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ORIGINAL RESEARCH ARTICLE

Analysis of the US Safety Data for Edaravone (Radicava®) From the Third Year After Launch

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Abstract

Background Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neuromuscular disease with no curative therapies. Edaravone (Radicava®) (Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan), approved in the United States (US) for ALS in adults in 2017, was shown in a clinical trial to slow the rate of physical functional decline in ALS and is administered intravenously. The aim of this paper is to summarize the observed safety profile from real-world patient use during the first 3 years of edaravone availability in the US.

Methods Edaravone usage data were collected, and adverse events (AEs) were identified from a postmarketing safety database from August 8, 2017 through August 7, 2020 (cutoff date).

Results As of October 3, 2020, 5207 ALS patients had been treated with edaravone. As of August 7, 2020, the most commonly reported AEs included death (not specified), drug ineffective, disease progression, therapeutic response unexpected, fall, asthenia, fatigue, muscular weakness, gait disturbance, and dyspnea. The most commonly reported serious AEs (SAEs) included death (not specified), pneumonia, disease progression, ALS, fall, dyspnea, respiratory failure, device-related infection, hospitalization, and injection-site infection. There were 687 deaths, with 494 reported as death without specifying the cause. Deaths were most commonly attributed to ALS, disease progression, respiratory failure, or pneumonia. Review for administration-site reactions revealed 95 AEs, including 34 site infections, with 22 SAEs (all non-fatal). Five non-fatal SAEs of anaphylaxis were reported.

Conclusion In the postmarketing reporting to date, no new safety signals were identified beyond those already known from the edaravone clinical trial program.

Key Points

Postmarketing safety analysis was conducted of edaravone usage in patients with ALS in the US.

In the postmarketing reporting to date, no new safety signals were identified beyond those already known from the edaravone clinical trial program.

1 Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neuromuscular disease characterized by the degeneration of motor neurons in the brain and spinal cord [1].

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Patients with ALS typically have a mortality rate of 50% within 30 months of symptom onset [2] and a diagnosis is on average reached after 10–12 months [3, 4], shortening the potential treatment time period. There is no cure for ALS; however, two therapies have been approved for treating ALS in a variety of countries: riluzole and edaravone (Radicava®) [5, 6]. Edaravone (Radicava®) (Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan) was approved in the United States for the treatment of ALS in adult patients in May 2017, and became available to patients in August 2017 [5]. It was shown in a clinical trial to slow the rate of physical functional decline in ALS, as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) [7]. Edaravone (Radicava®) can be administered by infusion at clinic sites and infusion centers or at home. It is administered once daily in a 60-mg dose over 60 min [5]. A recent analysis of postmarketing pharmacovigilance data for the first year of edaravone (Radicava®) use indicated that the most commonly reported adverse events (AEs) were not qualitatively different from those reported in other ALS trials or from ALS disease progression [8]. This current publication contains previously unpublished details from the postmarketing pharmacovigilance data during the first 3 years of availability of edaravone (Radicava®) in the US, with a focus on infusion-related safety data.

2 Methods

2.1 Edaravone (Radicava®)

Edaravone (Radicava®) use was calculated based on US prescription and usage data. The sources of prescription and usage data were collected from the Mitsubishi Tanabe Pharma America, Inc. patient hub (McKesson Searchlight) plus data from a prescription data aggregator (ValueCentric) that collects data for prescriptions that are not processed through the patient hub (e.g., the Veterans Health Administration and integrated managed care consortia such as Kaiser Permanente).

