Short Report

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Longer disease progression milestone-free time in people with amyotrophic lateral sclerosis treated versus not treated with intravenous edaravone: results from an administrative claims analysis

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Aim: To estimate time-to-progression milestones in people with amyotrophic lateral sclerosis (PALS) treated versus not treated with intravenous (IV) edaravone (Radicava® IV, Mitsubishi Tanabe Pharma America [MTPA], hereafter "IV edaravone") in a real-world setting. **Background:** IV edaravone is US FDA approved for the treatment of ALS and was shown in clinical trials to slow the rate of physical functional decline. **Patients & methods:** This retrospective observational analysis included PALS continuously enrolled in Optum's Clinformatics® Data Mart between 8 August 2017 and 31 December 2021. Cases treated with IV edaravone and controls not treated with IV edaravone were propensity score matched for: age, sex, race, US region of residence, pre-index disease duration, insurance, riluzole prescription; and pre-index claims for cardiovascular disease, artificial nutrition/gastrostomy tube, noninvasive ventilation and all-cause hospitalization. The index date was the first IV edaravone claim for cases; for controls, the index date was randomly assigned after IV edaravone market availability. Restricted mean time lost was calculated for the following disease progression milestones: new use of canes/walkers/wheelchairs, artificial nutrition, noninvasive ventilation, invasive ventilation, speech-generating devices and hospice. **Results:** Cases (n = 395) were matched to controls (n = 395). Cases had less restricted mean time lost, indicating longer disease progression milestone-free time, for all disease progression milestones. From 0 to 24 months post index, more cases (n = 129) than controls (n = 103) reported no milestones and more controls (n = 232) than cases (n = 131) reported deaths. **Conclusion:** In a US-based real-world setting, IV edaravone-treated PALS had a longer time to disease progression milestone events and fewer deaths in 2 years compared with PALS not treated with IV edaravone.

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Keywords: administrative claims database • amyotrophic lateral sclerosis • disease progression • edaravone • milestones • propensity score matching • real-world data • restricted mean time lost • survival

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative condition that causes neuron cell death and progressive muscular weakness [1]. There is no cure, and mean survival time is between 3 and 5 years after symptom onset [2]. In 2017, the estimated prevalence rate ranged from 5.5 to 9.9 per 100,000 people in the US and was highest in men, Whites and those 60–69 years of age [3]. At the time this study was conducted, the US FDA had approved riluzole and intravenous (IV) edaravone (Radicava® IV, Mitsubishi Tanabe Pharma America [MTPA], hereafter "IV edaravone") for the treatment of ALS [4,5]. IV edaravone received FDA approval in May 2017 [5]. FDA

approval of IV edaravone was based on a pivotal phase III trial (MCI186-19; Study 19) in which 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 at 24 weeks [6]. Of note, since the completion of the real-world study we report here, the US FDA has approved oral edaravone (Radicava ORS®, MTPA) in May 2022 [5] and sodium phenylbutyrate and taurursodiol (PB-TURSO; approved September 2022 but removed from the market in April 2024 due to negative phase III trial results) [7] for the treatment of people with ALS (PALS), and tofersen for PALS with a mutation in the superoxide dismutase 1 (*SOD1*) gene in April 2023 [8].

Research studies employing real-world data (RWD) can supplement evidence obtained from randomized controlled trials (RCTs), particularly in rare, heterogeneous diseases like ALS [9,10]. The US FDA recently created a framework to evaluate the use of real-world evidence (RWE) to support evidence generation and the regulatory approval process [11]. As a result, regulators are now examining the use of noninterventional RWE studies to evaluate the effectiveness of therapeutics [12]. The objective of this study was to estimate time-to-progression milestones in propensity score-matched PALS treated versus not treated with IV edaravone using RWD collected from a large US administrative claims database.

Methods

Data source

This was a retrospective, observational, propensity score-matched, comparative effectiveness cohort study using health claims data from the Optum Clinformatics® Data Mart (CDM; Optum, Inc.). The CDM is statistically de-identified 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. Therefore, it does not require an institutional review board assessment or approval for secondary analysis as it is not considered human patient research as defined in 45 CFR 46.102. The database includes approximately 17 to 19 million annual covered lives. The population is geographically diverse, spanning all 50 states, and is composed of members with commercial and Medicare Advantage plans. CDM administrative claims submitted for payment by providers and pharmacies are verified, adjudicated and de-identified 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.

Study population

Records from PALS who had previously been treated with IV edaravone (Radicava® IV) were included in the IV edaravone-treated case group if they met the following criteria:

- Adults aged at least 18 years on the IV edaravone index date (date of the first claim for IV edaravone)
- Diagnosis of ALS (International Classification of Diseases, 9th/10th Revision, Clinical Modification [ICD-10-CM] code G12.21; [ICD-9-CM] code 335.20) on any claim in any setting
- Initiated IV edaravone between 8 August 2017 and 31 September 2021 (claim for IV edaravone using Healthcare Common Procedure Coding System [HCPCS] codes J1301, J3490, or C9493 or the National Drug Code [NDC] 70510-2171-xx)
- May or may not have received treatment with riluzole

PALS may or may not have continued IV edaravone treatment until death or censoring. PALS not treated with IV edaravone were included in the control group if they met criteria 1, 2 and 4 above. For the control group, the index date was randomly assigned under the assumption that the index timepoint was uniformly distributed over the time interval between the diagnosis date and the last claim date.

