

Philadelphia College of Osteopathic Medicine

DigitalCommons@PCOM

---

PCOM Physician Assistant Studies Student  
Scholarship

Student Dissertations, Theses and Papers

---

2021

## Does Edaravone slow disease progression in patients with Amyotrophic Lateral Sclerosis?

J. Michael Rutledge

*Philadelphia College of Osteopathic Medicine*

Follow this and additional works at: [https://digitalcommons.pcom.edu/pa\\_systematic\\_reviews](https://digitalcommons.pcom.edu/pa_systematic_reviews)



Part of the [Medicine and Health Sciences Commons](#)

---

### Recommended Citation

Rutledge, J. Michael, "Does Edaravone slow disease progression in patients with Amyotrophic Lateral Sclerosis?" (2021). *PCOM Physician Assistant Studies Student Scholarship*. 577.

[https://digitalcommons.pcom.edu/pa\\_systematic\\_reviews/577](https://digitalcommons.pcom.edu/pa_systematic_reviews/577)

This Selective Evidence-Based Medicine Review is brought to you for free and open access by the Student Dissertations, Theses and Papers at DigitalCommons@PCOM. It has been accepted for inclusion in PCOM Physician Assistant Studies Student Scholarship by an authorized administrator of DigitalCommons@PCOM. For more information, please contact [library@pcom.edu](mailto:library@pcom.edu).

**Does Edaravone slow disease progression in patients with Amyotrophic Lateral Sclerosis?**

J. Michael Rutledge, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Suwanee, Georgia

December 16<sup>th</sup>, 2020

## ABSTRACT

**Objective:** The objective of this EBM review is to determine whether or not Edaravone is effective at slowing disease progression in patients with ALS.

**Study Design:** Review of three randomized control trials.

**Data Source:** All articles were published in English between 2014 and 2019. Articles were obtained from peer-reviewed journals and databases using Cochrane Collaboration, PubMed, Medline, and Embase.

**Outcomes:** The outcome measured was physical function assessed by the Amyotrophic Lateral Sclerosis Assessment and Questionnaire 40 Revised (ALSAQ-40R). Patients are asked to provide a perceived ability rating on a scale of 0 to 100, with 0 indicating perfect health and 100 a total loss of function.

**Results:** The Double blind RCTs of both Abe et al. (*Amyotroph Lateral Scler Frontotemporal Degener.* 2014;15:610-617. Doi: 10.3109/21678421.2014959024.) as well as The Writing Group on behalf of the Edaravone (MCI-186) ALS 17 Study Group. (*Amyotroph Lateral Scler Frontotemporal Degener.* 2017;18:20-31. Doi: 10.1080/21678421.2017.1362000) failed to demonstrate Edaravone efficacy against placebo ( $p=0.892$  and  $p=0.1651$ , respectively). Final trial conducted by The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. (*Lancet Neurol.* 2017;15:505-512. Doi: 10.106/S1474-4422(17)30115-1) found that Edaravone was more effective at slowing disease progression than placebo in a well-defined patient population ( $p=0.0309$ ).

**Conclusion:** A summation of results from three articles reviewed here would indicate that Edaravone does not slow disease progression in patients with ALS. There does appear to be some utility in early disease patients, but this finding requires further evaluation.

**Keywords:** ALS, amyotrophic lateral sclerosis treatment, edaravone, ALSAQ-40

## INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressive, degenerative motor neuron disease affecting both upper and lower tracts, leading to nerve dysfunction, paralysis, and ultimately death. Most recent reports indicate an incidence of 0.6 and 3.8 per 100,000 person-years and a prevalence of 4.1 and 8.4 per 100,000.<sup>1</sup> There is a profound degree of ambiguity in early disease manifestation. However, it is largely characterized by progressive muscle weakness originating in either limb or bulbar tracts; closely followed by atrophy, fasciculations, and cramping. Limb onset is most common at 58-82% of patients and traditionally begins at a distal, unilateral location and progresses proximally following neuronal distribution.<sup>2</sup> The final result being total paralysis that spares all sensory function. Mortality frequently occurs due to neurogenic respiratory failure. Like early disease symptoms, survival time from diagnosis to death in ALS can be highly varied; although most sources would indicate a median survival time from diagnosis is 3 years.<sup>2</sup> Mean age at onset is 58-63 years for sporadic and 40-60 years for familial ALS varieties.<sup>2</sup>

