Treatment Patterns and Survival Benefit of Edaravone–Treated People With Amyotrophic Lateral Sclerosis in the ALS/MND Natural History Consortium

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Introduction

- Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative condition that causes neuron cell death, progressive muscular weakness, and paralysis[1]
- Riluzole was approved by the US Food and Drug Administration (FDA) in 1995 and is considered the standard of care for the treatment of people with amyotrophic lateral sclerosis (PALS) due to the 60- to 90-day survival advantage it has demonstrated[2]
- Radicava® (edaravone) IV (intravenous) was FDA approved in 2017 for the treatment of ALS and has been shown in clinical trials to slow the rate of physical functional decline[3]
  - In a phase 3 trial, Radicava® IV was shown to slow down the rate of functional decline by 33% (*P*=0.0013), as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R), compared with placebo at 24 weeks[4]
- Radicava ORS® (edaravone) oral suspension was FDA approved for use in PALS in May 2022[3]
- ALS clinical trials present a challenge due to disease heterogeneity; therefore, although randomized controlled trials are considered the gold standard, research studies employing real-world data can complement their findings[5]
- In a previous real-world study using data from a large US administrative claims database, survival of propensity score-matched patients with ALS was evaluated based on treatment vs no treatment with Radicava® IV and found treatment was associated with prolonged median overall survival (*P*=0.005)[6]
- The ALS/Motor Neuron Disease (MND) Natural History Consortium (NHC) is a clinic-based registry that captures longitudinal clinical information from PALS

Objective

- To obtain real-world evidence on treatment patterns, clinical outcomes, and survival of Radicava® IV/ORS-treated PALS in the ALS/MND NHC database

Methods

Study Design

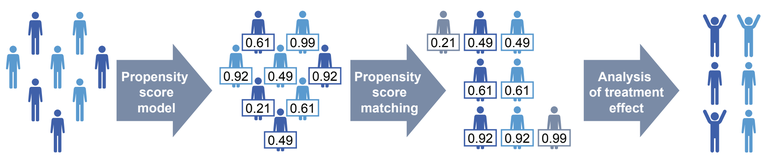
- This is an ongoing, prospective, observational, cohort study of PALS in the ALS/MND NHC database initiating Radicava® IV/ORS treatment
- Currently >2300 PALS have enrolled in this natural history study. NeuroBANK, a flagship clinical research platform run by the Neurological Clinical Research Institute at Massachusetts General Hospital, is collecting, curating, and analyzing data
- The index/start date for this analysis was the dose date of the first ALS treatment
- Baseline ALSFRS-R total scores and forced vital capacity (FVC) %–predicted measures represent values measured before but close to the index date

Propensity Score Matching

- PALS receiving Radicava® IV/ORS ± riluzole were propensity score matched 1:1 on 9 covariates to those receiving riluzole only based on the nearest-neighbor method[1] (**Figure 1**)

Figure 1. Propensity score matching

The objective of this method is to estimate the effect of a treatment in nonrandomized, interventional studies by adjusting for known confounding factors in a mixed population of treated or untreated patients with varying characteristics, to achieve a balanced covariate distribution between the treated and untreated groups[7]



Step 1
A group of patients who have been treated with either the intervention of interest (**light blue**) or a control intervention (**dark blue**) are identified

Step 2
Propensity score is estimated for each patient using logistic regression and accounting for the following covariates: sex, age, body mass index, race; and mean ± SD ALSFRS-R score and FVC%–predicted measures at baseline; and pre-index[a] non-invasive ventilation, artificial nutrition, riluzole use, disease duration, and hospitalization

Step 3
Patients in each group are then matched based on propensity score using the nearest-neighbor method

Patients for whom no matching partner has been found are excluded

Step 4
In this study, each treated patient was allocated up to 1 untreated patient (in 1:1 matching) with the same (or very similar) propensity score

Treatment effect was evaluated in the matched groups

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; FVC, forced vital capacity; SD, standard deviation.
[a]The index (start) date for this analysis was the dose date of the first ALS treatment.