Confirmation of ALS in individuals treated versus not treated with IV edaravone

Administrative claims for ALS-related symptoms and procedures identifying respiratory-, nerve-, limb- and bulbar-related symptoms in the pre-index period were tabulated for both individuals treated and not treated with IV edaravone and compared with the proportion of symptoms in the 2 groups [13]. These claims were extracted using ICD-9-CM and ICD-10-CM, Current Procedural Terminology (CPT), or HCPCS codes. HCPCS codes are a standardized coding system based on the American Medical Association's CPT that describe specific items and services.

Table 1. Codes for analyzed milestones.

Milestone description	CPT codes	HCPCS codes	ICD-10-CM codes	Revenue codes
M1: Canes/walkers/wheelchairs		E0100, E0105-0159, E0950-E1298, E2201-E2397, E2601-E2625, K0001-K0899		
M2: Artificial nutrition	43246, 43760, 43761, 44373, 49440, 49441, 49446, 49450, 49451, 49452, 97542	B4034-B9998		
M3: Noninvasive ventilation		A7030-A7039, A7044-A7046, E0464, E0470, E0471		
M4: Invasive ventilation	94002-94005	A4611-A4613, A4623-A4626, A4629, A4483, A7501-A7527, E0460-E0461, E0463, E0472, E0450		
M5: Speech-generating devices	92607, 92608, 92609	E2500-E2599		
M6: Hospice	99377, 99378		V66.7 or Z 51.5	0650, 0651, 0655, 0656, 0657, 0659

CPT: Current procedural terminology; HCPCS: Healthcare Common Procedure Coding System; ICD-10-CM: International Classification of Diseases 10th Revision Clinical Modification.

Propensity score matching

Propensity score matching (PSM) estimates the effect of a treatment in nonrandomized, interventional studies by adjusting for potential confounding factors in a mixed population of treated or untreated individuals with varying characteristics to achieve a balanced covariate distribution between the treated and untreated groups [14]. After identifying PALS who had been treated versus not treated with IV edaravone as noted above and described in prior studies [13], a propensity score was estimated for each individual using extreme gradient boosting algorithm and accounted for the following covariates: age, sex, race, US region of residence, pre-index disease duration, insurance (Medicare Advantage vs commercial insurance), riluzole prescription; and pre-index claims for cardiovascular disease, artificial nutrition/gastrostomy tube placement, noninvasive ventilation and all-cause hospitalization. Pre-index disease duration was defined as the period between the date of first claim for ALS diagnosis and the first claim of IV edaravone for IV edaravone-treated PALS. For PALS who were not treated with IV edaravone, the pre-index disease duration was calculated between the date of first claim for ALS diagnosis and the randomly assigned index date. PALS in each group were then matched based on propensity score using the nearest-neighbor method with a caliper width equal to 0.1 of the SD of the logit scores [15] and PALS for whom no matching partner had been found were excluded. Each treated individual was allocated up to 1 untreated individual (in 1:1 matching) with the same (or a very similar) propensity score and treatment effect was evaluated in the matched groups. Standardized mean difference (SMD) was used to examine the balance of covariate distribution between groups treated versus not treated with IV edaravone [15]. SMDs of less than 10% were considered negligible imbalances.

Additional statistical analyses

Demographics and clinical variables were assessed descriptively using counts and percentages for categorical variables and measures of central tendency (mean/median/SD/interquartile range [IQR]) for continuous variables. Analysis of disease progression milestones and deaths used weighted estimates that considered the weights obtained from PSM and the time restriction, since weighted estimates may reduce bias and improve efficiency of the estimates, and thus provide better generalizability to the whole patient population [16].

Disease progression milestones

Six disease progression milestones, including 1) use of gait assistive devices (canes/walkers/wheelchairs), 2) artificial nutrition, 3) noninvasive ventilation, 4) invasive ventilation, 5) speech-generating devices and 6) hospice, were analyzed and their CPT, HCPCS, ICD-10-CM and revenue codes are reported (Table 1). The milestones are not listed in the order that they occurred.

