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RESEARCH ARTICLE

Disease-Modifying Treatment for Amyotrophic Lateral Sclerosis – A Review on Edaravone

Daniel do Nascimento Antônio[1], Bruna Laila Tansini[2]

[1]*Serviço de Atenção Domiciliar. Hospital Bartholomeu Tacchini. Bento Gonçalves, Brazil.*

[2]*Serviço de Clínica Médica. Hospital Bartholomeu Tacchini. Bento Gonçalves, Brazil*.

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Corresponding Author: Bruna Laila Tansini, Serviço de Clínica Médica. Hospital Bartholomeu Tacchini. Bento Gonçalves, Brazil.

Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive, incurable neurodegenerative disease. There are non-pharmacological treatment options, such as supportive care, which help improve patients' quality of life. Among disease-modifying pharmacological therapies, very few medications with an established level of evidence are found. One of them is edaravone (EDA). This integrative review was based on the selection of articles on the search platforms PubMed and Biblioteca Virtual em Saúde/Virtual Health Library. It included articles published between 2022 and 2023, which studied evidence on edaravone in the modifying treatment for ALS. Studies carried out in humans, which administered the drug intravenously or orally, were selected, excluding articles that modified the edaravone (EDA) molecule. The objective is to discuss current and available findings in the literature about the relationship between the use of edaravone and the functional deterioration of patients with ALS.

Keywords: Amyotrophic Lateral Sclerosis, Edaravone, Disease-Modifying Treatment.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease. It was first described in the 19th century. It gradually affects motor neurons in both the brain and spinal cord (1). A study published in April 2022 estimated an incidence of 0.83 cases of ALS per 100 thousand inhabitants and a prevalence of 2.4 per 100 thousand inhabitants in 2019 in Brazil (2). ALS is characterized by causing muscle weakness, atrophy, and spasticity, leading to swallowing, speech, and breathing disorders. Survival time for the disease is 1.5 to 4 years after diagnosis. Most patients die due to respiratory muscle failure (1). Most cases of ALS are sporadic; however, there is a familial form of the disorder, responsible for 5-10% of cases (1).

ALS is a disease for which there is no cure, as the pathophysiological, genetic, and environmental mechanisms that contribute to its onset are uncertain. The treatment aims to slow the progression of the disease, as well as improve the patient's quality of life. Edaravone is a free radical scavenger, that is, it reduces cellular oxidative stress, which may be one of the pathophysiological components of ALS (1). Clinical trials of edaravone for ALS began to be performed in Japan in 2001. The use of edaravone to treat sclerosis in the country was approved in 2015 (14).

In 2017, the drug was approved by the U.S. Food and Drug Administration (FDA) for the treatment of ALS, after studies demonstrated its safety and efficacy (3). There are two formulations for administration: intravenously at a dose of 60 mg or oral suspension at a dose of 105 mg (4).

Given that riluzole is the only medicine approved by the Brazilian health authority, Agência Nacional