2.2 Pharmacovigilance

Cumulative patient cases and AEs were identified from a postmarketing safety database from August 8, 2017 through August 7, 2020 (cutoff date that was set to include 3 years of pharmacovigilance data). The Mitsubishi Tanabe Pharma Pharmacovigilance system assesses patient safety throughout the edaravone (Radicava®) life cycle by monitoring all potential sources of AEs. AEs are collected, processed, analyzed, and reported via the Global Safety Database repository, which collects data worldwide; however, this report includes only information for AEs reported in the United States. All AEs and serious AEs (SAEs), including deaths, whether attributed to edaravone (Radicava®) or not, are collected and captured in the Global Safety Database. The Global Safety Database repository includes AE safety reports received by Mitsubishi Tanabe Pharma from both spontaneous (unprompted) and solicited sources. Solicited sources include Mitsubishi Tanabe Pharma-sponsored programs, such as patient support programs. Additionally, AE safety reports are obtained less frequently from sources such as the FDA MedWatch program and articles published in the medical literature. Reports can be submitted by a variety of personnel, including physicians, nurses, and patients.

3 Results

As of October 3, 2020, 3 years post-launch, 5207 ALS patients had been administered edaravone (Radicava®) in the United States.

3.1 Edaravone (Radicava®) Safety Reports Through August 7, 2020

There were 3152 cases reported by US postmarketing sources by the cutoff date of August 7, 2020. Of the 3152 cases, there were 6235 total AEs, including 1583 that were SAEs (death, life-threatening, hospitalization, disability, other medically significant event) (Table 1).

3.2 Most Commonly Reported Adverse Events and Serious Adverse Events

The most commonly reported AEs (≥ 50 reports) were death (not specified), drug ineffective, disease progression, therapeutic response unexpected, fall, asthenia, fatigue, muscular weakness, gait disturbance, and dyspnea (Table 1). The most commonly reported SAEs (≥ 15 reports) were death (not specified), pneumonia, disease progression, amyotrophic lateral sclerosis, fall, dyspnea, respiratory failure, device-related infection, hospitalization, and injection-site infection (Table 1).

There were 687 cumulative death cases, with the most common reports consisting of death (without specifying the fatal condition), amyotrophic lateral sclerosis, disease progression, respiratory failure, pneumonia, respiratory disorder, myocardial infarction, cardiac arrest, dyspnea, and condition aggravated (Table 1).

Review for serious anaphylactic reaction/hypersensitivity revealed five reports (all non-fatal) from patients who experienced trouble breathing, swallowing, itching, and/or swelling; most of which resolved with antihistamine and/or steroid treatment.

Table 1 Adverse events (with ≥ 50 events reported), serious adverse events (with ≥ 15 events reported), and fatal adverse events (with ≥ 5 events reported)

	AE reports (*N* = 3152)	SAE reports (*N* = 1153)	Fatal AE reports (*N* = 687)
Total events reported	**6235**	**1583**	**739**
Death	494	494	494
Drug ineffective	417	4	4
Disease progression	381	73	56
Therapeutic response unexpected	300	0	0
Fall	239	54	0
Asthenia	207	12	4
Fatigue	195	2	1
Muscular weakness	191	7	0
Gait disturbance	143	2	0
Dyspnea	128	42	5
Condition aggravated	127	9	5
Headache	87	3	0
Pneumonia	84	83	19
Speech disorder	77	0	0
Amyotrophic lateral sclerosis	63	62	61
Aphasia	59	2	0
Weight decreased	53	4	0
Energy increased	51	0	0
Product dose omission	50	0	0
Respiratory failure	36	36	26
Respiratory disorder	34	12	7
Device-related infection	24	20	0
Hospitalization	17	17	0
Injection-site infection	18	15	0
Myocardial infarction	11	11	6
Cardiac arrest	9	9	5

AE adverse event, *SAE* serious adverse event

There were three serious hepatic events (one hepatic enzyme increased, one liver disorder, one hepatomegaly) and four serious renal events (two renal failure, one azotemia, one acute kidney injury) reported. Review for serious venous thromboembolic events revealed 14 pulmonary embolisms, 14 thrombosis unspecified, 12 deep vein thrombosis, and three pulmonary thrombosis.

3.3 Administration-Site Reactions

Review for administration-site reactions revealed 95 AEs in total (Table 2). The system grouped reactions into the following three categories: catheter, injection, and infusion. Site infections from all three categories comprised 34 AEs of which 22 were SAEs (all non-fatal). Of these 34 site infections, 12 were reported as resolved or resolving, 13 were unknown, and nine were not recovered. The time to onset of the infections ranged from 3 days to 1 year and 2 months after initiation of therapy.