Restricted mean time lost

Restricted mean time lost (RMTL) was measured and is defined as the increase/decrease in lost life expectancy due to a specific cause of death, or in the case of a non-fatal outcome, the difference in disease/milestone-free time,

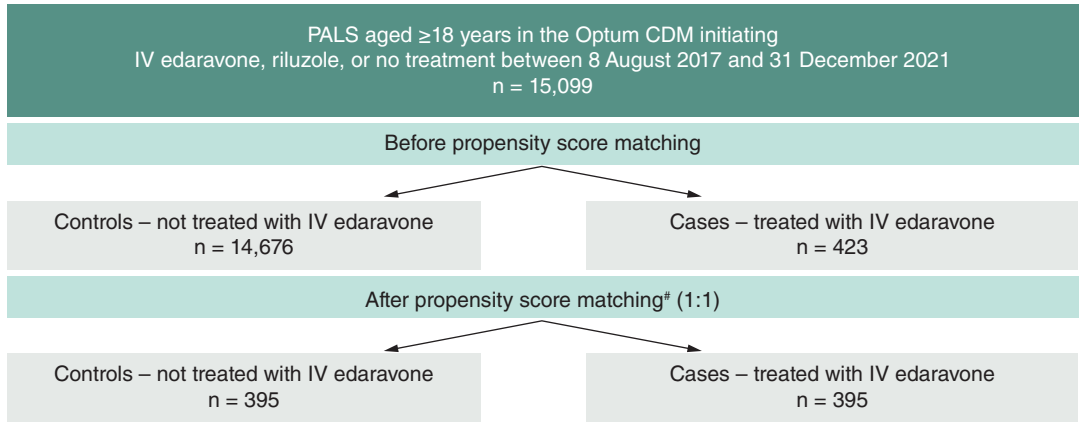

Figure 1. Patient disposition. Identification and propensity score matching of adult PALS from the Optum CDM who initiated IV edaravone, riluzole, or had no treatment between 8 August 2017 and 31 December 2021.
CDM: Clinformatics® Data Mart; IV: Intravenous; PALS: People with amyotrophic lateral sclerosis.

considering adjusting mortality as the competing risk [16]. RMTL is reported up to 24 months since the index date for each milestone, and differences in RMTL between groups are presented for controls not treated with IV edaravone and cases treated with IV edaravone. In both groups, PALS were analyzed as a group and also subdivided by whether they were covered by commercial or Medicare Advantage insurance.

A sensitivity analysis strategy proposed by Lin *et al.* was used to examine the robustness of calculated treatment effects for RMTL analyses to unmeasured confounding [17] using a strategy adapted from the E-value method [18,19]. For unmeasured binary confounder U, two sensitivity analysis parameters are defined: relative risk (RR) of the treatment on a level of U with a given propensity score value, and mean ratio (MR) of U on the RMTL outcome with a given propensity score value. For a pair of specified sensitivity parameters, corresponding 95% CI bounds can be calculated. The behavior of the 95% CI bounds shows the robustness of estimated treatment effects with respect to any unmeasured confounder.

All analyses were conducted using R (version 4.0.3, R Core Team, 2020). Propensity score estimating and matching were done using the MatchIt (version: 4.1.0, 2011) package.

Results

Study population selection & characteristics

Between 8 August 2017 and 31 December 2021, 15,099 adults with ALS in the Optum CDM had initiated IV edaravone, riluzole, or had no treatment (Figure 1). During 1:1 PSM, 7 out of 423 cases did not report sex information and were excluded. Additionally, there were no matches found for 21 patients. Therefore, the matching process resulted in a study population that included 395 PALS with at least 1 claim for IV edaravone and 395 controls not treated with IV edaravone. Demographic and clinical characteristics for both groups after PSM are presented in Table 2. Covariates were balanced between groups as indicated by an SMD of $\leq$0.1 for all variables. Median (IQR) IV edaravone treatment duration in the IV edaravone-treated group was 7.47 months (3.08, 14.55).

ALS-related symptoms & procedures

Claims for ALS-related symptoms and procedures were identified for both groups (Figure 2). These claims were not considered confounding factors and were evenly balanced between cases and controls – individuals in both groups reported a similar proportion of claims for ALS-related symptoms, including bulbar-, limb-, nerve- and respiratory-related symptoms, in the pre-index period. The most common symptoms for individuals in both groups were limb related. IV edaravone-treated PALS had more claims for the insertion of an IV catheter than PALS not treated with IV edaravone.

RMTL for reported disease progression milestones

RMTL was calculated for 6 disease progression milestones, including new use of canes/walkers/wheelchairs, artificial nutrition, noninvasive ventilation, invasive ventilation, speech-generating devices and hospice (Table 3). For all milestones, IV edaravone-treated cases had a smaller amount of time lost due to reaching disease progression

Table 2. Demographic and clinical characteristics of people with amyotrophic lateral sclerosis after propensity score matching.

