidant and free radical scavenger that was initially developed as an intravenous (IV) treatment of acute ischemic stroke.<sup>19</sup> Despite mixed clinical results, it was approved by the FDA in May 2017.<sup>20</sup>

### Proposed Mechanism of Action

Excessive production and inefficient neutralization of reactive oxygen species (ROS) leads to oxidative stress and cell death. Endogenous ROS are produced during normal metabolism in mitochondria and may increase during times of stress to cells.<sup>21</sup> During oxidative phosphorylation in mitochondria, electrons pass through the electron transport chain to power the electrochemical proton gradient that is used to produce adenosine triphosphate. The terminal receptor of the electron is oxygen, which is reduced to water. However, a small amount of oxygen, after receiving an electron, escapes as a free radical species. ROS can attack, destroy, and inactivate all manners of intracellular molecules (eg, proteins, lipids, nucleic acids). Buildup of these products leads to the activation of apoptotic cell death. Cells have developed multiple mechanisms to neutralize ROS before cell death is initiated. Superoxide dismutase, catalase, and the glutathione pathway are major pathways to neutralize ROS

and repair the damage caused by ROS.

At least 25 genes have been implicated in ALS pathogenesis, of which *SOD1* was the first to be described. The primary function of *SOD1* is to neutralize superoxide radicals ( $O_2^{\bullet-}$ ) by reacting with water to form  $O_2$  and  $H_2O_2$ . However, mutations in the *SOD1* gene may lead to neuron death and ALS via the following mechanisms:

- Increased aggregation
- Dimer destabilization
- Aberrant metal binding
- Oligomerization<sup>22</sup>

The most common mutations found in the human *SOD1* gene are:

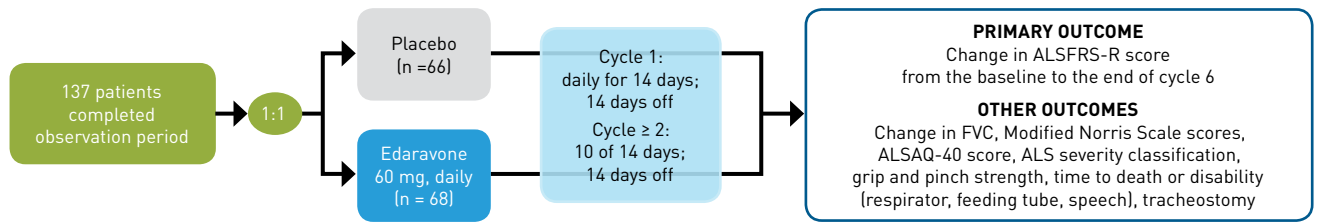
- D90A (most common mutation in the US population, but may not be associated with ALS)<sup>23</sup>
- A4V (responsible for approximately 50% of *SOD1* mutations associated with familial ALS in North America)<sup>24</sup>
- G93A (rare mutation, although very well characterized, as it can generate motor neuron syndrome in transgenic mice)<sup>22</sup>

Although *SOD1* mutations help highlight the importance of ROS in the pathology of ALS, just about 20% of ALS cases are associated with a mutation of the *SOD1* gene. Therefore, it is unclear why patients with sporadic ALS have increased ROS levels or why they are more susceptible to oxidative stress. Regardless, increased ROS levels are thought to be a primary pathological feature of ALS and edaravone aims to reduce oxidative stress.

### Landmark Studies

It took more than 13 years to bring edaravone through the clinical development process on the way to approval.<sup>25</sup> The first open-label study recruited 19 Japanese patients to receive 30 mg or 60 mg of edaravone IV daily on a schedule of 14 days on, followed by 14 days off.<sup>26</sup> The primary end point of this study was the change in the ALSFRS-R in the 6 months before treatment compared with changes observed following 6 months of treatment. In contrast, the primary end point of the riluzole studies was survival or time to tracheostomy. A statistically significant treatment effect was observed on the primary end point in the high-dose group ( $2.4 \pm 3.5$  points;  $P = .039$ ).<sup>27,28</sup>

