Assessment of Use and Safety of Edaravone for Amyotrophic Lateral Sclerosis in the Veterans Affairs Health Care System

Michelle Vu, PharmD, MPH; Kathryn Tortorice, PharmD, BCPP; Jennifer Zacher, PharmD, BCPP; Diane Dong, RN, MS, MPH; Kwan Hur, PhD; Rongping Zhang, MS; Chester B. Good, MD, MPH; Peter A. Glassman, MBBS, MSc; Francesca E. Cunningham, PharmD

Abstract

Importance Using real-world data, the US Department of Veterans Affairs (VA) initiated a surveillance evaluation of edaravone after its approval for amyotrophic lateral sclerosis (ALS) in 2017. The use and safety of edaravone for patients with ALS in the VA health care system remain to be assessed.

Objective To describe a pharmacovigilance surveillance initiative with edaravone to monitor patient characteristics, utilization (edaravone cycles and riluzole use), and safety and to evaluate safety/effectiveness.

Design, Setting, and Participants This propensity score–matched cohort study used data on 369 patients with documented definite or probable ALS in the Veterans Health Administration (VHA) with at least 1 prescription for edaravone between August 1, 2017, and September 30, 2019. The analysis compared edaravone (alone or with riluzole) with riluzole only. For chronic users (≥6 months of drug), a time-to-event model evaluated ALS-related outcomes, with censoring at outcome, death, or end of evaluation. Patients with Parkinson disease, dementia, schizophrenia, or significant respiratory insufficiency per diagnosis codes within 2 years before prescription initiation were excluded. In overall matched cohorts, 223 patients treated with edaravone were 1:3 propensity score matched based on predefined confounders. For the chronic user subgroup analysis, 96 patients receiving edaravone and 424 patients receiving riluzole only were included.

Exposures Edaravone (alone or with riluzole) vs riluzole only.

Main Outcomes and Measures Patient characteristics, ALS drug use, and mortality. Acute outcomes (within 6 months of index) included proportion and mean time to event for death, discontinuation, or all-cause hospitalization, and outcomes for chronic users (receiving >6 months of treatment) included hazard ratios of outcomes related to disease-state progression.

Results Of 369 patients who received edaravone, most were older (mean [SD] age, 64.6 [11.3] years), male (346 [93.8%]), and White (261 [70.7%]). As of September 2019, 59.9% of edaravone patients had discontinued treatment; of those, 49.5% (108 of 218) received only 1 to 3 treatment cycles. Approximately 30% (110 patients) died. In a matched evaluation, significantly more acute all-cause hospitalization events occurred with edaravone (35.4% vs 22.0% for riluzole only); 72.6% of the edaravone cohort received edaravone with riluzole. Among chronic users, edaravone patients (70.8% edaravone with riluzole) had an increased hazard ratio of ALS-associated hospitalization (2.51; 95% CI, 1.18-8.16). The death rate was lower with edaravone but the difference was not statistically significant.

(continued)

Key Points

Question What is the real-world experience with edaravone in patients with amyotrophic lateral sclerosis (ALS) within a national integrated health care system?

Findings In this cohort study of data from 369 US veterans with documented or probable ALS, a significantly greater proportion of acute all-cause hospitalizations was associated with edaravone treatment and, among users receiving at least 6 months of treatment, an increased likelihood of ALS-related hospitalization was associated with edaravone treatment compared with riluzole-only treatment.

Meaning While these findings should be interpreted with caution, in this evaluation, edaravone (mostly used with riluzole) was associated with more hospitalizations compared with riluzole-only therapy; more evidence is needed to evaluate edaravone treatment outcomes in real-world settings.

Downloaded From: https://jamanetwork.com/ by a Non-Human Traffic (NHT) User on 09/15/2021
CONCLUSIONS AND RELEVANCE  Early edaravone discontinuation was common in the VA. Although outcomes favored use of riluzole only in the matched analysis, results should be interpreted with caution, as unmeasured bias in observational data is likely.
self-feed, providing access to treatment for a much broader ALS population compared with clinical trial criteria or non-VA health plans. Selected exclusion criteria include significant respiratory insufficiency or difficulty as measured by ALS-FRS-R subscores and comorbidities that complicate assessment of ALS (eg, Parkinson disease, dementia, and schizophrenia). The ALS-FRS-R is an assessment scale for functional impairment, with cumulative scores from 12 items ranging from 0 indicating worst to 48 indicating best, and was used in edaravone clinical trials.

