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Review Article

Amyotrophic Lateral Sclerosis (ALS): Current Treatment Options and Efficacy

Ariana Z Turk[1] and Pooja Mohan Rao[2]*

[1]*Georgetown University School of Medicine, Washington, DC, USA*

[2]*Assistant Professor, Department of Neurology, Georgetown University Hospital, Washington, DC, USA*

***Corresponding Author:** Pooja Mohan Rao, Assistant Professor, Department of Neurology, Georgetown University Hospital, Washington, DC, USA.

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterised by upper and lower motor neuron dysfunction. Despite its devastating impact, and diagnostic challenges, a limited understanding of disease pathogenesis complicate effective management. Recent advancements in pharmacological therapies offer hope for improved outcomes. This review examines the current treatment landscape for ALS, including Riluzole (Rilutek, Tiglutik and Exservan), Edaravone (Radicava and Radicava ORS), and Tofersen (Qalsody), with a focus on their mechanisms, clinical efficacy, and implications for patient care. Additionally, we will briefly discuss the approval and subsequent withdrawal of Sodium Phenylbutyrate/taurusodiol (Relyvrio) as well as anecdotal evidence for Dextromethorphan-Quinidine (Nuedexta) and vitamin B12. Patients with ALS are best managed in a multidisciplinary clinic with access to specialists trained in neurology, pulmonology, physical therapy, occupational therapy, speech therapy, social work, nutrition and an ALS association representative. A multidisciplinary approach contributes to improving quality of life and survival.

Keywords: Amyotrophic Lateral Sclerosis (ALS); Upper Motor Neuron (UMN); Lower Motor Neuron (LMN)

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with a lifetime risk of approximately 1 in 350 individuals [1,2]. The incidence of ALS peaks between the ages of 60 and 79, and males are slightly more affected than females. Approximately 10% of ALS is genetic. Several genetic mutations have been described and known to cause familial ALS, the most common mutation being in the C9orf72 gene [3]. The disease presents with both upper motor neuron (UMN) and lower motor neuron (LMN) dysfunction, manifesting as progressive muscle weakness, dysphagia, dysarthria, and compromised respiratory function. The hallmark pathological feature of ALS is the presence of TDP-43 proteinopathy in nearly all cases [4]. The ALS Functional Rating Scale Revised (ALSFRS-R) score is a validated 12-item questionnaire used to grade the severity of the disease with a maximum score of 48 indicating an asymptomatic patient [5]. Patients are often scored at the time of diagnosis and subsequently during clinic visits. On average, the score drops by about 1 point per month [6]. Additionally, this scoring system is often used in clinical trials to monitor disease progression vs. slowing. Multidisciplinary care clinics, where patients can visit with the entire care team during one appointment has been found to positively affect outcomes for patients with ALS. Every three months, patients are evaluated by specialists trained in neurology, pulmonology, physical therapy, occupational therapy, speech therapy, social work, nutrition, and an ALS association representative. These visits allow for better interdisciplinary planning of treatment and a better understanding of the overall picture for the patient's goals. One study found that those who attend multidisciplinary clinics compared to those who attend individual specialist clinics had improved survival [7].

Treatment options

Riluzole (Rilutek, Tiglutik and Exservan)

Riluzole, an antiglutamate agent, was the first drug approved for ALS treatment in 1995. It operates under the hypothesis that glutamate accumulation at synaptic sites contributes to

neurotoxicity. A pivotal 1994 study demonstrated that Riluzole improved survival in ALS patients when compared with placebo after 12 months (74% vs 58%) oxidative [8]. Subsequent research supported Riluzole's efficacy, showing improved survival and a reduced need for tracheostomy (57 versus 50 per cent; adjusted relative risk 0.65, 95% CI 0.50-0.85) after 18 months of use [9]. Another examination of the effects of Riluzole from randomized control trials found Riluzole was able to prolong survival by 2-3 months [10].