Subsequently, 2 phase 3 studies were conducted. One study recruited 206 patients and the other recruited 25 Japanese patients with an FVC greater than 70%, disease duration less than 3 years, and a decrease in the ALSFRS-R score during the 12-week preobservation period of 1 to 4 points, and used the same endpoint of change in ALSFRS-R score.<sup>29,30</sup> Neither demonstrated an improvement in symptom control with edaravone. However, a post hoc analysis was conducted on patients who had a score of 2 or more on each item of the ALSFRS-R, disease duration of 2 years or less, and an FVC of at least 80% at baseline. This subset of patients represents a group that may be more prone to disease progression. Within this subgroup

**FIGURE 4.** Edaravone Study Trial Design<sup>25</sup>

ALS indicates amyotrophic lateral sclerosis; ALSAQ, Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; FVC, forced vital capacity.

of patients, those taking edaravone had a significantly slower rate of progression of the ALSFRS-R compared with the placebo group.

Based on the post hoc analysis described above, a third confirmatory phase 3 study was conducted.<sup>19</sup> The recruitment strategy for this study was stringent and based on the previously described post hoc analysis and included patients with the following:

- Definite or probable ALS
- Disease duration 2 years or less
- Normal respiratory function (FVC  $\geq$ 80%)
- High functionality (defined as scores of  $\geq$ 2 points on each individual item of the ALSFRS-R)

Of 213 screened patients, 137 completed the 12-week prerandomization observation period, during which they experienced a 1–4-point decrease in ALSFRS-R score, as in the previous trials. Patients were randomized to edaravone (60 mg IV) or saline placebo (Figure 4).<sup>25</sup> The primary endpoint was, again, change in ALSFRS-R score.

There were more women in the edaravone group (45% vs 40%, placebo) and more patients with grade 1 disease in the edaravone group (32% vs 24%, placebo). Other than that, patient cohorts were evenly matched for age, body mass index, ALS diagnosis, bulbar versus limb onset, decrease in ALSFRS-R score during observation, and prior riluzole use.

The primary endpoint analysis included all randomly assigned patients who received at least 1 dose of study drug, had at least 1 efficacy assessment post baseline, and reached the end of cycle 3.<sup>19</sup> Sixty-eight patients receiving edaravone reached cycle 6, while 66 patients receiving placebo reached the same point. For the primary efficacy analysis, the change from baseline to the end of cycle 6 (or last observation) in ALSFRS-R score was compared between treatment groups. The least-squares mean difference in mean ALSFRS-R scores between treatment groups was 2.49 in favor of edaravone (95% CI, 0.99–3.98,  $P = .0013$ ; Table 1).<sup>25</sup>

Patients receiving edaravone maintained higher scores on the Modified Norris Scale, which describes speech, swallowing, and lower extremity and upper extremity abilities, compared with placebo.<sup>19</sup> However, deterioration in quality of life, as measured by the

**TABLE 1.** Edaravone Efficacy Results<sup>25</sup>

	Least-Squares Mean Change (SE)		P
	Edaravone	Placebo (n)	
ALSFRS-R score	-5.01 (0.640)	-7.50 (0.66)	.0013
FVC (%)	-15.61 (2.41)	-20.40 (2.48)	.094
Modified Norris Scale scores			
Total	-15.91 (1.97)	-20.80 (2.06)	.039
Limb scale	-11.47 (1.61)	-14.91 (1.68)	.076
Bulbar scale	-4.44 (0.76)	-5.89 (0.79)	.11
ALSAQ-40 score	17.25 (3.39)	26.04 (3.53)	.031
Grip strength (kg)	-4.08 (0.54)	-4.19 (0.56)	.86
Pinch strength (kg)	-0.78 (0.14)	-0.88 (0.14)	.55

ALSAQ indicates Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; FVC, forced vital capacity; SE, standard error.

Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40), was slightly, but statistically significantly, lower in patients receiving edaravone compared with patients receiving placebo ( $P = .031$ ). There was no difference in FVC, subsets of Modified Norris Scale, grip strength, pinch strength, or ALS severity classification at the end of cycle 6 in patients receiving edaravone, compared with placebo.