For prior authorization drug review, an ALS-FRS-R score (that reflects function at the time of the request) and other documentation are submitted via an interfacility consultation to a central data set, where information is reviewed and, when indicated, approved centrally by a pharmacy team. While the CFU includes discontinuation criteria and recommendations for monitoring respiratory function and assessing ALS-FRS-R score every 6 months, decisions to continue therapy and follow-up are deferred to local facilities and professionals.

VAMedSAFE Surveillance Initiative

VAMedSAFE conducts biannual descriptive assessments of edaravone use and safety events among the cohort of patients who have received 1 or more prescriptions of edaravone within the VHA. The current cohort assessment includes data from August 1, 2017, to September 30, 2019 (n = 369). Per the CFU, all eligible patients must have documented definite or probable ALS, according to El Escorial-revised Airlie House criteria. Clinical data were collected until edaravone discontinuation or death, but all patients were assessed as part of the overall cohort.

Data Sources

Prescription data on edaravone and riluzole were obtained from VA PBM databases and Corporate Data Warehouse. Diagnostic, procedure, and demographic data were retrieved from the National Patient Care Database and Corporate Data Warehouse. Date of death was identified from the Vital Status file. The ALS-FRS-R score at the time of consultation was collected from the national prior authorization drug review database, where available. Edaravone adverse drug reactions (ADRs) reported by clinicians were obtained from the VA Adverse Drug Event Reporting System (VA-ADERS) database.

Patient Baseline Characteristics

Patient demographic characteristics included age, sex, race/ethnicity, and marital status (Table 1). Comorbidities per CFU exclusion criteria (eg, Parkinson disease, dementia, and schizophrenia) were identified using International Classification of Diseases, Ninth Revision (ICD-9) or International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes from

| Table 1. Baseline Characteristics of 369 Patients With at Least 1 Edaravone Prescription |
|--------------------------------------------|---------------------------------------------|
| Characteristic | Edaravone users, No. (%) |
| Age at initiation, mean (SD), y | 64.6 (11.3) |
| Male sex | 346 (93.8) |
| White race | 261 (70.7) |
| Married | 275 (74.5) |
| Exclusion comorbidity | 23 (6.2) |
| VA priority rating, service connection | |
| 50%-100% | 356 (96.5) |
| <50% | 3 (0.8) |
| VA copay | |
| No copay | 356 (96.5) |
| Prescription copay only | 7 (1.9) |
| Enrollment after fiscal year 2017 | 123 (33.3) |
| ALS-FRS-R score on consultation, median (IQR) | 36 (31-41) |

Abbreviations: ALS-FRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; IQR, interquartile range; VA, US Department of Veterans Affairs.

* Race, marital status missing for 7 patients, demographic information updated as of November 2019.

* Presence of diagnosis code for Parkinson disease, dementia, and/or schizophrenia.

* ALS-FRS-R includes 12 questions, each of which is rated on a 5-point scale, with 0 indicating inability to perform and 4 indicating normal ability, for a cumulative reported score ranging from 0 indicating worst to 48 indicating best. Missing prior authorization drug review consultation score for 12 patients.
inpatient or outpatient data. Veteran priority status and prescription benefits were assessed and included to confirm patient access to VA health care. Enrollment was assessed for fiscal year 2017 (October 1, 2016–September 30, 2017; first fiscal year of edaravone availability in the VHA) or later. The ALS-FRS-R score on the consultation was summarized.

**Descriptive Measures**

Descriptors included drug use and safety or mortality. Measures included treatment cycles, discontinuation rates, and riluzole use. CFU criteria require that edaravone be administered in accordance with the package insert. For maintenance treatment, edaravone is administered as an intravenous (IV) infusion daily for 10 of 14 days, followed by a 14-day drug-free period (28-day cycle). Given that some cycles were administered by community care professionals and likely not captured in VA data, cycles were estimated using the days from the first to last edaravone prescription fill, divided by 28. Discontinuation was assumed if no further treatment cycles were recorded within 60 days of the last dose and before the end of the evaluation period. Patients receiving edaravone included those with riluzole use (edaravone with riluzole), defined as receiving 1 or more riluzole prescription fills after initiation of and before discontinuation of edaravone treatment, and those without riluzole use (edaravone alone). Riluzole use prior to edaravone initiation was also categorized.

Measures of mortality and voluntarily reported edaravone ADRs were described. Proportion of deaths and time from edaravone initiation until death were summarized for the cohort of edaravone ever-users. Edaravone-related ADRs reported to VA-ADERS during the surveillance period were described by severity, ADR type, and frequency.