	Controls – not treated with IV edaravone	Cases – treated with IV edaravone	SMD
n	395	395	
Age (years), mean (SD)	63.7 (11.3)	63.2 (10.4)	0.0502
Sex, n (%)			
Female	156 (39.5)	168 (42.5)	0.0304
Male	239 (60.5)	227 (57.5)	
Insurance, n (%)			
Commercial	140 (35.4)	154 (39.0)	0.0354
Medicare Advantage	255 (64.6)	241 (61.0)	
Race, n (%)			
White	269 (68.1)	292 (73.9)	0.0582
Black	31 (7.8)	22 (5.6)	0.0127
Other	51 (12.9)	46 (11.6)	0.0127
Unknown	44 (11.1)	35 (8.9)	0.0288
Region, n (%)			
Midwest	98 (24.8)	103 (26.1)	0.0127
Northeast	71 (18.0)	69 (17.5)	0.0051
South	137 (34.7)	132 (33.4)	0.0127
West	89 (22.5)	91 (23.0)	0.0051
Pre-index disease duration (months), mean (SD)	6.9 (8.8)	6.0 (8.7)	0.1
Riluzole prescription, n (%)	230 (58.2)	265 (67.1)	0.0886
Pre-index cardiovascular disease, n (%)	52 (13.2)	49 (12.4)	0.0076
Pre-index artificial nutrition/gastrostomy tube, n (%)	68 (17.2)	42 (10.6)	0.0658
Pre-index noninvasive ventilation, n (%)	74 (18.7)	64 (16.2)	0.0253
Pre-index all-cause hospitalization, n (%)	112 (28.4)	91 (23.0)	0.0532

IV: Intravenous; PALS: People with amyotrophic lateral sclerosis; SMD: Standardized mean difference.

milestones than controls not treated with IV edaravone based on RMTL for PALS overall, and when grouping PALS based on commercial or Medicare Advantage insurance coverage.

Disease progression milestones & deaths from 0 to 24 months

Disease progression milestones and deaths are reported from 0 to 12 months, 12 to 24 months and 0 to 24 months after the index date (Table 4). Weights were estimated from the propensity score model and the resulting estimated percentages may be generalized to the patient population. Overall, more IV edaravone-treated cases (n = 129) reported an absence of milestones than controls not treated with IV edaravone (n = 103) from 0 to 24 months after the index date. Fewer deaths occurred in IV edaravone-treated cases (n = 131) than in controls not treated with IV edaravone (n = 232) from 0 to 24 months after the index date.

Sensitivity analyses

In Figure 3, contour plots show the lower bounds of 95% CI for use of canes/walkers/wheelchairs, artificial nutrition, noninvasive ventilation and speech-generating devices, which had relatively large estimated treatment effects. The gray scales represent different lower bound values of the lower 95% confidence bound of the treatment effect, with the lighter shades indicating large effect values and darker shades indicating negative values. The solid curve in the middle of the plots represents when the lower bound of the lower 95% confidence bound of the treatment effect is zero. For the disease progression milestones including use of canes/walkers/wheelchairs and artificial nutrition, the benefit of IV edaravone treatment still holds under RR <2 and MR <2, as the lower bound of the 95% confidence bounds of the treatment effect is above the solid zero curves. This indicates the estimated treatment effects for these 2 milestones are tolerable to relatively high deviations from the ignorability assumption, i.e., no unmeasured confounder. The RR <1.6 and MR <2 for noninvasive ventilation to hold the above-zero treatment effect also indicates a moderate robustness to unmeasured confounding.

Discussion

In this case–control study of PALS with commercial and Medicare Advantage insurance in a large database, IV edaravone-treated cases had a smaller amount of time lost due to reaching disease progression milestones than