A number of articles postulate a relationship between several environmental risk factors and ALS development. These include smoking, body mass index, physical exercise, occupational and environmental exposures to heavy metals (notably lead), pesticides, b-methylamino-L-alanine, head injury and viral infections.<sup>3,4</sup> The most explored modifiable risk factor to date is tobacco use (smoking) and the most studied non-modifiable risk factors remain male sex and increased age.<sup>5</sup> While research continues to be conducted on these relationships, the causation and pathogenetic effect of each remains obscure.<sup>3,4,5</sup>

The framework of ALS has shown itself to be exhaustingly convoluted, with variances and nuances between and even among distinct demographics. It is widely hypothesized that a genetic predisposition and epigenetic collusion prompt a number of biopathological alterations. Current

literature identifies approximately 20 aberrant genes correlated with disease manifestation.<sup>2,3,4</sup> Despite this, epigenetic collaboration and inter-gene architecture as well as disease penetrance has yet to be entirely understood. A number of subsequent biochemical transformations have been demonstrated as pervasive features, though far from definitive. Dysregulated RNA processing, protein aggregation, mitochondrial dysfunction, neuronal excitotoxicity, and oxidative stress all appear as commonalities across ALS pathogenesis research.<sup>2,3,4</sup> To add to the complexity of the disease, it is ambiguous as to what impact each feature has on the expression of the others.

Contrasting strides in foundational ALS discoveries, treatment targets have remained largely stagnant since Riluzole first became available for ALS patients in 1995. Riluzole is the only FDA approved pharmacological intervention other than Edaravone for ALS to date. It functions to abate neuronal excitotoxicity as a glutamic acid release inhibitor.<sup>6</sup> While Riluzole persists as a staple in ALS treatment, clinical trials have only shown the ability to extend time to intubation by 2-3 months.<sup>2,5-7</sup> The mechanism of action for Edaravone has yet to be solidified. It is hypothesized to be a free radical scavenger and has shown oxidant-stress mediating properties in mouse-models.<sup>7</sup> Thus working on another biochemical feature, not at the gene level, and not altogether dissimilar from Riluzole.

Few articles address the economic burden of ALS within the US. A 2015 systematic review approximates \$69,475USD per annum; a more recent German analysis suggests the cost can reach nearly \$300,000USD spent over the course of the disease.<sup>8,9</sup> While the total cost of illness (COI) may not seem as catastrophic as that of more prevalent diseases, it is important to note these expenses are incurred in the span of 2-5 years and carry with them no promise of disease remission or resolution. In best case scenarios, the high cost of treatment may only realize life prolongation

by a few months. It is reasonable to speculate that the COI remains relatively low due to the lack of pharmacological intervention, medication efficacy, and rapid disease progression.

## **OBJECTIVE**

The objective of this EBM review is to determine whether Edaravone is effective at slowing disease progression in patients with ALS.

## **METHODS**

This review evaluated articles obtained from Cochrane Library, Medline, PubMed, and Embase. Online databases were explored via keywords: “ALS,” “amyotrophic lateral sclerosis treatment,” “edaravone,” and “ALSAQ-40.” Selection criteria consisted of blinded, randomized controlled trials published during or after 2014, either written in or translated into English. Included articles had participants with a definitive or probable ALS diagnosis. Intervention selected was Edaravone with comparison to placebo control. Initial inclusion criteria consisted of articles with self-reported, health-related quality of life outcome measures (HRQoL). Later HRQoL was refined specifically to articles in which the Amyotrophic Lateral Sclerosis Assessment Questionnaire – 40 revised (ALSAQ40-R) was used to assess outcome measures. Articles that evaluated disease-oriented outcome measures, contained unblinded populations or evaluators, were post-hoc analysis or included late disease-states (determined by tracheal intubation) were excluded.

A single author reviewed articles in their entirety for methodological quality, completeness of data, adequate randomization, ethical soundness. Initially, 13 met inclusionary criteria and were examined. After the outcome measure assessment was refined to ALSAQ-40 alone, these were concentrated to the three double-blind, randomized controlled trials (RCT) contained in this

review. Each article contained analogous assessment reporting: 1) intergroup mean change from baseline, 2) P-value, 3) confidence interval.

