Real-World Survival in Edaravone-Treated ALS

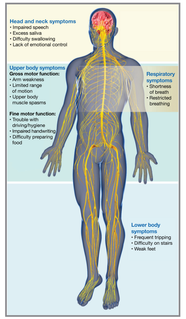
Benjamin Rix Brooks, MD[1]; James D. Berry, MD, MPH[2]; Malgorzata Ciepielewska, MS[3]; Jeffrey Zhang, PhD[4]; Ying Liu, PhD[4]; Gustavo Suarez Zambrano, MD[3]; Melissa Hagan, PhD, MPH[3]

[1]Atrium Health Neurosciences Institute, Carolinas Medical Center, University of North Carolina School of Medicine–Charlotte Campus, Charlotte, NC; [2]Massachusetts General Hospital, Boston, MA; [3]Mitsubishi Tanabe Pharma America, Inc., Jersey City, NJ; [4]Princeton Pharmatech, Princeton, NJ

BACKGROUND

- Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, characterized by motor neuron cell death and progressive paralysis (**Figure 1**)
- There is no cure, and most patients die within 3 to 5 years of symptom onset, usually of respiratory failure[1]
- Treatment consists primarily of symptom management and palliative care
- The US Food and Drug Administration (FDA) has approved riluzole and edaravone (intravenous [IV] and oral suspension) for the treatment of ALS
- IV and oral edaravone received FDA approval in May 2017 and May 2022, respectively
- In a phase 3 trial, IV edaravone was shown to slow the rate of functional decline by 33% (P = 0.0013) as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) compared with placebo treatment at 24 weeks[2]
- In short-term randomized trials of IV edaravone, no statistically significant survival effect was confirmed over the 6-month double-blind period of the clinical trials or during the follow-up 6-month open-label extension

Figure 1. ALS Symptoms



OBJECTIVE

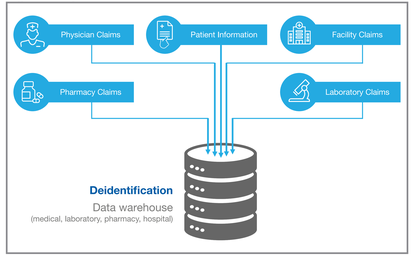
- To evaluate overall survival in patients with ALS receiving IV edaravone compared with patients with ALS not receiving IV edaravone

METHODS

Optum Clinformatics® Data Mart

- The Optum Clinformatics® Data Mart (CDM) is statistically deidentified under the expert determination method consistent with the Health Insurance Portability and Accountability Act of 1996, and is managed according to Optum customer data use agreements (**Figure 2**)[3]
- The database includes approximately 17 million to 19 million annual covered lives, for a total of more than 65 million unique lives over a 13-year period from January 2007 through December 2020. The population is geographically diverse, spanning all 50 states
- CDM administrative claims submitted for payment by providers and pharmacies are verified, adjudicated, and deidentified prior to inclusion. These data, including patient-level enrollment information, are derived from claims submitted for all medical and pharmacy healthcare services with information related to healthcare costs and resource utilization

Figure 2. Optum Clinformatics® Data Mart



Mortality status (all-cause)

- The Optum date of death table is sourced from the Death Master File (DMF) maintained by the Social Security Administration
- DMF data provide year and month of death, which were the basis for deriving mortality status

Key inclusion criteria

IV edaravone–treated cases

- Adults ≥18 years of age on the index IV edaravone date
- Diagnosis of ALS
  - Indicated by a diagnosis with the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code G12.21; International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 335.20 on at least 1 claim in any setting (outpatient or inpatient)
- Initiated IV edaravone between August 8, 2017, and March 31, 2020 (index date)
  - Indicated by at least 1 claim for IV edaravone using the Healthcare Common Procedure Coding System codes (J1301, J3490, C9493) or National Drug Code (70510-2171-xx)
- May or may not have received treatment with riluzole

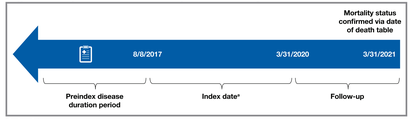
Non-IV edaravone–treated controls

- Adults ≥18 years of age on index date (date that IV edaravone was commercially available – August 8, 2017)
- Diagnosis of ALS
  - Indicated by a diagnosis with the ICD-10-CM code G12.21; ICD-9-CM: 335.20 on at least 1 claim in any setting (outpatient or inpatient)
- May or may not have received treatment with riluzole

Optum CDM retrospective study timeline

- Data were collected from patients with ALS before the index date (preindex disease duration period) and after the index date (follow-up; **Figure 3**)

Figure 3. Optum CDM Retrospective Study Timeline

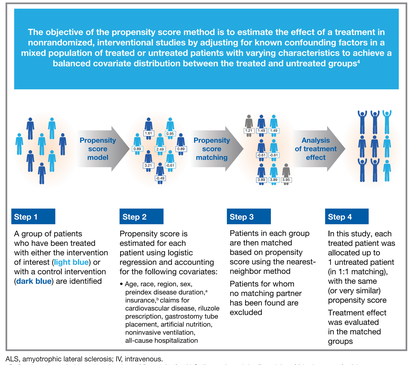


[a]**Index date:**
IV edaravone–treated cases – Date of the first claim of IV edaravone.
Non-IV edaravone–treated controls – Date that IV edaravone was commercially available (August 8, 2017).