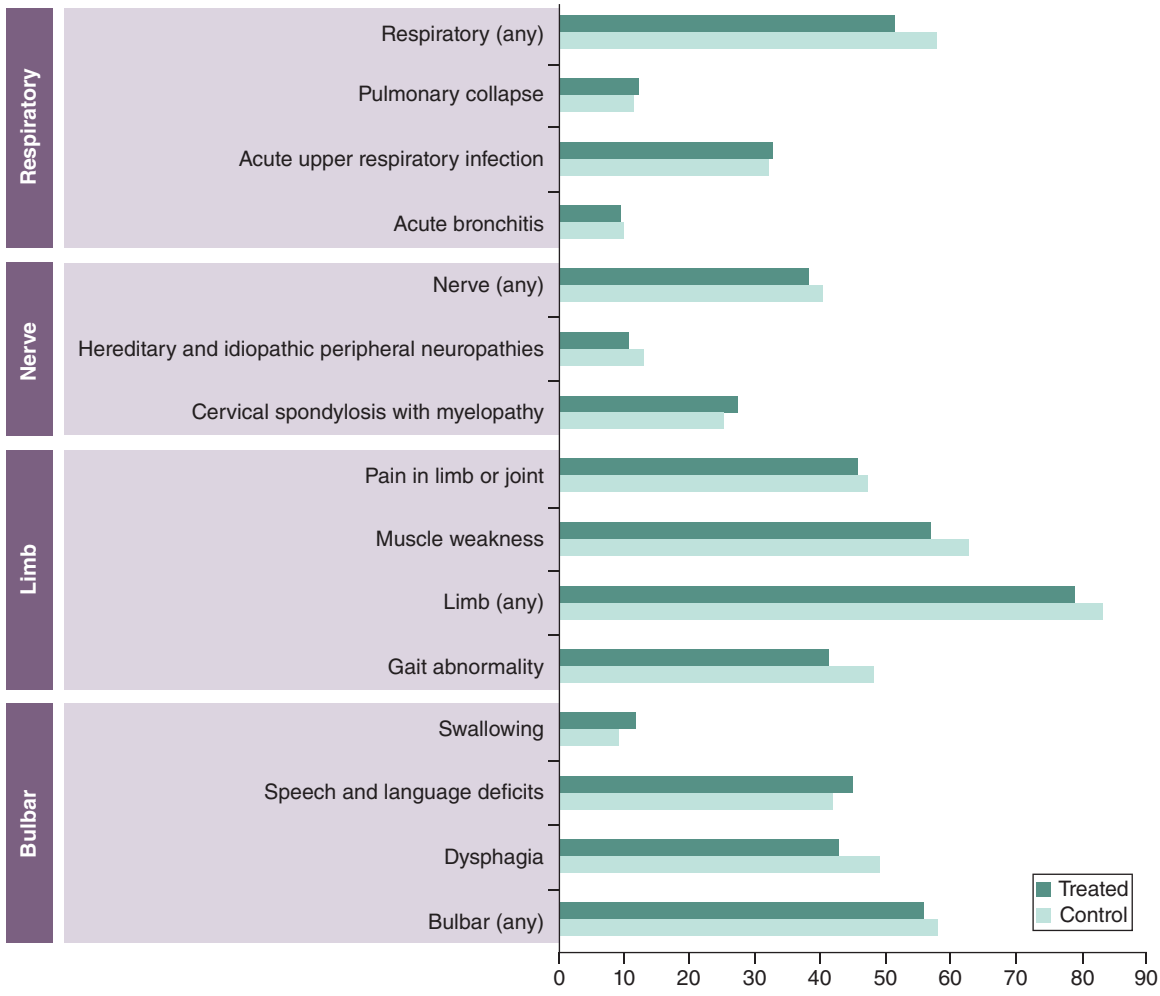

Figure 2. Claims for amyotrophic lateral sclerosis-related symptoms in the pre-index disease duration period. Claims for ALS-related symptoms, including bulbar-, limb-, nerve- and respiratory-related symptoms, are reported in the pre-index period for the groups treated with IV edaravone (treated; dark blue) versus not treated with IV edaravone (control; light blue). The pre-index disease duration period was defined as the period between the date of ALS diagnosis and the first claim of IV edaravone for IV edaravone-treated cases. For PALS not treated with IV edaravone, the index date was randomly assigned starting on 8 August 2017 (date IV edaravone was available on the market) and ending on 30 September 2021, assuming the index date was uniformly distributed over the time interval between the diagnosis date and last claim date, and pre-index disease duration was calculated based on this assigned index date. ALS: Amyotrophic lateral sclerosis; IV: Intravenous.

controls not treated with IV edaravone based on RMTL for all milestones: new use of canes/walkers/wheelchairs, artificial nutrition, noninvasive ventilation, invasive ventilation, speech-generating devices and hospice. Additionally, more IV edaravone-treated cases reported an absence of disease progression milestones or death from 0 to 24 months after the index date than controls who were not treated with IV edaravone.

The ALSFRS-R is a 12 item questionnaire aimed at assessing function in daily activities [20]. It is used to track ALS progression, and the degree of impairment and speed of progression varies by patient, with some patients experiencing severe limb symptoms but few bulbar (speech and swallowing) symptoms, and *vice versa* [21–26]. However, the ALSFRS-R does not directly report the timing of certain ALS milestones, such as the need for assistive devices used for walking or breathing, which are key to a patient's quality of life. Additionally, the King's and Milano-Torino Staging (MiToS) ALS staging systems do not provide much information about the timing of these critical milestones [27]. A more recent tool to describe ALS progression called the Tollgate-based ALS Staging System (TASS) measures ALS progression and consists of 27 tollgates, or critical clinical events, including the need for a walker/wheelchair or communication device [28]. One group developed and applied an ALSFRS-R-to-TASS

Table 3. Restricted mean time lost by milestones up to 24 months after the index date for people with amyotrophic lateral sclerosis with commercial or Medicare Advantage insurance.