## **OUTCOMES MEASURED**

The primary outcome measured in all three selected studies was physical ability and function and primary endpoint used for analysis was the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R).<sup>10-12</sup> However, the ALSFRS-R measures evaluator obtained data points and thereby does not meet HRQoL/POEM criteria. Patient perceived function was measured as a second endpoint in all three trials and subsequently selected for analysis in this review. Patient perceived function was assessed via the Amyotrophic Lateral Sclerosis Assessment Questionnaire 40 (revised). The ALSAQ-40R is a self-reported HRQoL questionnaire that assesses patients': A) physical mobility on 10 items. B) activities of daily living and independence on 10 items. C) eating and drinking ability on 3 items. D) communication on 7 items. E) emotional reactions on 10 items. Section parameters are based on a 0 to 100 scale with 0 indicating perfect health and 100 indicating a total loss of capacity in dimension.<sup>13</sup>

## **RESULTS**

In Abe et al. (2014) RCT, 206 patients meeting inclusion criteria (Table 1) were randomized via dynamic allocation into placebo (N = 102) or treatment (Edaravone) (N = 104) groups.<sup>10</sup> Their design consisted of a 12-week pre-observation period followed by a 24-week treatment phase, for a total of 36 weeks of data collection. The first treatment cycle involved 14 days in which Edaravone 60mg was administered daily via intravenous infusion in treatment group. Saline was administered for placebo group during this period.<sup>10</sup> During treatment cycles 2 through 6, Edaravone was administered daily for 10 days.<sup>10</sup>

**Table 1: Demographics and Characteristics of Included Studies**

Study	Type	# of Pts.	Mean Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/d	Treatment
Abe, K <sup>10</sup> (2014)	Double Blind RCT	205	58	<ol style="list-style-type: none"> <li>1. Forced vital capacity <math>\geq 70\%</math>.</li> <li>2. Disease duration of <math>\leq 3</math> years.</li> <li>3. ALSFRS Change in revised score during the 12-week pre-observation period of <math>-1</math> to <math>-4</math> points.</li> <li>4. Patients also had a Japanese ALS severity classification of 1 or 2</li> </ol>	<ol style="list-style-type: none"> <li>1. Reduced respiratory function or dyspnea.</li> <li>2. Comorbidities that influence evaluation of drug efficacy: Parkinson's disease, schizophrenia; dementia.</li> <li>3. Complications requiring hospitalization</li> <li>4. Infections requiring antibiotic therapy.</li> <li>5. deteriorated in general condition (judged by investigators)</li> <li>6. Creatinine Clearance <math>\leq 50</math> ml/min.</li> </ol>	23	Edaravone 60mg IV
Writing Group for ALS 17 Study <sup>11</sup> (2017)	Double Blind RCT	181	57	<ol style="list-style-type: none"> <li>1. Forced vital capacity <math>\geq 70\%</math>.</li> <li>2. Patients aged 20-75 years with a diagnosis of ALS and independent living status</li> <li>3. Japan ALS Severity Grade 1 or 2</li> </ol>	<ol style="list-style-type: none"> <li>1. ALSFRS-R score <math>&lt; 3</math>, history of spinal surgery; creatinine clearance <math>\leq 50</math>ml/min</li> </ol>	30	Edaravone 60mg IV
Writing group for ALS 19 Study <sup>12</sup> (2017)	Double Blind RCT	137	60	<ol style="list-style-type: none"> <li>1. Patients aged 20-75 years with a diagnosis of ALS and independent living status</li> <li>2. Japan ALS Severity Grade 1 or 2</li> <li>3. <math>\geq 2</math> on all 12 items of ALSFRS-R</li> </ol>	<ol style="list-style-type: none"> <li>1. Forced vital capacity <math>\leq 80\%</math>.</li> <li>2. Duration of disease from the first symptom (any ALS symptom) <math>\leq 2</math> years or less</li> </ol>	10	Edaravone 60mg IV



Each treatment cycle was followed by a 14-day observation period. Patients prescribed Riluzole (N = 182) were required to remain on treatment with the stipulation that no alterations be made to pre-trial regimen.<sup>10</sup> During the trial, two patients in the placebo group and three in the Edaravone group were lost due to death. Analysis of adverse events (AE) and serious adverse event (SAE) found no intergroup difference (p=1.000 and p=0.349 respectively).<sup>10</sup> As all reported AE and SAE fell within the spectrum of normative ALS progression, the authors did not conclude they were due to treatment.<sup>10</sup> Neither group demonstrated adverse drug reactions.