**Comprehensive Safety and Effectiveness Evaluation**

VAMedSAFE conducted a retrospective, propensity score–matched cohort evaluation comparing the safety and effectiveness of edaravone use (alone or with riluzole) with riluzole only. Data sources and variables were the same as described in Surveillance Methods, adding inpatient hospitalizations and ALS-FRS-R scores from the Corporate Data Warehouse that were manually entered into the electronic health record prespecified fields (ie, data in free text were not captured). The cohorts consisted of veteran patients with a diagnosis of ALS and 1 or more prescription fills of edaravone or riluzole between August 1, 2017, and December 31, 2018 (eFigure in the Supplement). Exclusion criteria reflect CFU exclusion and discontinuation criteria and included those with diagnosis codes for excluded comorbidities, dyspnea, or orthopnea, or procedure codes for bilevel positive airway pressure, mechanical ventilation, or tracheostomy within 2 years before prescription initiation.

Edaravone and riluzole-only users were matched 1:3, using a caliper width of 0.2 of the logit of the propensity score. The propensity score was developed using predefined baseline confounders of receipt of edaravone and ALS progression (age ≥65 years, sex, race/ethnicity, marital status, priority group, VA copay, and duration of ALS). Duration of ALS was categorized as less than or equal to 2 years, more than 2 years, or unknown, based on the first date of a documented ALS diagnosis code to date of edaravone initiation. If the first ALS diagnosis code occurred after edaravone initiation, the duration of ALS was categorized as unknown. Balance after matching was assessed by a standardized mean difference of less than 0.1.

The index date was the first prescription fill of edaravone or riluzole within the period August 1, 2017, to December 31, 2018. Acute outcomes, defined as events occurring within the 6-month follow-up period after the index date, were assessed for the overall matched cohorts. These included proportions of deaths, discontinuations (no treatment cycle received/prescription possession of riluzole within 60 days after the last dose and before the end of follow-up), or all-cause hospitalizations. Mean time to event and change in ALS-FRS-R score from baseline (closest score to the index date) to end of follow-up (closest score to the 6-month follow-up date) were also assessed.
Statistical Analysis
An analysis was conducted for chronic users of each cohort, defined as those receiving at least 6 months of treatment. As in the overall analysis, death was included. Additional outcomes were evaluated to assess ALS progression. These included hospitalization associated with ALS, dyspnea, or orthopnea (per diagnosis codes) and surrogate markers of functional decline (procedure codes for tracheostomy, mechanical ventilation, and percutaneous endoscopic gastrostomy [PEG] tube placement), reflecting CFU discontinuation criteria. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% CIs for chronic outcomes. Veteran patients were followed from the index date to the date of the first outcome, prescription discontinuation, death, or the end of evaluation, whichever came first. Additionally, frequency of events, mean time to event, and events per 100 person-years of follow-up were summarized. Analysis was conducted using SAS version 9.2 (SAS Institute Inc).

Results

Patient Baseline Characteristics
As of September 2019, 369 veteran patients had received edaravone through the VHA. At baseline, the mean (SD) age was 64.6 (11.3) years and 346 were male (93.8%), 261 White (70.7%), and 356 fully covered for prescription drugs (96.5%) (Table 1). Approximately one-third were enrolled in VA care after fiscal year 2017; these patients received their first dose of edaravone a mean (SD) of 197 (182.6) days after the date of enrollment. The median ALS-FRS-R score documented prior to edaravone initiation was 36 (interquartile range [IQR], 31-41).

Descriptive Measures
The estimated number of edaravone cycles per patient showed substantial variation (mean [SD] number of cycles, 8.7 [7.4]). Of patients who received at least 1 cycle, 40.1% (151 of 369) continued to receive edaravone until September 2019 (Table 2). The median number of edaravone cycles for patients who discontinued treatment was 4 (IQR, 1-9) (eg, 49.5% [108 of 218] received 1 to 3 treatment cycles). The ALS-FRS-R score on consultation was similar between those who continued (median, 35; IQR, 31-40) and discontinued treatment (median, 37; IQR, 32-41.5). Many patients (71.3% [263 of 369]) received edaravone with riluzole (eTable 1 in the Supplement). For patients with riluzole use prior to edaravone (255 of 369), many (92.5% [236 of 255]) continued use after initiating edaravone treatment (eTable 2 in the Supplement).

Of the 369 patients, 110 died (29.8%); a mean (SD) of 260.3 (170.5) days elapsed from their first edaravone prescription to the date of death. Twelve ADRs were reported to VA-ADERS: 3 mild, 5 moderate, and 4 severe. For mild or moderate ADRs, types of ADRs included IV port thrombosis,
product bag leakage, dyspnea or chest discomfort, anemia, chills or tremor, and rash. Among severe edaravone ADRs reported (eg, ADRs associated with hospitalization, urgent intervention, and/or risk of organ damage), there was 1 death, associated with progression of liver disease in a patient with liver disease prior to edaravone initiation. The other 3 severe ADR reports described dyspnea or leg edema, pneumonia and pulmonary embolism, and pneumonia or respiratory depression.