Propensity score matching

- 1:1 propensity score matching was applied to find non-IV edaravone–treated controls for IV edaravone–treated patients based on the nearest-neighbor method (**Figure 4**)[4]

Figure 4. Propensity Score Matching



ALS, amyotrophic lateral sclerosis; IV, intravenous.
[a]Defined as the period between the date of first claim for ALS diagnosis and the first claim of IV edaravone for IV edaravone–treated patients or the date IV edaravone was available on the market (August 8, 2017) for patients with no IV edaravone treatment.
[b]Medicare Advantage vs commercial.

Univariate analysis

- Chi-square analysis was used to compare categorical demographic and clinical characteristics between the 2 groups
- The Wilcoxon rank-sum test was applied for comparing continuous variables

Survival analysis

- Kaplan–Meier survival curve visualized the difference in survival between the treated and matched controls, using the log-rank test to detect significant differences
- Shared frailty Cox regression hazard ratio (HR) analysis was performed to estimate the benefit of IV edaravone by accounting for unobserved heterogeneity between the matched groups[5]
  - Mortality status was confirmed as of March 31, 2021

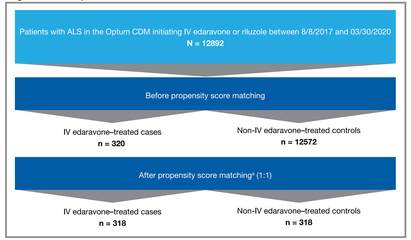
Sensitivity analysis[6]

- Examined the potential impact of unmeasured confounding on the result
- Examined the assumption of noninformative censoring

RESULTS

- The study population included 318 patients with ALS with at least 1 claim of IV edaravone and 318 non-IV edaravone–treated controls (**Figure 5**)

Figure 5. Disposition of Patients with ALS



ALS, amyotrophic lateral sclerosis; CDM, Clinformatics® Data Mart; IV, intravenous.
[a]Matching on age, race, region, gender, preindex disease duration, insurance, preindex claims for cardiovascular disease and riluzole prescriptions, gastrostomy tube placement, artificial nutrition, noninvasive ventilation, all-cause hospitalization.

- Covariates were balanced in the IV edaravone–treated cases and matched controls. Standardized mean difference values for all variables were below 0.1 (**Table 1**)

Table 1. Demographic and Clinical Characteristics (After Matching)

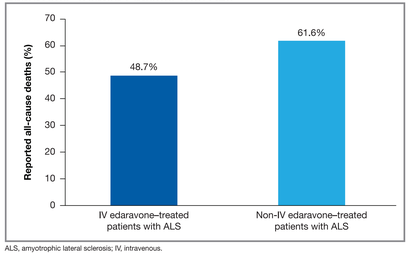
Demographic and clinical characteristics	IV edaravone case	Non-IV edaravone matched control	SMD
N (%)	318	318	
Age, mean (SD)	62.9 (10.1)	62.7 (10.2)	0.0194
Sex, n (%)			
Female	134 (42.1)	134 (42.1)	<0.001
Male	184 (57.9)	184 (57.9)	
Medicare Advantage, n (%)	189 (59.4)	189 (59.4)	<0.001
Race, n (%)			
White	226 (71.1)	236 (74.2)	0.0314
Black	28 (8.8)	18 (5.7)	0.0314
Other	35 (11.0)	33 (10.4)	0.0063
Unknown	29 (9.1)	31 (9.7)	0.0063
Region, n (%)			
Midwest	64 (20.1)	86 (27.0)	0.0692
Northeast	51 (16.0)	59 (18.6)	0.0252
South	131 (41.2)	101 (31.8)	0.0943
West	72 (22.6)	71 (22.3)	0.0031
Unknown	0 (0.0)	1 (0.3)	0.0031
Preindex disease duration (days), mean (standard deviation)	211.8 (187.6)	203.7 (285.5)	0.0282
Riluzole, n (%)	208 (65.4)	208 (65.4)	<0.001
Preindex cardiovascular disease, n (%)	29 (9.1)	29 (9.1)	<0.001
Preindex gastrostomy tube, n (%)	24 (7.5)	24 (7.5)	<0.001
Preindex artificial nutrition, n (%)	43 (13.5)	38 (11.9)	0.0157
Preindex noninvasive ventilation	48 (15.1)	54 (17.0)	0.0189
Preindex hospitalization, n (%)	73 (23.0)	73 (23.0)	<0.001

IV, intravenous; SD, standard deviation; SMD, standardized mean difference.