### AEs and Monitoring

The safety profile of edaravone is favorable. During the trial, 84% of patients in each arm experienced an AE, with 16% of patients receiving edaravone and 24% of those receiving placebo experiencing a serious AE (Table 2).<sup>19</sup> The most common AE was contusion (19% edaravone, 13% placebo).

### Pharmacokinetic Considerations

No changes in dosing are needed for patients with hepatic or renal insufficiencies.<sup>31</sup> Edaravone contains sodium bisulfite, which may cause allergic reactions in some people. Edaravone is metabolized to a pharmacologically inactive form that is excreted in the urine.

**TABLE 2.** Adverse Events With Edaravone<sup>19</sup>

	Adverse Events		Serious Adverse Events	
	Edaravone (n = 69)	Placebo (n = 68)	Edaravone (n = 69)	Placebo (n = 68)
Any	84%	84%	16%	24%
Contusion	19%	13%	0	2%
Constipation	12%	12%	0	0
Dermatitis contact	12%	4%	0	0
Dysphagia	12%	15%	12%	12%
Eczema	7%	3%	0	0
Insomnia	7%	6%	0	0
Upper respiratory tract inflammation	7%	3%	0	0
Back pain	6%	2%	0	0
Headache	6%	7%	0	0
Myalgia	6%	2%	0	0
Nasopharyngitis	4%	7%	0	0
Respiratory disorder	4%	3%	3%	3%
Diarrhea	3%	6%	0	0
Speech disorder	1%	3%	1%	3%
Pneumonia aspiration	0	3%	0	3%

Reprinted from Writing Group: Edaravone (MCI-186) ALS 19 Study Group. *Lancet Neurol.* 2017;16(7):505-512. Copyright 2017, with permission from Elsevier.

Edaravone is not believed to have significant interactions with CYP enzymes. Differences in pharmacokinetics between Japanese and Caucasian subjects were not seen. Lastly, high systemic levels of edaravone are achievable and may drive brain penetration.<sup>16</sup>

### Recommendations for Use

While edaravone should be recommended to all patients with ALS, there are many considerations for which we do not have enough data or experience to guide us. For the trial that was used to support approval, the selection criteria were strict: just about 7% of patients with ALS would have qualified for the trial.<sup>32</sup> Nevertheless, it is assumed that edaravone has applicability in patients who fall outside of these narrow criteria. This trial was also of short duration (6 months) and it is unclear as to the long-term outcomes with edaravone. Improved functional scores were seen, but long-term survival data are lacking. The current recommendations do not differentiate patient subsets that might have benefit from edaravone therapy, because this trial was not powered to identify those differences. The patients in this trial appeared to have disease that was likely to progress, and the utility of edaravone in patients with slower progressing disease has not been evaluated.

Patients should be educated about the potential benefits versus the costs.<sup>32</sup> “Costs,” in this case, should also include time and energy that is required to remain adherent to this dosing strategy. Dosing

can be cumbersome, requiring IV administration for 10 of 14 days per 28-day cycle. Initial cycle is 14 days on, then 14 days off. Subsequent cycles are 10 of 14 days on, then 14 days off. The monetary cost is quite high. The cost for edaravone is about \$1000 per treatment, which translates to a cost of almost \$146,000 per year.<sup>33</sup>

### Summary of Edaravone

- Mechanism of action: antioxidant and free radical scavenger<sup>19</sup>
- Efficacy: improves functional score, but long-term survival data are not fully evaluated<sup>32</sup>
- Safety: relatively well tolerated; most common AEs are contusion, gait disturbance, headache, dermatitis<sup>19</sup>
- Dosing: Initial cycle: 60 mg/day IV for 14 days followed by 14 days without drug. Subsequent cycles: 60 mg/day IV for 10 of 14 days, followed by 14 days without drug<sup>31</sup>
- Other considerations: pharmacokinetics less variable than riluzole; high cost (>\$145,000/year)<sup>31,33</sup>

### Symptomatic Therapies

There is no cure for ALS. Symptom management remains the foundation of care, and all efforts should be made to maintain quality of life.<sup>1,34</sup> Patients should try to maintain normalcy in their lives, for instance, employment, social activities, and standard and preventive medical care (eg, dental care, vaccinations). Patients with ALS and their caregivers are at risk for depression, feelings of hopelessness, and anxiety as the disease progresses.<sup>1</sup> Patients should prepare advanced directives for their care, including respiration and nutritional management, and end-of-life care.