There were 61 reports of site-reaction AEs that were not related to infections, and one of these was an SAE of catheter-site thrombosis which was treated with port placement. Of these 61 AEs, 25 were reported as resolved or resolving, 25 were unknown, and 11 were not recovered. The time to onset ranged from 1 day to 7 months after initiation of therapy.

4 Discussion

Because all the registrational clinical studies for edaravone (Radicava®) were conducted in Japan, there is considerable interest in how this drug is being utilized in clinical practice in the United States and, in particular, its safety in the real-world setting. From this data set, which most likely reflects an underreporting of events, the most commonly reported AEs included death (not specified), drug ineffective, disease progression, therapeutic response unexpected, fall, asthenia,

Table 2 Site reactions reported

Preferred term	AEs	SAEs
Catheter-site events	38	6
Catheter-site infection	10	5
Catheter-site swelling	6	0
Catheter-site erythema	4	0
Catheter-site rash	3	0
Catheter-site pain	2	0
Catheter-site discharge	2	0
Catheter-site pruritus	2	0
Catheter-site thrombosis	2	1
Catheter-site hemorrhage	1	0
Catheter-site hypersensitivity	1	0
Catheter-site irritation	1	0
Catheter-site related reaction	1	0
Catheter-site vesicles	1	0
Catheter-site cellulitis	1	0
Catheter-site pustule	1	0
Injection-site events	42	15
Injection-site infection	18	15
Injection-site rash	5	0
Injection-site bruising	4	0
Injection-site pain	3	0
Injection-site hemorrhage	2	0
Injection-site pruritis	2	0
Injection-site erythema	1	0
Injection-site extravasation	1	0
Injection-site hypersensitivity	1	0
Injection-site irritation	1	0
Injection-site edema	1	0
Injection-site pustule	1	0
Injection-site swelling	1	0
Injection-related reaction	1	0
Infusion-site events	15	2
Infusion-site extravasation	4	0
Infusion-site pain	4	0
Infusion-site infection	3	2
Infusion-site bruising	1	0
Infusion-site hemorrhage	1	0
Infusion-site pruritus	1	0
Infusion-related reaction	1	0
Total patients	83	23

AE adverse event, *SAE* serious adverse event

fatigue, muscular weakness, gait disturbance, disease progression, muscular weakness, fall, and dyspnea.

The AEs reported not typically seen in other ALS studies include the five serious cases of an anaphylaxis. Anaphylactic reactions were not seen in the randomized controlled ALS trials that were conducted in Japan. In the setting of the use of edaravone (Radicut®) in acute stroke in Japan, there have been postmarketing reports of AEs that may suggest anaphylaxis reactions, although determination of etiology may be difficult due to the clinical course and management of the underlying acute stroke. It has been postulated that one possible cause of allergic reactions may be the bisulfite stabilizing agent in the product. The occurrence of anaphylaxis or other reactions following parenteral injection of sulfites in the general population is unknown [9]. When evaluated, there are unique features of the interaction of bisulfites with vascular tissue [10, 11]. The occurrence of bisulfite reactions is higher in special populations such as asthmatic patients or patients with chronic urticaria [12, 13].

Anaphylaxis was not reported in the phase III clinical trials in Japan where vitamin B12 is commonly used as a treatment for ALS [7, 14, 15]. Vitamin B12 has been used to mitigate the immediate sensitivity to bisulfite based on controlled clinical studies and trials of its effectiveness [16–18]. One event of anaphylaxis was reported in the pharmacovigilance safety review for the first year after edaravone (Radicava®) launch [8]. Because of reports in the literature of at least two populations with increased sensitivity to sulfites, we recommend evaluating ALS patients for asthma as well as chronic urticaria and assessing their need for vitamin B12 supplementation that might mitigate allergic and anaphylactic responses to sulfites. Prevalence of asthma with ALS has been reported between 25 and 31% [19, 20], whereas there has been only one reported case of urticaria and ALS [21]. Anaphylaxis immediate sensitivity-type reactions in ALS patients have been reported following injections of human myelin and penicillin as well as oral levamisole [22–24].

