Poster #188

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Association of Edaravone Treatment With Slower Functional Decline in a Real-World Cohort of Patients With Amyotrophic Lateral Sclerosis With Elevated Neurofilament Light Chain

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Background

- Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by substantial heterogeneity in disease progression, making it challenging to detect treatment signals without a principled approach to patient stratification
- Riluzole and edaravone are United States (US) Food and Drug Administration (FDA)-approved treatments for all patients with ALS[1,2]
- Edaravone was initially FDA approved as an intravenous (IV) formulation (Radicava® IV) in May 2017, followed by approval of the oral suspension formulation (Radicava ORS®) in May 2022[2]
  - In a phase 3 trial, IV edaravone was shown to slow down the rate of physical functional decline by 33% (p=0.0013) in patients with ALS, as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R), compared with placebo at 24 weeks[3]
- Edaravone effectiveness in a biomarker-defined real-world ALS population remains incompletely understood
- Neurofilament light chain (NfL), a biomarker of active neuronal injury that correlates with ALS disease severity and progression rate, may identify patients with ALS most likely to benefit from neuroprotective therapy[4,5]

Objective

- Examine whether there is an association between edaravone treatment and ALSFRS-R score among patients with ALS who have ≥1 elevated NfL measurement vs edaravone-untreated patients

Methods/Implementation

- Data are from the ALS Therapy Development Institute (TDI) patient registry, a longitudinal real-world dataset
- Patients with ALS with ≥1 elevated NfL measurement (>10 pg/mL if <45 years; >15 pg/mL if ≥45 years) and ≥2 ALSFRS-R assessments were included; all data were merged at the patient level
- A linear mixed-effects model, adjusted for confounders, evaluated longitudinal ALSFRS-R trajectories between edaravone-treated and -untreated groups
  - Confounders accounted for included age (centered), sex, ethnicity, ALS disease duration, and baseline ALSFRS-R score
  - A random intercept per patient accounted for individual starting levels
- The primary parameter of interest was interaction between treatment status and time, with a positive estimate indicating treated patients had slower ALSFRS-R decline per month

Results

- A total of 48 patients in the ALS TDI registry had ≥1 elevated NfL measurement and met inclusion criteria for this analysis
- Of these, 39 patients had ≥2 ALSFRS-R scores and were included in the final cohort (n=16 edaravone treated, n=23 no edaravone exposure/edaravone untreated) (**Table 1**)
  - Groups were comparable on age and disease duration at baseline; difference in sex distribution was accounted for in the multivariable model

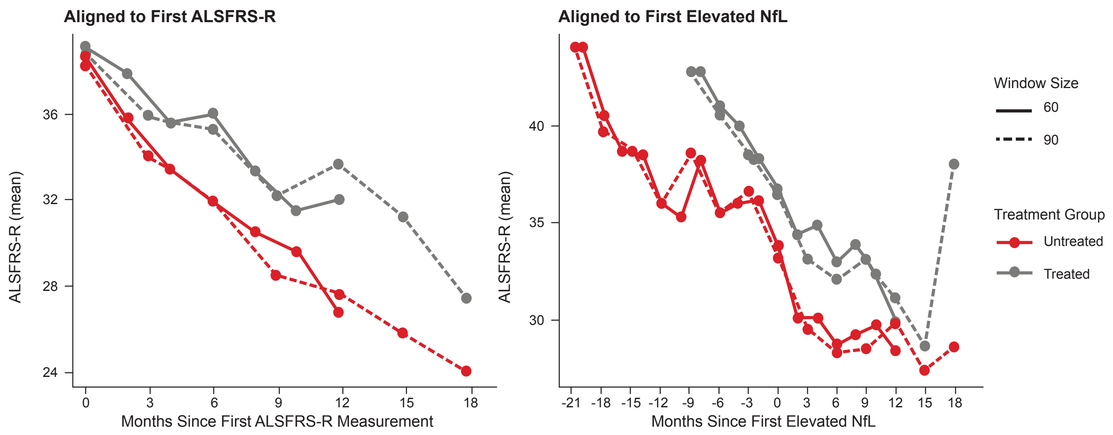
Table 1. Baseline Characteristics of the Elevated NfL Cohort by Treatment Group

Variable	Edaravone Treated (N=16)	Edaravone Untreated (N=23)
Sex, n (%)		
Female	12 (75%)	11 (48%)
Male	4 (25%)	12 (52%)
Ethnicity, n (%)		
Caucasian/White	15 (94%)	22 (96%)
Other	1 (6.3%)	1 (4.3%)
Age at baseline (years)		
Mean±SD	56±14	59±14
Median (Q1, Q3)	59 (43, 66)	63 (54, 70)
Min, Max	34, 76	26, 80
Disease duration (months)		
Mean±SD	22±15	22±23
Median (Q1, Q3)	18 (13, 31)	15 (10, 25)
Min, Max	6, 57	6, 109
Baseline ALSFRS-R score		
Mean±SD	40.8±4.7	39.4±6.9
Median (Q1, Q3)	41.5 (37.0, 45.0)	42.0 (37.0, 45.0)
Min, Max	33.0, 47.0	21.0, 47.0
Fast progressors[a]		
n (%)	5 (31%)	9 (39%)
Edaravone treatment duration (months)		
Mean±SD	10.3±6.2	—
Median (Q1, Q3)	9.8 (5.4, 11.9)	—
Min, Max	1.0, 23.9	—

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; NfL, neurofilament light chain; Q, quartile; SD, standard deviation.
[a]Fast progressors defined as ALSFRS-R decline >1 point/month in the 3 months prior to baseline.