Patients with ALS suffer from a wide range of symptoms that progressively worsen and eventually lead to ventilatory and nutritional compromise.<sup>1,34</sup> Neither riluzole nor edaravone was shown to improve symptomatology. Some of the common symptoms of ALS include:

- Cramps
- Fatigue
- Spasticity
- Sialorrhea
- Pseudobulbar affect
- Persistent saliva and bronchial secretions
- Excessive or violent yawning
- Laryngospasm
- Pain
- Emotional lability



- Communication difficulties
- Constipation
- Depression
- Insomnia
- Anxiety

### Muscle Cramps

Muscle cramps are a common problem for patients with ALS.<sup>35</sup> Physical and massage therapies can reduce cramping.<sup>36</sup> Exercise and stretching aid in cramp prevention. Pharmacologic therapies include levetiracetam, phenytoin, carbamazepine, baclofen, tizanidine, mexiletine, and others.<sup>34,37</sup> However, despite some studies suggestive of efficacy, a Cochrane review did not find sufficient evidence to support the use of any intervention for muscle cramps in patients with ALS, although, in many cases, the studies were underpowered.<sup>38</sup> Quinine has been removed as an agent for treating cramps because of a concern for significant and life-threatening AEs. Cinchonism is a cluster of symptoms of varying severity associated with quinine toxicity that includes tinnitus, dizziness, disorientation, nausea, visual changes, and auditory deficits. Quinine may cause QT prolongation and serious cardiac arrhythmias, including torsades de pointes.<sup>35</sup>

### Fatigue

There are many causes of fatigue in patients with ALS, including muscle dysfunction, depression, poor sleep, immobility, or respiratory dysfunction.<sup>34</sup> Resistance and respiratory exercises may improve endurance and reduce motor deterioration.<sup>39</sup> Fatigue and asthenia may be AEs of riluzole therapy. These patients should weigh the modest survival benefit of riluzole therapy versus reduced quality of life because of fatigue. Modafinil has demonstrated improved endurance in ALS with 1 study showing that 76% of patients with ALS responded to therapy versus 14% of patients who received a placebo.<sup>40</sup>

### Spasticity

Spasticity is characterized by tight or stiff muscles, a reduced ability to control spastic muscles, and hyperactive reflexes.<sup>41</sup> For example, a muscle that is stretched responds with a contraction (stretch reflex) to try to maintain the muscle at a constant length. A hyperactive stretch reflex will cause the muscle to contract sooner and more vigorously. Moderate exercise and physical and occupational therapies can improve spasticity.

Baclofen is considered the first-line therapy for spasticity and acts pre- and postsynaptically as a gamma aminobutyric acid (GABA) B agonist at the spinal level.<sup>41</sup> AEs include systemic muscle relaxation, sedation, fatigue, and hepatotoxicity. Due to the potential for excessive drowsiness, oral baclofen should be used with caution in elderly patients. Terminating baclofen therapy should be done gradually. Intrathecal baclofen may be delivered by an implanted pump in select individuals.

Tizanidine is an alpha-2 agonist that can be used as a substitute for baclofen or can be added to other oral therapies.<sup>41</sup> Tizanidine requires 3 or 4 doses per day, due to a short half-life. Tizanidine does not cause as much muscle weakness as other antispasmodic therapies, but is associated with sedation, moderate hypotension, xerostomia, muscle weakness, and hallucinations, and may prolong the QT interval. Other agents are less commonly used and include benzodiazepines, gabapentin, dantrolene, and botulinum toxin.