A question that providers are often asked in the clinic is whether Riluzole prolongs life during the initial vs later stages of the disease, as quality of life is often an important goal for patients. One retrospective analysis of the initial trial data suggested that Riluzole extended life in in King's clinical stage 4 of the disease, as inferred by vital capacity ≤75% of predicted or feeding tube insertion [11]. This finding has not been corroborated by prospective studies.

Riluzole is available in oral, liquid and oral film formulations. The dosing is 50 mg twice daily. Side effects include nausea, abdominal pain, and elevation of liver transaminases. Liver Function Tests are monitored monthly x 3 months after initiation of the medication then every 3 months thereafter.

Edaravone (Radicava and Radicava ORS)

Edaravone, approved for use in patients with ALS in 2017, functions as a free-radical scavenger, addressing oxidative stress- a key factor in ALS progression. An initial trial in patients with a diagnosis of ALS for 3 years living independently, and with a forced vital capacity of ≥ 70, did not reveal a benefit with this medication. Post-hoc analysis however showed an effect in a small subgroup of patients [12].

A second phase 3 randomized, double-blind trial in patients with ALS who met certain criteria (FVC ≥ 80, disease duration of 2 years or less, independent living status, scores of 2 or more on all items of the ALSFRS-R questionnaire) demonstrated that Edaravone resulted in a slower decline in the ALSFRS-R score compared to placebo.

Patients receiving Edaravone had an approximately 5-point decrease in ALSFRS-R versus a 7.5point decrease in the placebo group at 24 weeks. These findings confirm Edaravone's role in mitigating disease progression and improving quality of life in patients with early onset ALS [13].

Edaravone was initially approved as an intravenous injection. Subsequently, an oral liquid formulation (Radicava ORS) was created and approved for use in 2022 [14]. The effectiveness of Radicava ORS was based on a study that showed comparable levels of Radicava ORS in the bloodstream to the levels from the intravenous formulation [14]. Of note, the efficacy of Radicava ORS is unclear as a randomized trial failed to show slowing of disease progression when compared to placebo (ADORE study) [15].

The IV formulation is administered 60 mg once daily for 14 days followed by a 14 day drug-free period. Subsequent cycles are 60 mg daily for 10 days within 14 days, followed by a 14 day drug-free period. The oral formulation is dosed at 60 mg (5ml) daily for 14 days followed by a 14 day drug-free period. Subsequent cycles are 60 mg daily (5ml) for 10 days within 14 days, followed by a 14 day drug-free period. Side effects include injection site contusion and headaches. Edaravone contains sodium bisulfite, sulfites can cause asthmatic reactions in patients with a history of asthma.

Tofersen (Qalsody)

Tofersen was approved specifically for the treatment of SOD1 mutation-related ALS, a subtype associated with 15% of all familial cases of ALS. Tofersen, an antisense oligonucleotide, approved in April 2023, targets and silences SOD1 mRNA, reducing the total SOD1 protein level [16]. A phase 1/2 trial showed significant reductions in cerebrospinal fluid (CSF) SOD1 levels and serum neurofilament light chain levels, supporting Tofersen's potential as a targeted therapeutic for SOD1-linked ALS. At 52 weeks, the change in the ALSFRS-R score was −6.0 in the early start cohort of patients and −9.5 in the delayed start cohort of patients favoring the early start of Tofersen [17,18]. The potential effects of earlier initiation of Tofersen are being further evaluated in the extension phase.

Tofersen is administered as an intrathecal monthly injection with an initial loading phase of intrathecal administration every 2 weeks x 3 doses. The most common side effects included procedural pain, headache, pain in the arms or legs, falls, and back pain. Serious neurologic side effects were reported in 7% of patients including myelitis, radiculitis, papilledema and aseptic meningitis. CSF white blood cell and protein elevation has been reported as well [17].