Commercial Insurance					
Milestone†	Not treated with IV edaravone		Treated with IV edaravone		Difference in RMTL (95% CI)
	n (%)	RMTL (95% CI)	n (%)	RMTL (95% CI)	
Canes/walkers/wheelchairs	37.0 (24.0)	12.66 (8.95, 16.38)	29.7 (19.3)	6.29 (4.39, 8.19)	6.37 (2.2, 10.55)
Artificial nutrition	39.0 (25.3)	11.11 (7.3, 14.92)	23.2 (15.1)	5.02 (3.27, 6.77)	6.09 (1.9, 10.28)
Noninvasive ventilation	31.0 (20.1)	10.61 (6.41, 14.81)	24.1 (15.7)	5.91 (4.04, 7.78)	4.7 (0.1, 9.29)
Invasive ventilation	5.0 (3.2)	1.65 (-0.81, 4.12)	1.0 (0.7)	1.1 (0.14, 2.06)	0.55 (-2.09, 3.2)
Speech-generating devices	31.0 (20.1)	5.98 (2.05, 9.92)	16.0 (10.4)	2.83 (1.34, 4.31)	3.15 (-1.05, 7.36)
Hospice	18.0 (11.7)	4.79 (1.6, 7.97)	13.8 (9.0)	2.09 (0.79, 3.39)	2.7 (-0.74, 6.14)
Medicare Advantage					
Milestone†	Not treated with IV edaravone		Treated with IV edaravone		Difference in RMTL (95% CI)
	n (%)	RMTL (95% CI)	n (%)	RMTL (95% CI)	
Canes/walkers/wheelchairs	56.0 (23.2)	10.02 (7.32, 12.72)	42.4 (17.5)	5.39 (4.1, 6.67)	4.63 (1.64, 7.62)
Artificial nutrition	61.0 (25.3)	9.32 (6.4, 12.24)	48.8 (20.2)	5.42 (4.08, 6.75)	3.9 (0.69, 7.12)
Noninvasive ventilation	37.0 (15.4)	6.87 (4.31, 9.42)	24.5 (10.1)	3.99 (2.81, 5.17)	2.88 (0.06, 5.7)
Invasive ventilation	7.0 (2.9)	4.15 (1.71, 6.59)	3.1 (1.3)	0.58 (0.09, 1.07)	3.57 (1.08, 6.06)
Speech-generating devices	27.0 (11.2)	3.18 (0.96, 5.4)	14.0 (5.8)	1.52 (0.74, 2.29)	1.66 (-0.69, 4.02)
Hospice	24.0 (10.0)	3.87 (1.47, 6.27)	37.5 (15.5)	2.43 (1.47, 3.39)	1.44 (-1.14, 4.02)
Overall					
Milestone†	Not treated with IV edaravone		Treated with IV edaravone		Difference in RMTL (95% CI)
	n (%)	RMTL (95% CI)	n (%)	RMTL (95% CI)	
Canes/walkers/wheelchairs	93.0 (23.5)	10.9 (8.73, 13.07)	72.1 (18.2)	5.68 (4.61, 6.74)	5.22 (2.8, 7.64)
Artificial nutrition	100.0 (25.3)	8.2 (5.95, 10.44)	72.0 (18.2)	4.6 (3.59, 5.61)	3.6 (1.13, 6.06)
Noninvasive ventilation	68.0 (17.2)	3.52 (1.67, 5.38)	48.6 (12.3)	0.75 (0.29, 1.2)	2.78 (0.87, 4.69)
Invasive ventilation	12.0 (3.0)	4.02 (2.05, 5.98)	4.2 (1.1)	1.94 (1.23, 2.66)	2.07 (-0.02, 4.17)
Speech-generating devices	58.0 (14.7)	9.78 (7.46, 12.1)	30.0 (7.6)	5.27 (4.21, 6.33)	4.51 (1.95, 7.07)
Hospice	42.0 (10.6)	4.16 (2.29, 6.02)	51.3 (13.0)	2.32 (1.55, 3.09)	1.83 (-0.19, 3.85)

†Milestones are not listed in the order they occurred.
CI: Confidence interval; IV: Intravenous; PALS: People with amyotrophic lateral sclerosis; RMTL: Restricted mean time lost.

Table 4. Absence of milestones and deaths from (a) 0–12 months and 12–24 months after the index date and (b) 0–24 months after the index date.

(a)	Not treated with IV edaravone		Treated with IV edaravone	
	0–12 months	12–24 months	0–12 months	12–24 months
Absence of milestones, n (%)	47.6 (26.0)	55.8 (45.7)	67.0 (34.7)	62.0 (55.4)
Deaths, n (%)	136.8 (74.9)	94.7 (77.5)	79.0 (40.9)	52.0 (46.4)
(b)	**Not treated with IV edaravone**		**Treated with IV edaravone**	
	0–24 months		**0–24 months**	
Absence of milestones, n (%)	103 (33.9)		129 (42.3)	
Deaths, n (%)	232 (75.9)		131 (43.0)	

IV: Intravenous.

mapping methodology to a large database to estimate tollgate-based time trajectories that may be used to inform patients and clinicians about these life-changing milestones [29], since most databases do not provide patient records pertaining to TASS information. Due to the small amount of data in the ALS field regarding time-to-milestone progression, the current study helps to fill the knowledge gap by providing RWD on the general timing to milestones in PALS using different treatment regimens.