### Sialorrhea

Excessive sialorrhea (drooling), seen in more than half of patients with ALS, results from a reduced ability to swallow and not increased saliva production.<sup>34,42</sup> Anticholinergic medications are generally first-line therapies for patients with sialorrhea, although there are few clinical studies on the use of these agents in patients with ALS. These agents include:

- Amitriptyline
- Atropine
- Diphenhydramine
- Glycopyrrolate
- Hyoscyamine
- Oxitropium
- Scopolamine

AEs of anticholinergic medications include sedation, constipation, and cognitive issues. Ultrasound-guided botulinum toxin injections into the parotid and submandibular glands reduced sialorrhea 3 to 7 days after the injections.<sup>42</sup> Maximum saliva reduction occurs 2 to 4 weeks after treatment and lasts about 3.5 months, but may last up to 6 months.

Electron beam radiation to the submandibular gland and the lower part of the parotid gland provided benefit for 4 to 6 months.<sup>42</sup> Electron beam radiation appears to be better tolerated than photon-based therapy.

### Pseudobulbar Affect

Pseudobulbar affect (PBA) is excessive laughing or crying, or involuntary emotional expression. It affects 20% to 50% of patients with ALS.<sup>34</sup> Antidepressants are frequently used, although it is not a mood disorder, and may include:

- Tricyclic antidepressants (eg, amitriptyline)
- Fluvoxamine
- Nortriptyline
- Fluoxetine
- Sertraline

Another option for PBA includes the combination of dextromethorphan (DM) and quinidine (Q). This treatment has been studied and found to reduce the frequency and severity of laughing and crying

**TABLE 3.** Agents Tested in Human Trials<sup>6</sup>

Compound	Trial Outcome
Antiglutamatergic	
Ceftriaxone	Failure
Memantine	Failure
Riluzole	Mixed
Talampanel	Failure
Anti-inflammatory	
Celecoxib	Failure
Erythropoietin	Failure
Glatiramer acetate	Failure
Minocycline	Failure
NP001	Failure
Pioglitazone	Failure
Valproic acid	Failure
Antioxidative	
Coenzyme Q10	Failure
Creatine	Failure
Edaravone	Mixed
Neuroprotective	
Dexpramipexole	Failure
Olesoxime	Failure
TCH346	Failure
Xaliproden	Failure
Neurotrophic factors	
BDNF	Failure
CNTF	Failure
IGF-1	Failure
CSF1R inhibition	
Masitinib	Positive
Other	
Lithium	Failure
Tirasemtiv	Failure

behaviors in patients with ALS.<sup>43</sup> DM likely exerts its effect on PBA via uncompetitive NMDA glutamate receptor antagonism and a sigma-1 receptor agonism. Q is added to the formulation at a relatively low dose simply to block hepatic metabolism of DM. The dose of Q is well below that used to treat cardiac arrhythmia. DM may also protect neurons from glutamatergic excitotoxicity. The AEs of DM/Q include dizziness, diarrhea, nausea, and urinary tract infection.

### Emerging Therapies

Masitinib is an oral tyrosine kinase inhibitor that downregulates activated spinal cord glia cells and skeletal muscle mast cells

through inhibition of c-Kit and CSF-1R. In the AB10015 study, masitinib administered as an add-on to riluzole to patients with ALS, having a baseline ALSFRS-R progression rate of less than 1.1 points/month, delayed progression-free survival by 25% and slowed decline of function (ALSFRS-R) by 27%, quality of life (ALSAQ-40) 34%, and FVC by 17%.<sup>44</sup> A post hoc analysis suggested that earlier treatment of patients, whether progressing slowly or quickly, could stave off functional decline more effectively.<sup>45</sup> However, in April 2018, the National Institute for Health and Care Excellence (NICE) in the United Kingdom adopted a negative opinion of masitinib and decline to authorize the agent for the treatment of ALS.<sup>46</sup> In their view, the reliability of the data was not robust enough to support a registration (based on an inspection carried out on two of the main clinical investigation centers of the study). They felt the clinical relevance of the distinction made between patients with “normal” progression (85% of patients in the study) and those with “rapid” progression (15% of the patients) was not demonstrated. Furthermore, there was a suspicion of bias regarding the primary analysis of the ALSFRS score for patients who stopped the study prematurely. ALSFRS-R measures abilities such as walking, speech, hand control, and respiration. The company sponsoring this agent in trials was expected to address this decision and ask for reconsideration in July 2018.<sup>47</sup>

Other agents continue to be explored, including antisense oligonucleotides, although just for carriers of mutated *SOD1* gene.<sup>18</sup> However, as can be seen in **Table 3**, many disease-modifying therapies have been investigated over the years, but with little success.<sup>6</sup> Fortunately, prospects for new therapies are improving, as new information is obtained on the molecular pathology of ALS.