- Mean ALSFRS-R score over time for patients treated and untreated with edaravone were summarized in 60- and 90-day windows, with trajectories anchored to each patient's first ALSFRS-R measurement (left) and to the date of the first elevated NfL reading (right) (**Figure 1**)
  - Edaravone-treated patients maintained higher average ALSFRS-R scores than edaravone-untreated patients across the follow-up period
  - The gap between groups widened progressively over time on both alignments

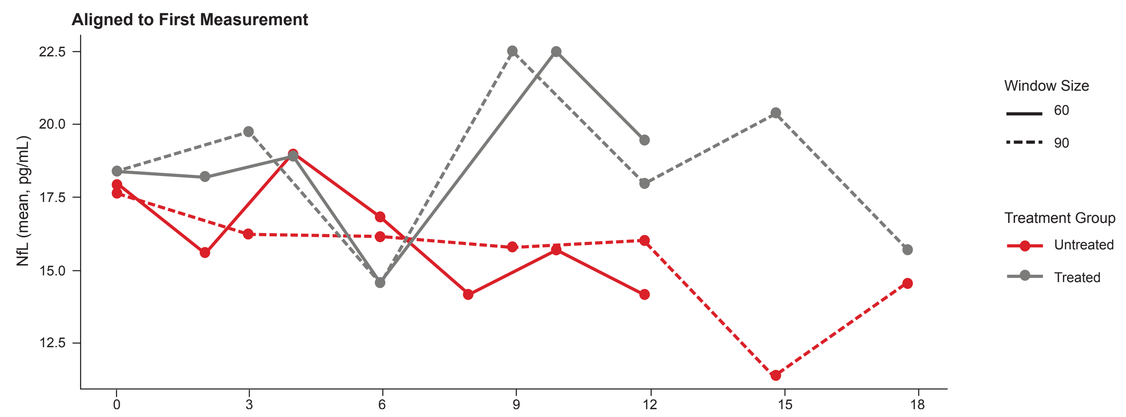
Figure 1. Mean ALSFRS-R Score Over Time by Treatment Group (60- and 90-Day Windows)[a]



ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; NfL, neurofilament light chain.
[a]For months 15-18, there were 6 patients for whom mean ALSFRS-R values were available.

- Mean NfL levels were examined over time in 60- and 90-day windows aligned to each patient's first NfL measurement, by treatment group, with both groups starting with similar NfL levels (**Figure 2**)
  - Both groups maintained elevated NfL throughout follow-up, suggesting that the functional difference, based on ALSFRS-R score, between groups was associated with edaravone treatment rather than differential disease burden

Figure 2. Mean NfL Levels Over Time by Treatment Group (60- and 90-Day Windows Aligned to Each Patient's First NfL Measurement)



NfL, neurofilament light chain.

- Across all patients, the linear mixed-effects model estimated an ALSFRS-R decline of 1.13 points/month (95% confidence interval [CI]: −1.29, −0.96; p<0.001) (**Table 2**)
- Results from this model suggest edaravone treatment was associated with a significantly slower rate of functional decline vs patients not treated with edaravone after adjusting for confounders, reflected by a positive treatment-by-time interaction (0.39 ALSFRS-R points/month; 95% CI: 0.13, 0.65; p=0.004) (**Table 2**)

Table 2. Linear Mixed-Effects Model Results

Model Term	Estimate (95% CI)	*p* value
Intercept (baseline ALSFRS-R)	40.39 (38.96, 41.81)	<0.001
Months from baseline	−1.13 (−1.29, −0.96)	<0.001
Edaravone: treated vs untreated	−0.21 (−1.76, 1.33)	0.784
Age (centered)	0.04 (−0.01, 0.08)	0.137
Sex: female vs male	−0.88 (−2.31, 0.55)	0.220
Ethnicity: other vs Caucasian/White	2.46 (−0.50, 5.41)	0.101
Disease duration (months)	0.01 (−0.02, 0.04)	0.563
Baseline ALSFRS-R (centered)	1.07 (0.96, 1.18)	<0.001
Time × Edaravone interaction[a]	0.39 (0.13, 0.65)	0.004

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; CI, confidence interval.
[a]A positive estimate indicates edaravone-treated patients have a slower ALSFRS-R decline per month.

- Model-derived estimates demonstrated higher mean ALSFRS-R scores at 12 months among edaravone-treated vs edaravone-untreated patients (37.42 vs 35.29), a between-group difference of 2.13 points (**Table 3**)

Table 3. Model-Estimated Mean ALSFRS-R Scores at 12 Months by Treatment Group and the Between-Group Difference

Group	Predicted ALSFRS-R at 12 Months (95% CI)	Difference (95% CI)
Edaravone treated	37.42 (35.40, 39.44)	2.13 (0.41, 3.85)
Edaravone untreated	35.29 (33.49, 37.08)	—

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; CI, confidence interval.

Conclusions

- In this real-world analysis of patients with ALS and elevated NfL, edaravone treatment was associated with significantly slower functional decline over 12 months compared with no edaravone treatment
  - The observed 35% reduction in monthly ALSFRS-R decline corresponded to an estimated 2.13 additional ALSFRS-R points preserved at 12 months
- Given the observational, nonrandomized design, small sample size, and treatment-date imputation for some patients, these findings should be confirmed in larger cohorts and with causal inference methods

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Disclosures

MC and **SA** are employees of Shionogi Inc.

JZ and **YL** are employees of Princeton Pharmatech, which has received consultancy fees from Shionogi.

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