Statistical Analyses

- Survival (mortality) between treatment arms was estimated using the Kaplan-Meier model
- Differences in restricted mean survival time (RMST) were computed and hypothetically examined considering adjustment for potential confounding

Results

Demographic and Clinical Characteristics of PALS

- Demographic and clinical characteristics of PALS in the ALS/MND NHC database treated with Radicava® IV/ORS ± riluzole (treated; n=205) vs riluzole only (n=560) are presented in **Table 1**
- PALS treated with Radicava® IV/ORS ± riluzole (n=176) were propensity score matched to PALS treated with riluzole only (n=176) on sex, age, body mass index, race; and pre-index non-invasive ventilation, artificial nutrition, and disease duration. Cases and controls were also matched on mean ± standard deviation (SD) ALSFRS-R score and FVC% predicted measures at baseline (**Table 2**)
- All matched variables had a standardized mean difference ≤0.1 (**Figure 2**)

Table 1. Demographic and clinical characteristics in PALS treated with Radicava® IV/ORS ± riluzole (treated) vs riluzole only

	Treated (n=205)	Riluzole Only (n=560)	*P* value
Sex, n (%)			
Male	116 (56.6)	326 (58.2)	0.748
Female	89 (43.4)	234 (41.8)	
Age			
Mean (SD)	60.7 (9.68)	63.7 (10.9)	<0.001
Median [Min, Max]	61.0 [23.0, 81.0]	65.0 [25.0, 89.0]	
Race, n (%)			
White	191 (93.2)	498 (88.9)	0.22
Black	7 (3.4)	30 (5.4)	
Other	7 (3.4)	32 (5.7)	
BMI			
Mean (SD)	27.3 (5.22)	27.0 (5.46)	0.473
Median [Min, Max]	26.8 [15.4, 44.3]	26.3 [15.9, 58.6]	
Missing, n (%)	10 (4.9)	24 (4.3)	
Pre-Index Non-invasive Ventilation, n (%)			
Yes	12 (5.9)	19 (3.4)	0.186
No	193 (94.1)	541 (96.6)	
Pre-Index Artificial Nutrition, n (%)			
Yes	5 (2.4)	13 (2.3)	1
No	200 (97.6)	547 (97.7)	
Pre-Index Disease Duration			
Mean (SD)	559 (666)	639 (788)	0.162
Median [Min, Max]	384 [21.0, 7130]	389 [20.0, 7390]	
ALSFRS-R Total Score at Baseline			
Mean (SD)	39.1 (4.81)	38.3 (4.57)	0.0313
Median [Min, Max]	40.0 [30.0, 47.0]	39.0 [30.0, 48.0]	
%FVC at Baseline			
Mean (SD)	78.7 (24.0)	77.9 (21.4)	0.692
Median [Min, Max]	82.5 [14.0, 139]	80.0 [19.0, 135]	
Missing, n (%)	21 (10.2)	85 (15.2)	

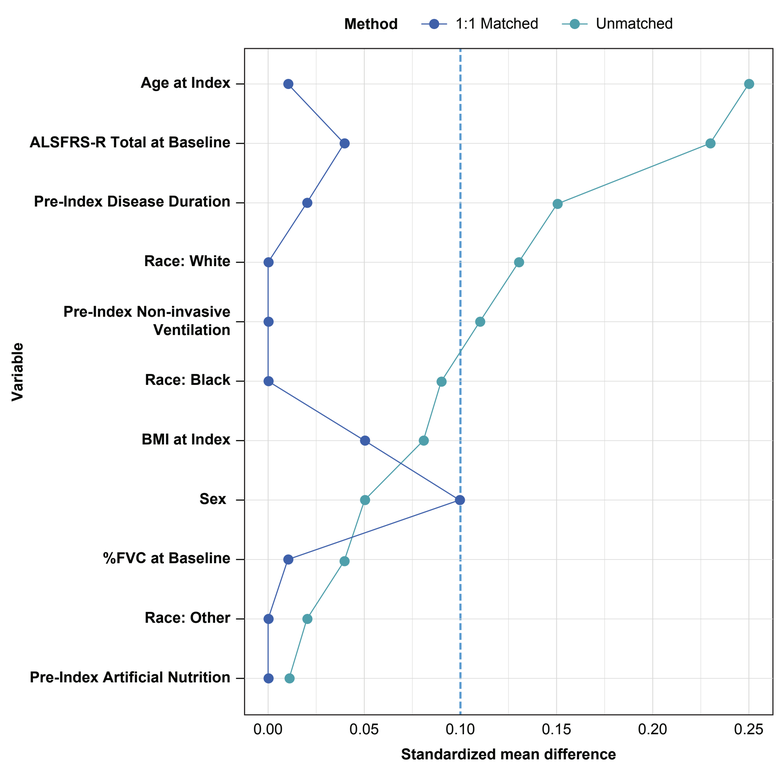
ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI, body mass index; FVC, forced vital capacity; SD, standard deviation.