### Conclusions

ALS is a spectrum of motor system diseases for which adequate therapies are lacking. Riluzole has been the mainstay of active therapy for 2 decades. Recently, edaravone was approved in the United States and European Union based on improved functional score. It is unclear at this time if these improvements will translate to longer survival. Until the time that a truly remarkable drug for ALS is identified, people with ALS, and their caregivers, will be challenged by the wide array of symptoms facing these patients. It is incumbent on all members of the care team to provide appropriate support and counseling as the patient transitions through stages of their disease. ■

**Author affiliations:** Clinical Pharmacy Specialist, Department of Pharmaceutical Care, University of Iowa Hospitals and Clinics; Adjunct Assistant Professor, Department of Neurology, Carver College of Medicine at University of Iowa; Adjunct Assistant Professor, Department of Pharmacy Practice and Sciences, University of Iowa College of Pharmacy, Iowa City, IA.

**Funding source:** This activity is supported by an educational grant from Mitsubishi Tanabe Pharma America, Inc.



**Author disclosure:** Dr Schultz has no relevant financial relationships with commercial interests to disclose.

**Authorship information:** Concept and design, drafting of the manuscript, and critical revision of the manuscript for intellectual content.

**Address correspondence to:** jordan-schultz@uiowa.edu.

Dr Schultz gratefully acknowledges David Modrak, PhD, for his contributions to the development of this article.