In this study, RMTL was selected to represent the treatment effect for 2 reasons, even though alternative approaches – the cause-specific hazard function (which calculates the cause-specific hazard ratio [cHR]) and the subdistribution hazard function (which calculates the subdistribution hazard ratio [sHR]) – are generally used for

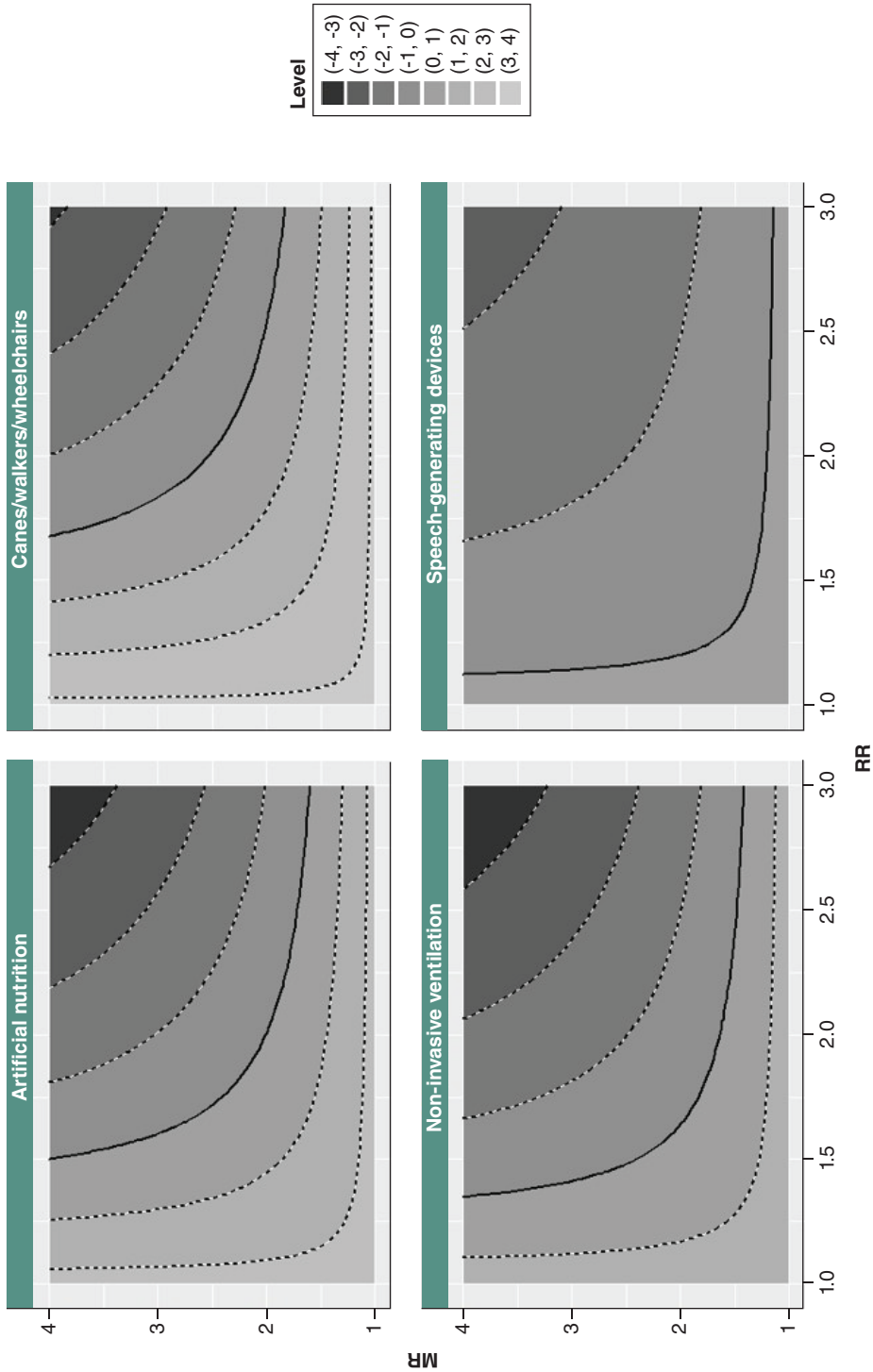

Figure 3. Contour plots for lower bounds of treatment effect by milestones. Contour plots show the lower bounds of the 95% confidence interval for use of artificial nutrition, canes/walkers/wheelchairs, noninvasive ventilation and speech-generating devices. The gray scales represent different lower bound values of the lower 95% confidence bound of the treatment effect, with lighter shades indicating large effect values and darker shades indicating negative values. The solid curve in the middle of the plots represents when the lower bound value of the lower 95% confidence bound of the treatment effect is zero.
MR: Mean ratio; RR: Relative risk.

competing risk analysis based on hazards. First, estimations and statistical analyses based on cHR and sHR have several limitations; these limitations have been previously described [30]. Second, in our study, disease progression milestones competed with each other, and death was another competing event. Median survival would no longer be useful as it would become a biased parameter in the scenario with competing risks. By contrast, RMTL is estimated as the area under the cumulative incidence function (CIF) curve up to a certain time. As the CIF curve can identify the probability of one event occurring in a given time period in the presence of other events, the analysis captured the mean amount of time lost due to a particular cause Therefore, RMTL was analyzed in this study, and may be better understood by clinicians and PALS.

In 2023, a literature review that discussed the epidemiology and economic burden of ALS in the US highlighted costs associated with ALS stratified by disease stage/milestone and reported substantially higher costs for later-stage milestones as compared with earlier-stage milestones [31]. Additional studies examining the association of treatment for ALS with time-to-milestone progression and survival, together with an understanding of the economic burden of these factors, would be beneficial for ongoing clinical trials and cost-effectiveness models for ALS treatments.