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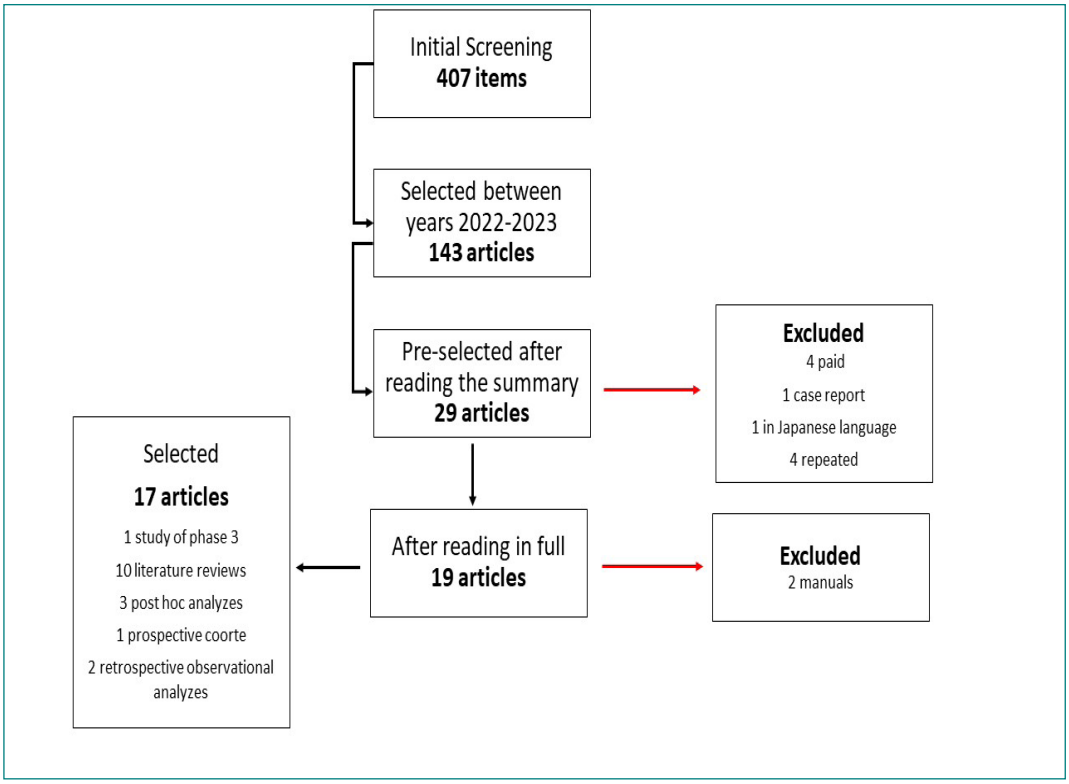
de Vigilância Sanitária (Anvisa), for the specific treatment for ALS, this review article discusses the most up-to-date and available findings on edaravone and its efficacy in the treatment that modifies the quality of life of ALS patients, besides questioning the need to implement new therapies in the country.

2. Materials and Methods

The search for articles was carried out in the databases PubMed and Biblioteca Virtual em Saúde/Virtual Health Library. The descriptors "amyotrophic lateral sclerosis" and "edaravone" were used in Portuguese and English, together with the Boolean operator "and". The selection only included articles written in English, with free access to the full text, and studies on humans, published between 2022 and 2023. After an initial screening, articles that modified the molecular structure of the medication or that tested its intranasal administration were excluded. Clinical practice guides or manuals were also not analyzed. The methodological approach adopted to select the articles included in the main text is summarized in flowchart 1.

3. Results

The data search resulted in 407 items found. When the publication time was restricted (between 2022 and 2023), 143 articles were selected. After a pre-selection – carried out by reading the title and abstract of each article – 29 publications were excluded. The full reading excluded 4 articles that were not available for free, 1 case report, 1 article in Japanese, and 4 articles that were repeated on both search platforms. Two health manuals were also eliminated. Thus, 17 articles remained; they met the inclusion criteria for this review.



Flowchart 1. *Articles included and excluded according to pre-selected criteria.*

4. Discussion

The intravenous formulation of the free radical scavenger is used in 14-day cycles, with a dose of 60 mg once a day, followed by a 14-day drug-free period. Subsequent cycles consist of 60 mg once a day for 10 days in a 14-day period, followed by a 14-day drug-free period. There is no need to adjust this dosage for liver or kidney dysfunction; there are also no drug interactions (13).

The Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) encompasses 12 question items in the four fields affected by the disease: bulbar functions, fine motor skills, gross motor skills, and respiratory function (12). Each item has a score rating ranging from 4 to 0 – 4 is the normal state and 0 is a state completely dependent on care. Thus, many studies assess the association between decreasing progression on this scale and the use of edaravone.

Edaravone slowed the rate of functional decline, as assessed by the ALSFRS-R score, in subjects with ALS in the phase-3 study MIC186-19 (Study 19).

It was a randomized, double-blind, parallel-group, placebo-controlled study with a 24-week double-blind treatment regimen, followed by open-label treatment for 24 weeks, where all subjects received edaravone (12). The primary outcome was the change in the slope curve of the ALSFRS-R score from baseline, measured as least squares mean change. The mean difference between the groups was 2.49 (CI of 95%: 0.99-3.98; p = 0.0013) in favor of the intervention group (3). The FDA approved the use of the drug in the United States based on this study.

However, it is important to highlight that the disease duration, from the first symptom to inclusion, of the patients selected for this trial was less than two years, that is, ALS in the early stage.