Statistical analysis of efficacy endpoints was calculated via Analysis of Covariance (ANCOVA) and reported in least squares mean change, intergroup difference, and p-value.<sup>10</sup> Evaluation revealed an extremely narrow intergroup ALSAQ-40R mean change from baseline of 0.48 (SD  $\pm$ 3.50; 95% CI: -0.44, 7.39) which failed to meet statistical significance (p = 0.892).<sup>10</sup>

**Table 2** - ALSAQ-40R expressed as mean change  $\pm$  SD from pre-observation to post treatment<sup>10</sup>

	Adjusted mean change	Inter-group difference in adjusted mean change (95% CI)	P-value
Edaravone	19.6 $\pm$ 3.82	0.48 $\pm$ 3.50 (- 0.44, 7.39)	0.892
Placebo	19.13 $\pm$ 3.79		
Statistical significance (P < 0.05)			

The second article examined was the Writing Group on Behalf of the Edaravone ALS 17 Study Group (2017).<sup>11</sup> This trial was an extension to ALS Study Group 16. During this follow-through, the 180 of the original 183 patients who completed the initial 24-week study and failed to meet exclusion criteria (Table 1) were enrolled into the extension.<sup>11</sup> Treatment group assignments during ALS 16 Study were indicated by preceding letter: “E” for Edaravone, “P” for placebo. Treatment group assignments during the extension indicated by following letter; “E” for Edaravone, “P” for placebo. The final full analysis set (FAS) was comprised of 180 participants randomly assigned via minimization method into three groups E-E (N = 48), E-P (N = 44), P-E (N = 88).<sup>11</sup> Of note, placebo-placebo group was disallowed from extension randomization.

Treatment protocol during the initial trial and its extension was analogous to the 24-week design used by Abe et al. (2014) with a caveat that no 12-week pre-observation period was incorporated.<sup>11</sup> Treatment cycle entailed Edaravone 60 mg IV administered daily for 10 days in E-E and P-E groups; saline was administered at the same time in E-P group.<sup>11</sup> Treatment cycle was immediately followed by a 14-day observation period for all participants. Patients prescribed Riluzole (N = 161) were required to remain on treatment with the stipulation that no alterations be made to pre-trial regimen.<sup>11</sup>

The authors noted a statistical difference in E-E versus E-P serious adverse events (SAE) between the group ( $p=0.0344$ ).<sup>11</sup> 25 of 48 participants (52.1%) of the E-E group while only 13 of 45 participants in the E-P group developed SAE's.<sup>11</sup> They suggest SAEs were attributable to normative ALS progression and not related to serious ADRs. They go on to suggest that an age discrepancy existed between E-E and E-P despite minimization allocation. No further attempt to establish causation was made.<sup>11</sup>

Statistical analysis of efficacy endpoints was calculated via Analysis of Covariance (ANCOVA) and reported in least squares mean change, intergroup difference, and p-value.<sup>11</sup> Evaluation revealed an extremely narrow intergroup ALSAQ-40R mean change from baseline of -5.45 (SD  $\pm 3.89$ ; 95% CI: -13.19, 2.29) which failed to meet statistical significance ( $p = 0.165$ ).<sup>11</sup>

**Table 3** – ALSAQ-40R expressed as mean change  $\pm$  SD from pre-observation to post treatment<sup>11</sup>

	Adjusted mean change	Inter-group difference in adjusted mean change (95% CI)	P-value
E-E	13.54 $\pm$ 2.89	-5.45 $\pm$ 3.89 (- 13.19, 2.29)	0.1651
E-P	18.99 $\pm$ 3.03		
Statistical significance (P < 0.05)			

Post-hoc analysis of previous Stage II and III trials suggested that early-stage ALS patients may realize more favorable treatment effects compared to later stage patients.<sup>12</sup> This prompted The Writing Group on Behalf of the Edaravone ALS 19 Study Group (2019) to conduct a trial with limited disease progression criteria. Investigators restricted patient demographic to only include participants with ALSFRS-R scores of at least 2 in all 12 dimensions, FVC of 80% (opposed to 70% in previous trials), and shortened disease duration to patients with less than 2 years since first symptom (Table 1).<sup>12</sup>

After additional exclusion criteria (Table 1) were applied, 134 patients were randomized via dynamic allocation by an independent registration center into placebo (N = 66) or treatment (Edaravone) (N = 68) groups.<sup>12</sup> Their design consisted of a 12-week pre-observation period followed by a 24-week treatment phase, for a total of 36 weeks of data collection. The first treatment cycle involved 14 days in which Edaravone 60mg was administered daily via intravenous infusion in treatment group. Saline in visually matched packaging was administered for placebo group during this period. During treatment cycles 2 through 6, Edaravone was administered daily for 10 days. Each treatment cycle was followed by a 14-day observation period. Patients prescribed Riluzole (N = 182) were required to remain on treatment with the stipulation that no alterations be made to pre-trial regimen.