Reports of pneumonia in large groups of ALS patients without edaravone (Radicava®) treatment help assess the occurrence of pneumonia in ALS patients without treatment with edaravone (Radicava®) [3]. Pneumonia occurred without edaravone (Radicava®) in the placebo-treated arm of MCI186-19 and in the combined placebo-treated arms of the MCI186-16, -18, and -19 clinical trials [7, 15]. Pneumonia occurred in edaravone (Radicava®)-treated ALS patients participating in the MCI186-19 open-label extension arms. In the first year after edaravone (Radicava®) launch in the US, pneumonia was reported at a similar prevalence as in this current analysis [8]. Because of the large range of reported cases of pneumonia in ALS patients without edaravone (Radicava®) and the possibility of underreporting in this current analysis, we believe that there is no increased reporting of pneumonia in the two post-launch pharmacovigilance analyses of edaravone (Radicava®) in the US.

Site reactions ($n = 95$) are also notable as they would not occur in ALS outside of the administration of intravenous (IV) treatment. It is worth noting that the administration protocols utilized in the United States are different than the protocol used in the randomized control trials in Japan where

only peripheral IVs were used for administration. The US administration protocols increase the risk of complications but reduce the patient burden.

All AE and SAE mentions of catheter, injection-site, and infusion-site infections with edaravone (Radicava®) over 38 months appear to be less than all mentions of line infection with ceftriaxone and placebo over 33 months [25]. In the supplement to the original peer-reviewed report of the ceftriaxone randomized placebo-controlled clinical trial, all mentions of line infection with ceftriaxone over 33 months were less than all mentions of line infection with placebo over 33 months, which was one of the reasons that the clinical trial was stopped, because there was no benefit of ceftriaxone compared with placebo injection on survival or function due to ALS while placebo patients had increased prevalence of line infections [25].

The AE mentions of catheter, injection-site, and infusion-site infections in the current analysis and in the previous analysis for the first year of treatment [8] appear to be lower than the AE mentions of line infections in the placebo group of the ceftriaxone clinical trial [25]. The AE mentions of line infections also appear to be lower than the rates of line infection from central venous catheter placement in home infusion settings in the US, Spain, Denmark, and Canada [26–30]. Previous concern regarding the risk–benefit assessment of edaravone (Radicava®) treatment from a Canadian Medical Center may have been based on the high risk of line infections being observed in Canada [31–34].

Thrombotic events on edaravone (Radicava®) with or without riluzole reported in this 3-year analysis were similar to the report for the 1-year 2017–2018 pharmacovigilance safety database [8]. Thrombotic events on edaravone (Radicava®) in the first six cycles of edaravone (Radicava®) treatment in MCI186-16, -18, and -19 clinical trials combined were not present while there were thrombotic events in the placebo-treated ALS subjects. Thrombotic events did not occur in MCI186-19 in the double-blind or open-label extension cohorts. There was no apparent increase in thrombotic events between the 1-year and 3-year pharmacovigilance safety reports.

Rash, without mention of anaphylactoid type reaction, on edaravone (Radicava®) with or without riluzole reported in this analysis was similar to that reported for the 1-year 2017–2018 pharmacovigilance safety database [8], and may have been lower than that reported for the MCI186-19 clinical trial [7]. Further analysis is ongoing because rash, without mention of anaphylactoid type reaction, on riluzole has been reported [35, 36].