**Comprehensive Safety and Effectiveness Evaluation**

For the propensity score–matched analysis, 223 patients receiving edaravone (72.6% edaravone with riluzole, 27.4% edaravone alone) (eTable 1 in the Supplement) were matched to 669 patients receiving riluzole-only treatment (eFigure in the Supplement). Propensity score–matching diagnostics showed balance between edaravone and riluzole-only groups (eTable 3 in the Supplement). The overall matched groups were mostly diagnosed with ALS in the past 2 years (68.6% edaravone; 68.5% riluzole) (Table 3). The ALS-FRS-R scores were not well populated in VA databases; where available, baseline scores were similar. Chronic users consisted of 43% of patients receiving edaravone (n = 96) and 63% of patients receiving riluzole-only treatment (n = 424), and their baseline characteristics were similar. Of edaravone chronic users, 70.8% received edaravone with riluzole (eTable 1 in the Supplement).

Acute outcomes were summarized for the overall matched cohorts (Table 4). Death rates were similar between cohorts. There was a significantly greater proportion of acute all-cause hospitalization events in the edaravone cohort (35.4% edaravone; 22.0% riluzole-only; Bonferroni-corrected \( P < .001 \)). Moreover, time to hospitalization was shorter within the edaravone cohort (mean [SD], 44.5 [47.7] days for edaravone; 68.2 [53.2] days for riluzole-only treatment; \( P = .001 \)).

Time to treatment discontinuation was significantly shorter for edaravone (mean [SD], 93.8 [81.7] days for edaravone; 161.8 [113.7] days for riluzole only; \( P < .001 \)). Decrease from baseline ALS-FRS-R score was greater in the riluzole-only cohort (median, −8; IQR, −14 to −4 for riluzole-only vs −2; IQR, −6 to −1 for edaravone).

Among chronic users, the riluzole-only subcohort (n = 424) had longer time to follow-up (thus drug exposure) compared with edaravone (n = 96) (mean [SD], 403.9 [113.6] days for riluzole-only; Table 3. Comprehensive Safety and Effectiveness Evaluation: Select Baseline Characteristics for Matched Patients

| Variable                  | Overall matched cohorts* | Riluzole only (n = 669) | Riluzole only (n = 424) |
|---------------------------|--------------------------|-------------------------|-------------------------|
| Age ≥65 y                 | 130 (58.3)               | 389 (58.2)              | 54 (56.3)               | 229 (54.0)               |
| Male                      | 216 (96.9)               | 649 (97.0)              | 95 (99.0)               | 410 (96.7)               |
| White race                | 164 (73.5)               | 489 (73.1)              | 81 (84.4)               | 322 (75.9)               |
| Duration of ALS, y^c       |                          |                         |                         |
| ≤2                        | 153 (68.6)               | 458 (68.5)              | 66 (68.8)               | 296 (69.8)               |
| >2                        | 20 (9.0)                 | 62 (9.3)                | 12 (12.5)               | 45 (10.6)                |
| Unknown                   | 50 (22.4)                | 149 (22.3)              | 18 (18.8)               | 83 (19.6)                |
| ALS-FRS-R score, median (IQR)^d | 38 (37-42)              | 35 (30-39)              | 39.5 (30-42)            | 35 (31-38)              |

Abbreviations: ALS, amyotrophic lateral sclerosis; ALS-FRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; IQR, interquartile range; VA, US Department of Veterans Affairs.

* Propensity score matched on age 65 years or older, sex, race, marital status, priority group, VA copay, and duration of ALS.

b Receiving at least 6 months of treatment.

c Based on the first date an ALS diagnosis code was listed in an encounter to the date of edaravone initiation. If the first ALS diagnosis code occurred after edaravone initiation, the duration of ALS was categorized as unknown.

d Available for 215 edaravone (from consultation) and 26 riluzole patients (from VA Corporate Data Warehouse) for overall and 95 edaravone (from consultation) and 17 patients who received riluzole (from VA Corporate Data Warehouse) for chronic users.
305.1 (77.8) days for edaravone). The discontinuation rate was also higher with riluzole-only treatment vs edaravone (19.3% vs 11.5%). Hazard ratios of hospitalization associated with ALS progression (HR, 2.51; 95% CI, 1.18-8.16) and PEG tube placement (HR, 3.04; 95% CI, 1.25-10.66) were higher with edaravone compared with riluzole-only treatment (Table 5). There were few (<10%) incident mechanical ventilation and tracheostomy events. Decreases in ALS-FRS-R score from baseline (available for 4 edaravone; and 17 patients who received riluzole only) were greater within the riluzole-only subcohort (median, −8; IQR, −14 to −6 for riluzole-only; −3.5; IQR, −8 to 0.5 for edaravone). In addition, there was no statistically significant difference between subgroups, although death rates (per 100 patient-years) were lower for edaravone (29.3 riluzole-only; 18.0 edaravone; HR, 0.77; 95% CI, 0.43-1.18).