## REFERENCES

- Wijesekera LC, Leigh PN. Amyotrophic lateral sclerosis. *Orphanet J Rare Dis*. 2009;4:3-3. doi: 10.1186/1750-1172-4-3.
- Al-Chalabi A, Hardiman O, Kiernan MC, Chiò A, Rix-Brooks B, van den Berg LH. Amyotrophic lateral sclerosis: moving towards a new classification system. *Lancet Neurol*. 2016;15(11):1182-1194. doi: 10.1016/S1474-4422(16)30199-5.
- Chiò A, Logroscino G, Traynor BJ, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. *Neuroepidemiology*. 2013;41(2):118-130. doi: 10.1159/000351153.
- Riva N, Agosta F, Lunetta C, Filippi M, Quattrini A. Recent advances in amyotrophic lateral sclerosis. *J Neurol*. 2016;263(6):1241-1254. doi: 10.1007/s00415-016-8091-6.
- Elamin M, Bede P, Montuschi A, Pender N, Chiò A, Hardiman O. Predicting prognosis in amyotrophic lateral sclerosis: a simple algorithm. *J Neurol*. 2015;262(6):1447-1454. doi: 10.1007/s00415-015-7731-6.
- Petrov D, Mansfield C, Moussy A, Hermine O. ALS clinical trials review: 20 years of failure. Are we any closer to registering a new treatment? *Front Aging Neurosci*. 2017;9:68. doi: 10.3389/fnagi.2017.00068.
- Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med*. 1994;330(9):585-591. doi: 10.1056/NEJM199403033300901.
- Rilutek [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US, LLC; 2012. products.sanofi.us/rilutek/rilutek.pdf. Accessed July 10, 2018.
- Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev*. 2012;14(3):CD001447. doi: 10.1002/14651858.
- Brooks BR, Brawer EK, Langford VL, Bockenek WL, Lindblom SS. Stage of prolonged survival in ALS. *Lancet Neurol*. 2018;17(7):579. doi: 10.1016/S1474-4422(18)30207-2.
- Fang T, Al Khleifat A, Meurges JH, et al. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study. *Lancet Neurol*. 2018;17(5):416-422. doi: 10.1016/S1474-4422(18)30054-1.
- Seibold H, Zeileis A, Hothorn T. Individual treatment effect prediction for amyotrophic lateral sclerosis patients. *Stat Methods Med Res*. 2017;962280217693034. doi: 10.1177/0962280217693034.
- Munsat TL, Hollander D. Excitotoxins and amyotrophic lateral sclerosis. *Therapie*. 1990;45(3):277-279.
- Foran E, Trotti D. Glutamate transporters and the excitotoxic path to motor neuron degeneration in amyotrophic lateral sclerosis. *Antioxid Redox Signal*. 2009;11(7):1587-1602. doi: 10.1089/ars.2009.2444.
- Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. *Lancet*. 1996;347(9013):1425-1431.
- Dash RP, Babu RJ, Srinivas NR. Two decades-long journey from riluzole to edaravone: revisiting the clinical pharmacokinetics of the only two amyotrophic lateral sclerosis therapeutics. *Clin Pharmacokinet*. 2018. doi: 10.1007/s40262-018-0655-4.
- Miller RG, Jackson CE, Kasarskis EJ, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2009;73(15):1218-1226. doi: 10.1212/WNL.0b013e3181bc0141.
- Dorst J, Ludolph AC, Huebers A. Disease-modifying and symptomatic treatment of amyotrophic lateral sclerosis. *Ther Adv Neurol Disord*. 2018;11:1-16. doi: 10.1177/1756285617734734.
- Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16(7):505-512. doi: 10.1016/S1474-4422(17)30115-1.
- FDA approves drug to treat ALS [news release]. May 5, 2017. FDA website. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm557102.htm. Updated March 28, 2018. Accessed May 28, 2018.
- Holzerová E, Prokisch H. Mitochondria: much ado about nothing? How dangerous is reactive oxygen species production? *Int J Biochem Cell Biol*. 2015;63:16-20. doi: 10.1016/j.biocel.2015.01.021.
- Pansarasa O, Bordonni M, Diamanti L, Sproviero D, Gagliardi S, Cereda C. SOD1 in amyotrophic lateral sclerosis: "ambivalent" behavior connected to the disease. *Int J Mol Sci*. 2018;19(5). pii: E1345. doi: 10.3390/ijms19051345.
- Felbecker A, Camu W, Valdmanis PN, et al. Four familial ALS pedigrees discordant for two SOD1 mutations: are all SOD1 mutations pathogenic? *J Neurol Neurosurg Psychiatry*. 2010;81(5):572-577. doi: 10.1136/jnnp.2009.192310.
- Saeed M, Yang Y, Deng HX, et al. Age and founder effect of SOD1 A4V mutation causing ALS. *Neurology*. 2009;72(19):1634-1639. doi: 10.1212/01.wnl.0000343509.76828.2a.
- Brooks BR, Jorgenson JA, Newhouse BJ, Shefner JM, Agnèse W. Edaravone in the treatment of amyotrophic lateral sclerosis: efficacy and access to therapy—a roundtable discussion. *Am J Manag Care*. 2018;24(suppl 9):S175-S186.