Survival of IV edaravone–treated vs non-IV edaravone–treated patients with ALS

- As of March 31, 2021, there were 155 reported all-cause deaths (48.7%) among the IV edaravone–treated patients vs 196 (61.6%) among the matched controls (**Figure 6**)

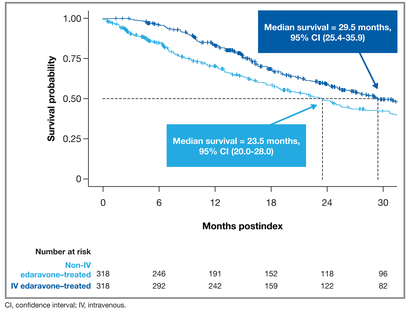
Figure 6. All-Cause Deaths of IV Edaravone–Treated vs Non-IV Edaravone–Treated Patients With ALS



ALS, amyotrophic lateral sclerosis; IV, intravenous.

- Initiation of IV edaravone resulted in a 6-month longer median survival compared with the non-IV edaravone–treated controls (**Figure 7**)
- The risk for death was 27% lower among IV edaravone–treated cases compared with non-IV edaravone–treated controls (HR, 0.73; 95% CI, 0.59-0.91; P = 0.005)
- To examine the effect of uncontrolled confounding using nonrandomized data, a sensitivity analysis using inverse probability weighting (IPW)[6] was performed. The IPW sensitivity analysis confirmed the statistically significant effect of IV edaravone on survival (HR, 0.65; 95% CI, 0.53-0.79; P <0.0001)

Figure 7. Kaplan–Meier Curve of IV Edaravone–Treated Cases vs Non-IV Edaravone–Treated Controls



CI, confidence interval; IV, intravenous.

LIMITATIONS

- This study was limited to patients with ALS who had commercial health coverage
- This study relied on administrative claims data, which are subject to coding limitations and entry error
- The possibility of underdiagnosis of ALS may have led to a selection bias and/or smaller sample sizes, as patients with ALS who were untreated or who did not have a relevant diagnosis recorded on their medical claims, or were no longer enrolled in the Optum CDM database during the postindex period, were excluded from the analysis
- Although differences between cohorts were controlled for by propensity score matching, adjustment was limited to those characteristics that were captured in an administrative database

CONCLUSIONS

- This analysis demonstrated that patients with ALS prescribed IV edaravone demonstrated increased survival compared with those patients with ALS not prescribed IV edaravone in a real-world setting
- Combined with the phase 3 pivotal trial demonstrating that IV edaravone was shown to slow the rate of functional decline by 33% (P = 0.0013) compared with placebo as measured by the ALSFRS-R at 24 weeks,[2] these results suggest that IV edaravone may have both functional and real-world survival benefits in patients with ALS
- Real-world data are not intended to replace the prospective clinical trial, but in studies of rare diseases, which are more difficult to evaluate in a clinical trial setting, real-world data studies have the potential to expand our understanding of the clinical effects of edaravone treatment in larger numbers of patients with ALS treated after regulatory approval
- This information may be useful to payers and healthcare providers in optimizing the utilization of IV edaravone

REFERENCES

1. Mehta P, et al. *MMWR Morb Mortal Wkly Rep*. 2018;67(46):1285-1289.
2. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. *Lancet Neurol*. 2017;16(7):505-512.
3. Guidance Regarding Methods for De-identification of Protected Health Information in Accordance With the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Dated September 4, 2012, as first released on November 26, 2012. Accessed February 28, 2022. 45 CFR 164.514(b)(1). https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html
4. Austin PC. *Am J Epidemiol*. 2010;172(9):1092-1097.
5. Balan TA, Putter H. *Stat Med*. 2019;38(18):3405-3420.
6. Shen C, et al. *Biom J*. 2011;53(5):822-837.

DISCLOSURES

B.R. Brooks and **J.D. Berry** are consultants for Mitsubishi Tanabe Pharma America, Inc.; **M. Ciepielewska** and **G. Suarez Zambrano** are employees of Mitsubishi Tanabe Pharma America, Inc.; **Y. Liu** and **J. Zhang** are employees of Princeton Pharmatech, which has received consultancy fees from Mitsubishi Tanabe Pharma America, Inc.; **M. Hagan** is a former employee of Mitsubishi Tanabe Pharma America, Inc.

This study was sponsored by Mitsubishi Tanabe Pharma America, Inc.

ACKNOWLEDGMENTS

p-value communications provided editorial support.

Scan here to view a PDF of this poster. Copies obtained through Quick Response (QR) code are for personal use only and may not be reproduced without written permission from the authors.

MA-RC-US-0340