A reanalysis of data from Study 19 using intravenous edaravone compared the effects of the medication against a placebo on cumulative outcomes of death, tracheostomy, ventilator-associated pneumonia, and hospitalizations in ALS patients. The benefit of the treatment was evident for the group that first received edaravone over 48 weeks (5). Other post-hoc analyses of the same study, which analyzed the same time period, i.e., a 24-week double-blind treatment followed by a 24-week open-label treatment with edaravone, corroborated the findings of the first review (9-12). Besides providing important information for future clinical trials, these reanalyses show that edaravone may provide benefits for ALS patients in terms of quality of life.

Even though this medication has only been on the market in the United States for a few years, an analysis of data referring to the first three years post-commercialization did not identify any new adverse effects of the drug other than those already reported in previous clinical trials (10), such as lesions at the administration site and headache (17).

A Korean observational study in a specialized ALS center found a favorable association between the extended use of edaravone – 72 weeks, 18 administration cycles – and the ALS Functional Rating Scale (ALSFRS-R) and forced vital capacity (FVC); (8) however, it displays some biases, mainly relating to selection, since it included patients with advanced-stage ALS, unlike the propositions of study 19. Therefore, it is not applicable to patients with early-stage ALS.

Another study analyzing long-term treatment – a multicenter cohort study that assessed treatment with edaravone combined with riluzole against riluzole therapy alone – did not substantiate the treatment with edaravone for any clinically relevant benefits in disease progression (11), revealing the discrepancy of scientific findings.

A systematic review including 11 studies with 2,845 patients demonstrated, through a significant p-value, that edaravone improved the survival rate at 18, 24, and 30 months, but showed no statistical difference in scores (change in Amyotrophic Lateral Sclerosis Assessment Questionnaire - ALSAQ 40 and ALSFRS-R scores) between the control group and the group that received the medication (6).

Oral edaravone was approved by the FDA in May 2022, after studies demonstrated its safety (4). A positive aspect is that the drug can be administered through a gastrostomy tube. A global, open-label, phase-3 study evaluated the tolerability of the medication in patients who received a dose of 105 mg orally over 48 weeks of treatment (7). The population had received a definitive or probable diagnosis of ALS less than 3 years before, with a baseline forced vital capacity greater than or equal to the predicted 70%. No adverse events related to the drug were reported in this study, thus outlining a favorable safety profile in this population in the non-advanced stages of the disease.

A literature review that developed a cost calculator to quantify the effect of introducing oral edaravone in a scenario where intravenous EDA is sold demonstrated that, at the end of one year, the oral formulation would save around US$ 13,700 in direct costs, i.e., expenses associated with changes in formulation administration. When indirect costs, resulting from the loss of productivity of patients and their caregivers, are included, the savings over the same period of time are estimated at US$ 16,000 (15). These findings are favorable to the oral administration route, in terms of efficacy and effectiveness, when compared to the intravenous administration.

5. Conclusion

ALS is a rare progressive motor neurodegenerative disease that causes loss of voluntary muscle control. It progresses to death within two to five years, due to muscular atrophy, paralysis, and respiratory failure. Despite being the most common motor neuron disease, there is no cure for it.

Besides there being few therapeutic options, riluzole is the only medication approved for the specific treatment for ALS in Brazil (3).

Edaravone, which is currently administered orally and intravenously, is believed to help delay the loss of motor function in ALS patients. Its exact mechanism of action in ALS remains unclear, but it appears to be a free radical scavenging technology with the potential to reduce neuronal death by decreasing oxidative stress (16).

This mechanism of action seems to improve the quality of life related to the development of the disease. However, the benefits are more substantial in the early stages of the disorder (5).

The oral route seems to be innovative and to lower treatment costs, as well as improve quality in drug administration (4-15).

Existing studies differ markedly; therefore, further research is needed to assess the efficacy of the medication in intermediate and advanced stages of ALS. In consequence, it will be possible to carry out a careful analysis to add a new drug to the list of medications provided by the Brazilian health care system, named Sistema Único de Saúde, in order to combat this rare, multimorbid disease.

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Abbreviations

ALS – Amyotrophic Lateral Sclerosis

ALSFRS-R – Revised Amyotrophic Lateral Sclerosis Functional Rating Scale

FVC – Forced Vital Capacity

ALSAQ-40 – Amyotrophic Lateral Sclerosis Assessment Questionnaire

EDA – Edaravone

FDA – Food and Drug Administration

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