Discussion

To our knowledge, this evaluation is the largest pharmacovigilance initiative of edaravone users in a US health care system, providing a real-world analysis of patient characteristics, use, safety, and effectiveness of edaravone use within the VHA. As of September 2019, 369 veteran patients, with relatively high ALS-FRS-R scores at initiation, had received edaravone. The VA provides an important point of access to this treatment option, given that most edaravone users had no prescription copay (97%) and 33% enrolled in VA care in fiscal year 2017 or later. In this descriptive monitoring of use, edaravone discontinuation was common (approximately 60%). Additionally, in those who discontinued, a clinically significant proportion (49.5%) received only 1 to 3 infusions.

Table 4. Comprehensive Safety and Effectiveness Evaluation: Acute Outcomes (Within 6 Months of Drug Initiation) for Matched Cohorts

| Variable                        | No. (%)                  | P value<sup>a</sup> |
|--------------------------------|--------------------------|---------------------|
|                                | Edaravone (n = 223)     | Riluzole-only (n = 669) |                  |
| Events overall                 | 122 (54.7)               | 340 (50.8)          | .35               |
| Death                          | 25 (11.2)                | 101 (15.1)          | .18               |
| Discontinuation<sup>b</sup>    | 64 (28.7)                | 227 (33.9)          | .16               |
| Hospitalization (all-cause)    | 79 (35.4)                | 147 (22.0)          | <.001<sup>c</sup> |
| Time to event, mean (SD), d    |                          |                     |                   |
| Death                          | 76.3 (48.0)              | 99.1 (54.0)         | .06               |
| Discontinuation<sup>b</sup>    | 93.8 (81.7)              | 161.8 (113.7)       | <.001<sup>c</sup> |
| Hospitalization (all-cause)    | 44.5 (47.7)              | 68.2 (53.2)         | .001<sup>c</sup> |
| Change in ALS-FRS-R score, median (IQR)<sup>d</sup> | −2 (−6 to −1) | −8 (−14 to −4) | |

Abbreviations: ALS, amyotrophic lateral sclerosis; ALS-FRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; IQR, interquartile range.

<sup>a</sup> Bonferroni-corrected significance is at P = .017.

<sup>b</sup> Defined as no treatment cycles were received within 60 days before the end of follow-up (June 30, 2019).

<sup>c</sup> Bonferroni corrected.

<sup>d</sup> Available for 9 edaravone and 26 riluzole patients.

Table 5. Outcomes of Chronic User Subcohorts<sup>a</sup>

| Outcome                                | Cohort (No.) | Events, No. (%) | Time to event, mean (SD), d | Follow-up, person-years | Events per 100 person-years | HR (95% CI)<sup>b</sup> |
|----------------------------------------|--------------|-----------------|-----------------------------|-------------------------|-----------------------------|-------------------------|
| Death                                  | Edaravone (96) | 22 (22.9)       | 340.4 (80.8)                | 122.3                   | 18.0                        | 0.77 (0.43-1.18)         |
| Hospitalization (ALS, dyspnea, or orthopnea) | Riluzole-only (424) | 18 (18.8)       | 254.4 (174.7)               | 111.5                   | 16.1                        | 2.51 (1.18-8.16)         |
| Tracheostomy                           | Edaravone (96) | 4 (4.2)         | 395.8 (99.4)                | 120.8                   | 3.3                         | 1.22 (0.29-1.63)         |
| Mechanical ventilation                 | Edaravone (96) | 9 (9.4)         | 320.1 (167.2)               | 118.1                   | 7.6                         | 2.63 (0.90-6.45)         |
| PEG tube placement                     | Edaravone (96) | 14 (14.6)       | 255.9 (167.0)               | 112.8                   | 12.4                        | 3.04 (1.25-10.66)        |

Abbreviations: ALS, amyotrophic lateral sclerosis; HR, hazard ratio; PEG, percutaneous endoscopic gastrostomy.

<sup>a</sup> Receiving at least 6 months of treatment.