Statistical analysis of efficacy endpoints was calculated via Analysis of Covariance (ANCOVA) and reported in least squares mean change, intergroup difference, and p-value.<sup>12</sup> Evaluation revealed an extremely narrow intergroup ALSAQ-40R mean change from baseline of -8.79 (SD  $\pm$ 4.03; 95% CI: -16.76, 0.82) which failed to meet statistical significance (p = 0.0309).<sup>12</sup>

**Table 4** - ALSAQ-40R expressed as mean change  $\pm$  SD from pre-observation to post treatment<sup>12</sup>

	Adjusted mean change	Inter-group difference in adjusted mean change (95% CI)	P-value
Edaravone	17.25 $\pm$ 3.39	-8.79 $\pm$ 4.03	0.0309
Placebo	26.04 $\pm$ 3.53	(-16.76, 0.82)	
Statistical significance (P < 0.05)			

## DISCUSSION

ALS is a disease defined by definite, drastic reduction in life expectancy, rapid progression, and lack of treatment options. The combination lends to the sense of absolute futility in patients, their families, and their providers. As such, it is an arena of mounting research. Unfortunately for the immediate period, much of that research is directed towards uncovering pathogenetic factors which may not appreciate effective treatment regimens for some time. In the interim, Edaravone is a treatment targeted at oxidative stress, a feature prevalent in nearly all ALS physiological research.

The three articles evaluated in this review had entirely equivalent treatment protocols, randomization methods, efficacy determinants, primary and secondary endpoints, and statistical analysis. The only deviation in method being the population restriction to early disease states implemented in ALS Study 19 (2019).<sup>12</sup> Though this final trial exclusively demonstrated efficacy ( $p = 0.0309$ ), the implications of failing to meet statistical significance may be noteworthy.<sup>10,11,12</sup>

In their discussion, the authors of ALS Study Group 19 (2019) propose the more robust exclusion criteria as a design limitation and go on to question Edaravone's efficacy in total.<sup>12</sup> Their suspicion has merit based on results from the previous two trials which failed to show any treatment effect ( $p=0.892$ ;  $p=0.1651$ ).<sup>10,11</sup> However, rudimentary physiology would indicate that relieving neuronal oxidative stress would not render any benefit if the neuron were already deceased. Subsequently, if Edaravone's mechanism of action is to mitigate free radicals as

hypothesized, one can easily infer that it must be administered early in the disease course, prior to neuronal death, in order to have any effect. While that association is speculative on multiple levels, it is a logical deduction made more intriguing by the observation of treatment failure with the inclusion of moderate disease stage patients. Additional data points are required to support this theory. But as Edaravone has been approved by the FDA for use in ALS patients, this hypothesis could be easily verified via cost-effective clinical trials employing study designs that parallel those reviewed in this article.

It should be understood that despite reaching statistical significance for efficacy ( $p=0.0309$ ) in ALS Study Group 19 (2019), the treatment effect size remains marginal (intergroup mean change:  $-8.79 \pm 4.03$ ; 95% CI:  $-16.76, 0.82$ ) compared to the ALSAQ-40R total 100-point scale.<sup>12</sup> This lends credit to the authors of ALS Study 19 (2019) suspicions.<sup>12</sup> That said, a longitudinal study may realize an expansion of intergroup mean changes if Edaravone can continue to abate free radicals. As a prevailing notion throughout this review, more data points are required to support this hypothesis.

All three trials appear to be of sound design and free of limitations. As the mean time from diagnosis to death is approximately 3 years, an active intervention design of 24-weeks represents approximately 15% of total disease duration and is well long enough to determine statistical efficacy. However, data collected from extended clinical trials that initiate with early course ALS patient must be performed to truly answer the objective sought in this review. Randomization was conducted via minimization method, which has grown favor in contemporary oncological trials. Minimization method is not true randomization but a restricted, dynamic form of allocation that seeks to balance prognostic factors across study arms. This does not appear to have an impact on

any of the RCT results as the only trial that met statistical significance employed an independent randomization center.<sup>11</sup>

ALS researchers, by large, appear to be on correct footing with regards to targeting future research. It is readily apparent that mediation of physiological effects subsequent to genetic alterations will only manifest marginal, short-term results. This is made obvious by the negligible benefit exhibited by Riluzole, as well as the statistical results of the trials reported in this review.<sup>6,7,10-12</sup> This suggests that prolonged benefit might only be possible with intervention at the genetic and epigenetic level. This level of investigation does little in the way of immediate hope for ALS patients and their families but provides far better possibilities of uncovering extensive disease modification over current treatment targets.