Sodium Phenylbutyrate and taurursodiol (Relyvrio)-withdrawn

Relyvrio is a coformulation of two compounds - sodium phenylbutyrate and taurursodiol - targeting endoplasmic reticulum stress and mitochondrial dysfunction respectively, however the exact mechanism by which Relyvrio works is unknown. The CENTAUR trial assessed Relyvrio's impact on ALS progression, revealing a slower rate of functional decline as measured by the ALSFRS-R [19]. Additionally, an extended study showed a median overall survival benefit of approximately 6.5 months for Relyvrio-treated patients compared to placebo [20]. Although initial findings suggested that Relyvrio offered a modest but clinically meaningful benefit in functional outcomes and survival, the drug was withdrawn from the market in April 2024. This decision was based on the results of the large Phase III PHEONIX trial, which found that Relyvrio did not achieve its intended efficacy goals. Specifically, the trial indicated that Relyvrio failed to slow disease progression, improve muscle strength, or demonstrate superiority over placebo in enhancing breathing, swallowing, and speaking abilities. Patients who had already started the medication based on the CENTAUR trial were offered a continuation of the medication vs discontinuation after the second trial results were announced [21].

In addition to the lack of effect found in the 2023 trial, patients often complained of the significant bitter taste of the powdered formulation that required dissolution in water. The solution was dosed twice daily after the initial dosing of drinking the solution once a day for 3 weeks. Common side effects included GI-related-nausea, abdominal pain and diarrhoea [21].

Off-label use of other medications

Methylcobalamin

A phase II/III study in Japan reported ultra-high dose methylcobalamin (25 or 50 mg) intramuscular injections twice per week revealed a trend towards clinical benefit [22]. While a subsequent study did not show clinical benefit, post hoc analysis of data revealed that this treatment may prolong survival and slow symptomatic progression when started early [23]. A subsequent phase 3 clinical trial published in 2022 revealed an approximately 2-point (-2.66 with methylcobalamin vs -4.63 with placebo) difference in the ALSFRS-R between the methylcobalamin and placebo groups indicating a slowing of decline during the 16-week treatment period. All the included patients were enrolled within 1 year from symptom onset [24]. Based on this data, high-dose methylcobalamin injections may slow functional decline in early-stage ALS.

Dextromethorphan and Quinidine (Nuedexta)

Nuedexta, approved in 2011 for the management of pseudobulbar affect, combines dextromethorphan and quinidine and acts as a sigma-1 receptor agonist. Although it is approved for pseudobulbar affect, a study reported alleviation of bulbar symptoms of ALS. The trial demonstrated significant improvements in bulbar symptoms, such as speech and swallowing, with Nuedexta. The medication did not affect motor or respiratory functions, highlighting its targeted efficacy in alleviating bulbar symptoms and enhancing patient quality of life [25]. Although not FDA-approved for bulbar symptoms, patients with ALS often have pseudobulbar affect and this drug may have the dual benefit of additionally helping with the improvement of bulbar dysfunction.

Nuedexta is an oral capsule initially taken at a dosing frequency of 1 capsule once a day followed by 1 capsule twice a day after 7 days. A baseline EKG is typically obtained before starting this medication as it can cause QT interval prolongation. Typical side effects include diarrhoea, asthenia, vomiting, and oedema [25].

Conclusion

The management of ALS has evolved with the development of various therapeutic agents targeting different mechanistic aspects of the disease. Riluzole remains a foundational treatment with proven survival benefits. Edaravone offers additional options for possibly slowing disease progression and improving functional outcomes in a certain subset of ALS patients. Tofersen introduces a promising approach for a genetic form of ALS caused by mutations in the SOD1 gene. While none of these medications has shown to cure ALS, these disease-modifying agents have shown advancements in slowing the progression of disease symptoms. Ongoing research and clinical trials will continue to refine these treatments and potentially uncover new therapeutic strategies for this challenging disease.

Of note, this review did not cover symptom-based management of ALS such as spasticity, sialorrhea, thick secretions, pain, depression, and insomnia. The use of devices such as BIPAP, gastrostomy tube, eye gaze for communication, and power wheelchair were not discussed.

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