<sup>b</sup> Comparing hazard ratios of the edaravone group to riluzole-only subgroups and Bonferroni-corrected confidence intervals.
When comparing use of edaravone (alone or with riluzole) with riluzole-only use, we found that significantly greater acute all-cause hospitalization events were associated with edaravone compared with riluzole-only use. Among chronic users, edaravone was similarly associated with increased hazard ratios of ALS-associated hospitalization. Notably, although times to PEG placement, tracheostomy, and mechanical ventilation were longer for edaravone chronic users compared with riluzole-only, edaravone was significantly associated with increased hazard ratios for PEG placement and not significantly associated with tracheostomy and mechanical ventilation benefits. Death was less common among edaravone chronic users (18.0 per 100 patient-years; 29.3 per 100 patient-years riluzole-only treatment); however, this finding was not statistically significant (HR, 0.77; 95% CI, 0.43-1.18). Overall, the comprehensive evaluation findings may suggest mixed results with disease-progression and safety events as well as increased hazard ratios of ALS-associated hospitalization with edaravone use relative to riluzole-only use.

Strengths and Limitations
The strengths of this comprehensive surveillance initiative are its large size and its comparative evaluation. Our measures for use, safety, and effectiveness are consistent with those reported from other health systems.10-12,20 Additionally, database methods allowed for timely national surveillance compared with retrospective medical record review.10 In the propensity-matched cohort evaluation, the edaravone cohort included many patients who used edaravone with riluzole (72.6%), which reflects the real-world dual use of these treatments. Notably, the edaravone clinical trial allowed patients to continue receiving riluzole, and its use was common (91%).18

These results supplement the only other published US evaluation of edaravone use and safety by Jackson et al.20 By 1 year after approval, 3007 patients received edaravone, with 1006 discontinuing use. The authors surveyed 75 physician prescribers of edaravone, and based on 40 respondents, 67% of edaravone patients used riluzole concurrently and 43% opted for home-infusion treatment. Additionally, from the manufacturer’s safety database, 817 ADRs were reported. There were 272 severe ADRs, including death (104 of 272), dyspnea (19 of 272), and pneumonia (17 of 272).20 Overall, these postmarketing ADRs were similar to those reported to VA-ADERS and may reflect ALS progression. Exceptions noted were pulmonary embolism (6 severe reports in manufacturer database; 1 in VA-ADERS) and injection-related complications (9 severe injection-site infections in manufacturer database; 2 portal vein thrombosis events at infusion in VA-ADERS). VAMedSAFE will continue to conduct biannual surveillance of these and other safety signals.

To our knowledge, this is the first evaluation within a US health care system to use a matched-cohort, time-to-event analysis to assess safety and effectiveness of edaravone compared with an active comparator. Okada et al13 used survival analysis to compare tracheostomy-free survival between Japanese edaravone users (n = 27) and a historical control cohort (n = 30), for up to 80 months; a survival benefit was associated with edaravone treatment (HR for death, 0.37, 95% CI, 0.20-0.74). However, 37% (10 of 27) discontinued edaravone but were not censored, meaning survival was not associated with drug exposure. Within an Italian ALS clinic, edaravone users (n = 31) were compared with a historical-control cohort (n = 50); findings suggested no clinically or statistically significant differences in ALS-FRS-R score, respiratory function, or muscle strength, at 3- or 6-month follow-up.12 Abraham et al11 compared edaravone users with at least 6 months of treatment (n = 20) with contemporaneous non-edaravone users (71) at 1 Israeli clinic. There was no difference in effectiveness, but mortality was numerically greater in the edaravone group. None of these studies used matching, and the latter 2 studies11,12 did not account for differential follow-up or censoring due to death or tracheostomy.

This evaluation has limitations. First, the edaravone cohort was overall less healthy14 than edaravone clinical trial participants,8 which may explain the disease progression observed. Importantly, because riluzole is not regulated by VA CFU and is an oral drug whereas edaravone requires infusions, riluzole-only users are likely different from edaravone users in complex ways. Potentially, some riluzole users were sicker; edaravone is reserved for ALS patients with good...
functional status per CFU. Alternatively, edaravone patients may include those who progressed while receiving riluzole, and hence were different from those continuing to receive riluzole only. Consequently, despite our efforts to match patients receiving edaravone and those receiving riluzole-only treatment, residual confounding or baseline differences are likely. To maintain a larger pool of matching candidates, we did not use a new-user design for the riluzole-only cohort, which introduces bias toward favorable responders to riluzole. Matching on additional factors may improve comparison, including ALS-FRS-R score components, ALS-onset type (bulbar vs nonbulbar), and pulmonary and muscular function.10 Second, some outcomes were infrequently captured in VA databases (eg, ALS-FRS-R score and functional-status surrogate markers). Edaravone exposure was based on only the first and last prescription fill dates within the VHA, as we could not capture cycles received in non-VHA settings. In addition, we did not exclude PEG-tube use at baseline (allowed per CFU) and could not assess if PEG-tube outcomes were incident (reflecting decreases in function or discontinuation criterion).