Table 2. Demographic and clinical characteristics in matched PALS treated with Radicava® IV/ORS ± riluzole (treated) vs riluzole only

	Treated (n=176)	Riluzole Only (n=176)	SMD
Sex, n (%)			
Male	98 (55.7)	107 (60.8)	0.1
Female	78 (44.3)	69 (39.2)	
Age			
Mean (SD)	61.1 (9.83)	61.2 (8.10)	0.011
Median [Min, Max]	62.0 [23.0, 81.0]	61.0 [38.0, 78.0]	
Race, n (%)			
White	162 (92.0)	162 (92.0)	0
Black	7 (4.0)	7 (4.0)	0
Other	7 (4.0)	7 (4.0)	0
BMI			
Mean (SD)	27.4 (5.22)	27.6 (5.99)	0.045
Median [Min, Max]	26.9 [15.4, 44.3]	26.9 [18.2, 58.6]	
Pre-Index Non-invasive Ventilation, n (%)			
Yes	6 (3.4)	6 (3.4)	0
No	170 (96.6)	170 (96.6)	
Pre-Index Artificial Nutrition, n (%)			
Yes	5 (2.8)	5 (2.8)	0
No	171 (97.2)	171 (97.2)	
Pre-Index Disease Duration			
Mean (SD)	561 (682)	545 (621)	0.025
Median [Min, Max]	381 [21.0, 7130]	392 [96.0, 6660]	
ALSFRS-R Total Score at Baseline			
Mean (SD)	39.5 (4.77)	39.3 (4.79)	0.039
Median [Min, Max]	40.0 [30.0, 47.0]	41.0 [30.0, 47.0]	
%FVC at Baseline			
Mean (SD)	79.3 (23.5)	79.4 (21.4)	0.005
Median [Min, Max]	83.5 [14.0, 139]	82.0 [25.0, 133]	

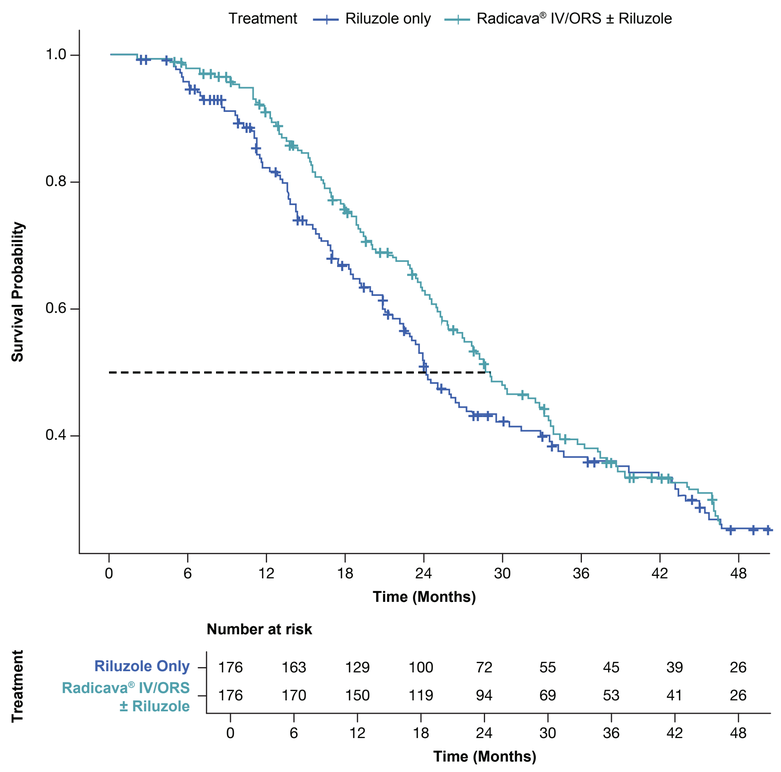
ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI, body mass index; FVC, forced vital capacity; SMD, standardized mean difference.