- Yoshino H, Kimura A. Investigation of the therapeutic effects of edaravone, a free radical scavenger, on amyotrophic lateral sclerosis (phase II study). *Amyotroph Lateral Scler*. 2006;7(4):241-245. doi: 10.1080/17482960600881870.
- Goodman SN. Toward evidence-based medical statistics. 1: the P value fallacy. *Ann Intern Med*. 1999;130(12):995-1004.
- Sullivan GM, Feinn R. Using effect size—or why the P value is not enough. *J Grad Med Educ*. 2012;4(3):279-282. doi: 10.4300/JGME-D-12-00156.1.
- Abe K, Itoyama Y, Sobue G, et al; the Edaravone ALS Study Group. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. *Amyotroph Lateral Scler Frontotemporal Degen*. 2014;15(7-8):610-617. doi: 10.3109/21678421.2014.959024.
- Tanaka M, Akimoto M, Palumbo J, Sakata T. A double-blind, parallel-group, placebo-controlled, 24-week, exploratory study of edaravone (MCI-186) for the treatment of advanced amyotrophic lateral sclerosis (ALS) [P3.191]. *Neurology*. 2016;86(suppl 16).
- Radivaca [prescribing information]. Jersey City, NJ: Mitsubishi Tanabe Pharma America; 2017. radivaca.com/assets/dist/pdfs/radivaca-prescribing-information.pdf. Accessed July 17, 2018.
- Hardiman O, van den Berg LH. Edaravone: a new treatment for ALS on the horizon? *Lancet Neurol*. 2017;16(7):490-491. doi: 10.1016/S1474-4422(17)30163-1.
- Frequently asked questions about Radivaca (edaravone). ALS Association website. als.org/research/radivaca/radivaca-frequently-asked-questions.html. Accessed June 2, 2018.
- Miller RG, Jackson CE, Kasarskis EJ, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2009;73(15):1227-1233. doi: 10.1212/WNL.0b013e3181bc014a.
- FDA. Drug products withdrawn from sale for reasons other than safety or effectiveness: quinine-containing drug products; enforcement action dates. *Federal Register*. 2006;71(241):75557-75560.
- ALS: amyotrophic lateral sclerosis, medical management. Muscular Dystrophy Association website. mda.org/disease/amyotrophic-lateral-sclerosis/medical-management. Accessed June 17, 2018.
- Weiss MD, Macklin EA, Simmons Z, et al; Mexiletine ALS Study Group. A randomized trial of mexiletine in ALS: safety and effects on muscle cramps and progression. *Neurology*. 2016;86(16):1474-1481. doi: 10.1212/WNL.0000000000002507.
- Ng L, Khan F, Young CA, Galea M. Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev*. 2017;10(1). doi: 10.1002/14651858.CD011776.pub2.
- Lunetta C, Lizio A, Sansone VA, et al. Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial. *J Neurol*. 2016;263(1):52-60. doi: 10.1007/s00415-015-7924-z.
- Rabkin JG, Gordon PH, McElhiney M, Rabkin R, Chew S, Mitsumoto H. Modafinil treatment of fatigue in patients with ALS: a placebo-controlled study. *Muscle Nerve*. 2009;39(3):297-303. doi: 10.1002/mus.21245.
- Chang E, Ghosh N, Yanni D, Lee S, Alexandru D, Mozaffar T. A review of spasticity treatments: pharmacological and interventional approaches. *Crit Rev Phys Rehabil Med*. 2013;25(1-2):11-22. doi: 10.1615/CritRevPhysRehabilMed.2013007945.
- Banfi P, Ticozzi N, Lax A, Guidugli GA, Nicolini A, Silani V. A review of options for treating sialorrhea in amyotrophic lateral sclerosis. *Respir Care*. 2015;60(3):446-454. doi: 10.4187/respcare.02856.
- Piolo EP. Review of dextromethorphan 20 mg/quindine 10 mg (Nuedexta) for pseudobulbar affect. *Neural Ther*. 2014;3(1):15-28. doi: 10.1007/s40120-014-0018-5.
- Mora JS, Barbeito L, Hermine O. Masitinib as an add-on therapy to riluzole is beneficial in the treatment of amyotrophic lateral sclerosis (ALS) with acceptable tolerability: results from a randomized controlled phase 3 trial. *ENCALS Annual Meeting*. May 18-20, 2017. Ljubljana, Slovenia.
- Mora JS, Genge A, Mansfield C, Hermine O. Initiation of masitinib at a less severe stage of disease produces greater treatment-effect: Subgroup analyses from masitinib study AB10015. *ENCALS Annual Meeting*. June 20-22, 2018. Oxford, England: Abstract C35.
- Masitinib for treating amyotrophic lateral sclerosis [D967]. National Institute for Health and Care Excellence website. nice.org.uk/guidance/indevelopment/gid-ta10157. Accessed June 3, 2018.
- Henriques C. European agency issues negative opinion on marketing authorization for masitinib in ALS [news release]. April 23, 2018. ALS News Today website. alsnewstoday.com/2018/04/23/ema-issues-negative-opinion-masitinib-conditional-marketing-authorization. Accessed July 17, 2018.