Overall, the challenge of assessing edaravone safety and effectiveness is that ALS progression is unpredictable and heterogeneous.3,3,11,13 Simply, are adverse events related to disease progression, treatment, or both? Disease complications, death, or treatment discontinuation may occur prior to evaluation of drug effectiveness. In our evaluation, patients receiving riluzole-only treatment continued to receive treatment longer (mean 403.9 days, riluzole-only treatment; mean 305.1 days, edaravone), given differential censoring. This censoring bias may be addressed in future studies (if effectiveness is the primary interest) by applying survival models accounting for competing risks22 (eg, accounting for differential death or discontinuation between comparators).

Conclusions

The results of this study should be construed as exploratory given inherent methodologic limitations. Notably, this surveillance evaluation identified that patients using edaravone (mostly with riluzole) had unexpected outcomes, which raises questions about its benefit in VHA patients and underscores the importance of further studies. To confirm these findings, robust research designs with in-depth medical record review are needed to better characterize drug exposure, reasons for discontinuation, outcomes, and covariates. The VA will continue to track and monitor the safe and appropriate use of edaravone and provide timely information to optimize veteran ALS care.

ARTICLE INFORMATION

Accepted for Publication: June 13, 2020.
Published: October 5, 2020. doi:10.1001/jamanetworkopen.2020.14645

Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2020 Vu M et al. JAMA Network Open.

Corresponding Author: Francesca E. Cunningham, PharmD, Pharmacy Benefits Management Services, Center for Medication Safety, Department of Veterans Affairs, First Ave, 1 Block North of Cermak Rd, Building 37, Hines, IL 60141 (fran.cunningham@va.gov).

Author Affiliations: Pharmacy Benefits Management Services, Center for Medication Safety, Department of Veterans Affairs, Hines, Illinois (Vu, Dong, Hur, Zhang, Good, Glassman, Cunningham); Center for Health Equity Research and Promotion, Department of Veterans Affairs, Pittsburgh, Pennsylvania (Vu, Good); Pharmacy Benefits Management Services, Department of Veterans Affairs, Hines, Illinois (Tortorice, Zacher); Division of Insurance, UPMC Health Plan, Pittsburgh, Pennsylvania (Good); Greater Los Angeles Healthcare System, Department of Veterans Affairs, Los Angeles, California (Glassman); Pharmacy Benefits Management Services, Department of Veterans Affairs, Washington, DC (Glassman).

Author Contributions: Drs Hur and Cunningham had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Vu, Tortorice, Zacher, Hur, Good, Glassman, Cunningham.
Acquisition, analysis, or interpretation of data: Vu, Dong, Zhang, Cunningham.

Drafting of the manuscript: Vu, Zacher, Zhang, Cunningham.

Critical revision of the manuscript for important intellectual content: Vu, Tortorice, Zacher, Dong, Hur, Good, Glassman, Cunningham.

Statistical analysis: Vu, Dong, Hur, Zhang.

Administrative, technical, or material support: Vu, Tortorice, Cunningham.

Supervision: Zacher, Good, Glassman, Cunningham.

Conflict of Interest Disclosures: Dr Vu reported a fellowship scholarship from the Rho Chi Society to support clinical research during the conduct of the study. No other disclosures were reported.

Additional Contributions: Jeanne Tuttle, PharmD (VA PBM), collected and managed the data (prior authorization drug review); Xingming Wei, MS, and Lucy Pandey, MS (PBM VAMedSAFE), provided programming support; Huned Patwa, MD, Stephen Selkirk, MD, and Ileana Howard, MD (VA ALS group), provided clinical input and understanding relevant to clinical practice. No compensation was received by these contributors.

REFERENCES

1. Veterans Benefits Administration. Presumptive disability benefits. Published November 2018. Accessed January 1, 2020. https://www.benefits.va.gov/BENEFITS/factsheets/serviceconnected/presumption.pdf

2. Nelson LM, Topol B, Kaye W, et al. Estimation of the prevalence of amyotrophic lateral sclerosis in the United States using national administrative healthcare data from 2002 to 2004 and capture-recapture methodology. Neuroepidemiology. 2018;51(3-4):149-157. doi:10.1159/000488798

3. Mehta P, Kaye W, Raymond J, et al. Prevalence of amyotrophic lateral sclerosis—United States, 2015. MMWR Morb Mortal Wkly Rep. 2018;67(46):1285-1289. doi:10.15585/mmwr.mm6746a1