Figure 2. Standardized mean difference of variables for PALS treated with Radicava® IV/ORS ± riluzole vs riluzole only before and after matching



ALSFRS-R, amyotrophic lateral sclerosis Functional Rating Scale-Revised; BMI, body mass index; FVC, forced vital capacity.

Figure 3. Survival probability of PALS treated with Radicava® IV/ORS ± riluzole vs riluzole only



RMST Analyses

- After adjustment for baseline covariates, RMST analyses over 50 months suggested a statistically significant survival benefit for PALS receiving Radicava® IV/ORS ± riluzole (30.5 months; SD: 4.0; 95% CI: 22.6, 38.3) vs those receiving riluzole only (27.2 months; SD: 3.9; 95% CI: 19.4, 35.0), which is a difference between treatment groups of 3.2 months (*P*<0.03) (**Table 3**)

Table 3. Difference in RMST between PALS treated with Radicava® IV/ORS ± riluzole vs riluzole only over 50 months

Variable	Estimate	Standard Error	Lower Limit	Upper Limit	*P* value
Treatment	3.23	1.485	0.32	6.15	**0.0294**
Age at the Index Time	-0.46	0.098	-0.65	-0.27	**0.0000**
Sex	0.16	1.618	-3.02	3.33	0.9232
BMI at the Index Time	0.21	0.176	-0.14	0.55	0.2354
Race: White	-9.39	3.488	-16.23	-2.55	**0.0071**
Race: Black	-8.80	4.654	-17.92	0.32	0.0587
Pre-Index ALSFRS-R Score	1.35	0.184	0.99	1.71	**0.0000**
Pre-Index FVC%	-0.03	0.039	-0.10	0.05	0.4790
Pre-Index Disease Duration	9.08	0.579	7.95	10.22	**0.0000**
Pre-Index Non-invasive Ventilation	7.33	5.016	-2.50	17.16	0.1441
Pre-Index Artificial Nutrition	-11.02	4.072	-19.00	-3.04	**0.0068**

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI, body mass index; FVC, forced vital capacity; RMST, restricted mean survival time.

Limitations

- These results may be impacted by the limitations of real-world data, which may be subject to coding and/or entry errors
- This study was limited only to patients with ALS enrolled in the ALS/MND NHC database. Consequently, the results of this analysis may not be generalizable to patients with ALS without health insurance coverage
- The ALSFRS-R may be insensitive to changes during the initial stages of disease as well as during advanced disease, namely the floor effect[8]

Conclusions

- This ongoing real-world study of Radicava® IV/ORS-treated PALS in the ALS/MND NHC database suggests an additional survival benefit of 3.2 months with Radicava® IV/ORS ± riluzole compared to riluzole only treatment
- These data may be useful to inform choices made by clinicians, payers, and other ALS decision-makers

References

1. Goutman SA, et al. *Lancet Neurol.* 2022;21(5):465-479.
2. Rilutek® (riluzole). Prescribing Information. Cary, NC: Covis Pharmaceuticals, Inc; April 2016.
3. Radicava® (edaravone) IV and Radicava ORS® (edaravone) oral suspension. Prescribing information. Mitsubishi Tanabe Pharma Corporation; 2022.
4. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. *Lancet Neurol.* 2017;16(7):505-512.
5. Berger ML, et al. *Pharmacoepidemiol Drug Saf.* 2017;26:1033-1039.
6. Brooks BR, et al. *EClinicalMedicine* 2022;52:101590.
7. Austin PC. *Am J Epidemiol*. 2010;172(9):1092-1097.
8. Wicks P, et al. *Eur J Neurol*. 2009;16(3):353-359.

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