The other reported AEs appeared to be associated with (or after review, could be attributed to) the underlying ALS disease condition. The nature of this data set and how the information was collected most likely results in a significant underreporting of AEs. Fatigue ($n = 195$) is a symptom reported by 90% of ALS patients [37]. Asthenia ($n = 207$) is a synonym of fatigue and no specific definition was provided for the protocol; it has not been a symptom studied specifically in ALS. Apathy is another symptom that has been studied in ALS that we recognize as different from fatigue and possibly could be reported as asthenia; it is estimated to affect roughly one-third of patients [38]. Muscular weakness ($n = 191$) is a defining feature of ALS and it is expected to progressively affect all patients. Falls ($n = 239$) are a common occurrence in ALS with 25.1% of a recent US cohort reporting the symptom [3]. Gait disturbance ($n = 143$) to the point of needing a wheelchair or scooter was reported at 32.8% in the same cohort, deep venous thrombosis ($n = 12$) was experienced by 3.9% [3], and dyspnea ($n = 128$) was reported by 66% in another cross-sectional dataset [37]. Disease progression ($n = 381$) is also an obligate feature of ALS with current therapies and there has not been a suggestion that edaravone can stop disease progression; it is ineffective as a cure of ALS [7]. The response "therapeutic response unexpected" ($n = 300$) primarily described ALS/neurological symptom improvement, including improvement in energy, strength, muscular twitching/cramping, range of motion, and speech.

Compared with the frequencies in the literature for these commonly reported AEs, they appear to be less frequently reported in the edaravone (Radicava®) users than in a general ALS population. We do not believe that this is necessarily due to an effect of edaravone (Radicava®) to reduce these events, we hold it more likely to be due to ascertainment bias. Thus, no new safety signals were identified beyond what has been previously recognized. In addition, because edaravone (Radicava®) is not a cure, nor expected to reverse the disease process, these aforementioned AEs are anticipated in a pharmacovigilance program.

Because of the interest in edaravone (Radicava®) use in ALS, several retrospective analyses and literature reviews have been published. A recent literature review found that some of the retrospective studies supported the benefit of edaravone (Radicava®) in slowing disease progression (e.g., a study in Asia [39]), while other single-arm pragmatic clinical studies that used unspecified generic edaravone formulations (not edaravone [Radicava®]) did not provide conclusive results (including studies in Europe [40] and Israel [41]) [42].

The limitations stemming from voluntary reporting and occasional missing information should be considered when interpreting these results. However, administration of edaravone (Radicava®) as an IV medication provides multiple points of contact with health care providers, which may improve the reporting of AEs. Moreover, Mitsubishi Tanabe Pharma America, Inc. has a patient services program in place that interfaces with patients and establishes another potential avenue for AE reporting, reducing the risk that an

unexpected AE is commonly occurring. Additional limitations of this study stem from a lack of a control population of patients and the lack of detailed information about most of the AEs that were reported.

Additional information on the use of edaravone (Radicava®) in patients with ALS will come from ongoing programs and future data-gathering initiatives. For example, patient registries are currently being conducted in Japan and South Korea with patients with ALS who are receiving edaravone (Radicava®) therapy [43]. The most recent report from the Japanese SUNRISE registry included 805 patients receiving edaravone (Radicava®) and, in accord with this current analysis, there were no unexpected safety signals or inconsistencies with the clinical trials [43]. In addition, a phase IV clinical study in the US started in 2019. This is a biomarker study, analyzing the effects of edaravone (Radicava®) therapy on a variety of biomarkers related to oxidative stress and other processes potentially involved in ALS [44].

As discussed in this article, several of the reported adverse events were related to the IV administration of edaravone. As an alternative to the IV formulation, an oral formulation of edaravone is under development [45, 46].

5 Conclusion

In this 3-year postmarketing reporting, no new safety signals were identified beyond those already known from the edaravone (Radicava®) clinical trial program. Prevalence of anaphylaxis and potential treatable causes were identified. Infectious complications of the central venous catheter delivery systems were noted but at apparently reduced rates compared with literature reports. Pneumonia rates were not increased in treated patients.

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Declarations

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Conflict of interest AG, BRB, and BO are consultants for MTPA. BW, AK, MJ, and LB are employees of Mitsubishi Tanabe Pharma Development America, Inc. SA is an employee of Mitsubishi Tanabe Pharma America, Inc.

Ethics approval Not applicable.

Consent to participate Not applicable.

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