4. Radicava (edaravone injection). Package insert. Jersey City, NJ: Mitsubishi Tanabe Pharma Corporation; 2018.

5. Rilutek (riluzole). Package insert. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2012.

6. Bensimon G, Lacombie L, Meinering V; ALS/Riluzole Study Group. A controlled trial of riluzole in amyotrophic lateral sclerosis. N Engl J Med. 1994;330(9):585-591. doi:10.1056/NEJM199403303300901

7. Bensimon G, Lacombie L, Delumeau JC, Bejuit R, Truffinet P, Meinering V; Riluzole/ALS Study Group II. A study of riluzole in the treatment of advanced stage or elderly patients with amyotrophic lateral sclerosis. J Neurol. 2002;249(5):609-615. doi:10.1007/s004150200071

8. Abe K, Aoki M, Tsuji S, et al; Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16(7):505-512. doi:10.1016/S1474-4422(17)30115-1

9. Hardiman O, van den Berg LH. Edaravone: a new treatment for ALS on the horizon? Lancet Neurol. 2017;16(7):490-491. doi:10.1016/S1474-4422(17)30163-1

10. Park JM, Kim SY, Park D, Park JS. Effect of edaravone therapy in Korean amyotrophic lateral sclerosis (ALS) patients. Neurol Sci. 2020;41(1):119-123. doi:10.1007/s10072-019-04055-3

11. Abraham A, Nefussy B, Fainmesser Y, Ebrahimi Y, Karki A, Drory VE. Early post-marketing experience with edaravone in an unselected group of patients with ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(3-4):260-263. doi:10.1080/21678421.2019.1572191

12. Fortuna A, Gizi M, Bello L, et al; Edaravone Study Group. Safety and efficacy of edaravone compared to historical controls in patients with amyotrophic lateral sclerosis from North-Eastern Italy. J Neurol Sci. 2019;404:47-51. doi:10.1016/j.jns.2019.06.006

13. Okada M, Yamashita S, Ueyama H, Ishizaki M, Maeda Y, Ando Y. Long-term effects of edaravone on survival of patients with amyotrophic lateral sclerosis. eNeurologicalSci. 2018;1:11-14. doi:10.1016/j.ensci.2018.05.001

14. Medical Advisory Panel and VISN Pharmacist Executives. Edaravone (Radicava) Criteria for Use. Published December 2017. Accessed January 19, 2020. https://www.pbm.va.gov/apps/VANationalFormulary

15. Radicava (Edaravone)–2018. Blue Cross/Blue Shield of Rhode Island. Published June 1, 2018. Accessed February 13, 2020. https://www.bcbsri.com/sites/default/files/policies/2018%20Radicava%20%28Edaravone%29%206_1_2018.pdf

16. Cedarbaum JM, Stambler N, Malta E, et al; BDNF ALS Study Group (Phase III). The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci. 1999;169(1-2):13-21. doi:10.1006/jns.1999.1365-3

17. Luo L, Song Z, Li X, et al. Efficacy and safety of edaravone in treatment of amyotrophic lateral sclerosis—a systematic review and meta-analysis. Neurol Sci. 2019;40(2):235-241. doi:10.1007/s10072-018-3653-2
18. Arnold N, Sohn M, Maynard C, Hynes D. VIReC Technical Report 2: VA NDI Mortality Data Merge Project. VA Information Resource Center; 2006.
19. Emmendorfer T, Glassman PA, Moore V, Leadholm TC, Good CB, Cunningham F. Monitoring adverse drug reactions across a nationwide health care system using information technology. Am J Health Syst Pharm. 2012;69(4):321-328. doi:10.2146/ajhp110026
20. Jackson C, Heiman-Patterson T, Kittrell P, et al. Radicava (edaravone) for amyotrophic lateral sclerosis: US experience at 1 year after launch. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(7-8):605-610. doi:10.1080/21678421.2019.1645858
21. Zhang Z, Kim HJ, Lonjon G, Zhu Y; written on behalf of AME Big-Data Clinical Trial Collaborative Group. Balance diagnostics after propensity score matching. Ann Transl Med. 2019;7(1):16. doi:10.21037/atm.2018.12.10
22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144

SUPPLEMENT.
eFigure. Flowchart of Descriptive Assessment, Matched Cohort Design, and Chronic User Sub-Analysis
eTable 1. Riluzole Use Patterns Among Edaravone Patients
eTable 2. Riluzole Use Continuation Among Patients With Riluzole Use Prior to Edaravone Initiation
eTable 3. Comprehensive Safety and Effectiveness Evaluation-Matched Edaravone and Riluzole-Only Users