## **CONCLUSION**

Analysis of treatment options in ALS appear to be just as opaque as the disease itself. As a broad answer to the question presented in this review, Edaravone does not slow disease progression in patients with ALS.<sup>10,11</sup> Moreover, it is reasonable to near-definitively state that Edaravone provides no benefit in middle to late-stage ALS patients.<sup>10,11</sup> However, there does seem to be utility in early-stage administration with respect to prolonging physical function.<sup>12</sup> The duration that function can be maintained has yet to be explored. In summation, there are not enough data points to conclusively state that Edaravone is effective at slowing disease progression.

## REFERENCES

- [1] Longinetti E and Fang F. Epidemiology of amyotrophic lateral sclerosis: An update of recent literature. *Curr Opin Neurol.* 2019;32:771–776. doi:10.1097/WCO.0000000000000730
- [2] Mason P, Van Damme P. Amyotrophic lateral sclerosis: A clinical review. *Eur J Neurol.* 2020; 27(10):1918-1929. doi: 10.1111/ene.14393
- [3] Van den Bos MA, Geevasinga N, Higashihara M, Menon P and Vucic S. Pathophysiology and Diagnosis of ALS: Insights from Advances in Neurophysiological Techniques. *Int J Mol Sci.* 2019;20(11):2818. doi: 10.3390/ijms20112818
- [4] Nowicka N, Juranek J, Juranek J.K, Wojtkiewicz J. Risk Factors and Emerging Therapies in Amyotrophic Lateral Sclerosis. *Int J Mol Sci.* 2019;20(11), 2616; doi: 10.3390/ijms20112616
- [5] Calvo A, Canosa A, Bertuzzo D, Cugnasco P, Solero L, Clerico M, et al. Influence of cigarette smoking on ALS outcome: A population-based study. *J Neurol Neurosurg Psychiatry.* 2016;87(11):1229-1233. doi: 10.1136/jnnp-2016-313793
- [6] Saitoh Y, Takahashi Y. Riluzole for the treatment of amyotrophic lateral sclerosis. *Neurodegener Dis Manag.* [published ahead of print August 27, 2020]. doi: 10.2217/nmt-2020-0033
- [7] Manoj Kumar Jaiswal. Riluzole and edaravone: A tale of two amyotrophic lateral sclerosis drugs. *Med Res Rev.* 2018; 39(2): 733-748. DOI: 10.1002/med.21528
- [8] Gladman M, Zinman L. The economic impact of amyotrophic lateral sclerosis: a systematic review. *Expert Rev Pharmacoecon Outcomes Res.* 2015;15(3):439-50. doi: 0.1586/14737167.2015.1039941.
- [9] Schönfelder E, Osmanovic A, Müschen LH, Petri S, Schreiber-Katz O. Costs of illness in amyotrophic lateral sclerosis (ALS): a cross-sectional survey in Germany. *Orphanet J. Rare Dis.* 2020;15:149. doi: 10.1186/s13023-020-01413-9
- [10] Abe K, Itoyama Y, Sobue G, Tsuji S, Aoki M, Doyu M, et al. 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 Degener.* 2014;15:610-617. doi: 10.3109/21678421.2014959024.
- [11] The Writing Group on behalf of the Edaravone (MCI-186) ALS 17 Study Group. Exploratory double-blind, parallel-group, placebo-controlled extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener.* 2017;18:20-31. doi: 10.1080/21678421.2017.1362000

- [12] The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: A randomized, double-blind, placebo-controlled trial. *Lancet Neurol.* 2017;15:505-512. doi: 10.106/S1474-4422(17)30115-1
- [13] Jenkinson C, Harris R, Fitzpatrick R. The Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40): Evidence for a method of imputing missing data. *Amyotrophic Lateral Sclerosis.* 2007;8: 90–95. doi: 10.1080/17482960600989343
- [14] EDARAVONE (MCI-186) ALS 16 STUDY GROUP. A post-hoc subgroup analysis of outcomes in the first phase III clinical study of edaravone (MCI-186) in amyotrophic lateral sclerosis *Amyotroph Lateral Scler Frontotemporal Degener.* 2017;18(1):11-19. doi: 10.1080/21678421.2017.1363780.