In line with this, the current study assessed time to milestones, and additionally provided RWD on the mortality of PALS who were treated versus not treated with IV edaravone, adding to our previous RWD study reporting that PALS who were prescribed IV edaravone and continued using it over 31 months after the index date survived longer than those who were not treated with IV edaravone [13]. That study contained similar limitations to the current study, which are described below.

When evaluating the results of this study, we do need to consider several limitations. The current study was comprised only of PALS who had commercial health coverage or Medicare Advantage plans. Therefore, results of this analysis may not be generalizable to PALS who have different or no health insurance coverage. Another limitation is that administrative claims data, upon which this study is based, may be impacted by social determinants of health, which were not collected for adjustment in this analysis. Additionally, administrative claims data may be impacted by coding limitations and entry error. Also, selection bias and/or smaller sample sizes may have resulted from underdiagnosis of ALS, as some PALS were excluded from this analysis, including untreated PALS, those without an appropriately recorded diagnosis and those not enrolled in the Optum CDM during the post-index period. While PSM was used to help control differences between cohorts, adjustment was restricted to measurable administrative claims characteristics. Consequently, PALS in our study may have been healthier than the total cohort of PALS in the database.

At the same time, this is a large, carefully conducted retrospective analysis with a number of strengths. The analysis drew from a large, real-world population of PALS during a similar time frame using the Optum CDM administrative claims database, following them for up to 2 years after their index date. To minimize differences due to the heterogeneity of ALS, individuals from the treated and control groups were propensity score matched on 12 items to ensure balance. This methodology is meant to overcome as many potential limitations as possible. Future studies could assess time to disease progression milestones and survival analyses in other large retrospective datasets, including electronic medical records or other insurance databases, to corroborate these results.

Conclusion

This retrospective, observational, propensity score-matched study suggests that MTPA IV edaravone treatment in PALS in a real-world setting is associated with fewer reported disease progression milestones and deaths during the first 2 years after the index date. These results provide an example of real-world impact of IV edaravone in PALS that supports the findings of a 33% slowing of functional loss, as measured by the ALSFRS-R in the pivotal RCT of IV edaravone [6]. This RWD may be useful to payers, healthcare providers, PALS and caregivers in evaluating the real-world impact of edaravone treatment.

Author contributions

All authors contributed to the study's conception and design. M Ciepielewska and M Hagan performed data collection. J Zhang and Y Liu performed data analysis and interpretation. All authors drafted, reviewed, revised and commented on previous versions of the article. All authors read and approved the final version to be published.

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Competing interests disclosure

JD Berry reports research funding from Alexion, Biogen, Mitsubishi Tanabe Pharma America, Inc. (MTPA), Brainstorm Cell Therapeutics, Amylyx Pharmaceuticals, nQ Medical, MT Pharma Holdings of America (MTPHA), Transposon Therapeutics, RAPA Therapeutics, National Institute of Neurological Disorders and Stroke, Muscular Dystrophy Association, ALS Finding a Cure, ALS Association and ALS One. He has consulted on scientific advisory boards for Amylyx, MTPA, MTPHA. He has acted as a consultant for Amylyx, Alexion and Biogen. He is a member of a DSMB for Sanofi and a trial support committee for Biogen. And, he has been an educational speaker for Projects in Knowledge, Inc. M Hagan is a former employee of MTPA. J Zhang and Y Liu are employees of Princeton Pharmatech, which has received consultancy fees from MTPA. M Ciepielewska is an employee of MTPA. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Data sharing statement

All data generated or analyzed during this study are included in this published article.

Summary points

- Intravenous (IV) edaravone has been FDA approved for the treatment of amyotrophic lateral sclerosis (ALS) and was shown in clinical trials to slow the rate of physical functional decline.
- People with amyotrophic lateral sclerosis (PALS) continuously enrolled in Optum's Clinformatics® Data Mart (CDM) between 8 August 2017 and 31 December 2021 were included in this retrospective observational analysis.
- Cases treated with IV edaravone (n = 395) and controls not treated with IV edaravone (n = 395) were propensity score matched for: age, sex, race, US region of residence, pre-index disease duration, Medicare Advantage versus commercial insurance, riluzole prescription; and pre-index claims for cardiovascular disease, artificial nutrition/gastrostomy tube placement, noninvasive ventilation and all-cause hospitalization.
- Restricted mean time lost (RMTL) was calculated for the following 6 disease progression milestones up to 24 months after the index date: new use of canes/walkers/wheelchairs, artificial nutrition, noninvasive ventilation, invasive ventilation, speech-generating devices and hospice.
- Cases had a smaller amount of time lost due to reaching disease progression milestones than controls based on RMTL for all six milestones.
- More cases (n = 129) than controls (n = 103) reported no milestones from 0 to 24 months after the index date.
- More controls (n = 232) than cases (n = 131) reported deaths from 0 to 24 months after the index date.
- The results of these analyses provide evidence of a real-world impact of IV edaravone and may help payers and clinicians when assessing the utility of edaravone use.

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