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ORIGINAL ARTICLE

Logistics and safety of edaravone treatment for amyotrophic lateral sclerosis: experience in Argentina

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Abstract

Since 2015, edaravone is the second drug available for the treatment of Amyotrophic lateral sclerosis (ALS). In this study we analyzed the characteristics and experience of ALS patients treated with this new medication in our country. Sixteen ALS patients were treated with edaravone infusions in three ALS clinics. Most of them were male, had a spinal onset of the disease and a definite diagnosis of ALS. Mean age at first infusion was 53.5 years. Since the diagnosis of ALS, delay in starting treatment with edaravone was five times greater than that of riluzole. Edaravone therapy was usually initiated at a health care facility and was followed by domiciliary cycles. Adverse effects and the need of a special catheter for infusion were rare. Access to edaravone through health insurance was possible in only 43.8% of patients. Altogether, treatment access was limited but feasible and edaravone was well tolerated.

Keywords Amyotrophic lateral sclerosis · Edaravone · Adverse effects · Safety

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting upper and lower motor neurons. Patients develop progressive muscular weakness which in the majority of cases leads to death in a three-year period [1, 2]. In 1995, riluzole was approved as treatment aiming to delay the clinical course of this disease [3]. It was the only available option until recently, since after a series of trials conducted in Japan, edaravone emerged as a medication related to a mild retardation of functional decline in ALS [4–6].

Edaravone is a 2-pyrazolin-5-one derivative with reactive oxygen species scavenging proprieties [7]. In Japan, it has been used since 2001 as a neuroprotective drug for acute ischemic stroke treatment [8]. Edaravone was first suggested as a possible ALS treatment in a phase II trial in 2006 [6]. Its observations gave rise to a phase III trial that demonstrated, after a 6-month period, a reduction of approximately two points of the revised ALS functional rating scale (ALSFRS-R) decline among treated ALS patients with disease duration of less than 2 years, scores of at least two points in every item of the ALSFRS-R and FVC (forced vital capacity) of at least 80% [4, 9–11]. It was since approved for ALS treatment in Japan (2015) [12], Korea (2015) [13], Italy (2017) [12], USA (2017) [14]and Canada [15]. Although not yet marketed in Argentina, its importation is regulated and feasible. With the aim of describing the experience with edaravone in our country, we analyzed the demographics of the ALS patients that have so far received this medication in three ALS clinics, along with its safety.

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Methods

Medical records of ALS patients treated with edaravone in three ALS clinics were reviewed. All of them had a definite or probable ALS diagnosis (according to El Escorial criteria), FVC greater than or equal to 80%, scored at least two points in every item of the ALSFRS-R and a symptom-onset period of less than 2 years at the beginning of treatment with edaravone. Data such as age, gender, site and date of onset of symptoms, time since treatment indication to first infusion, infusion place (clinic or patient's home) and adverse effects were recollected. Categorical variables are expressed in number and percentage and continuous ones in mean and standard deviation (or median and interquartile range if the analytical or graphic evaluation showed lack of normality).

Results

Sixteen patients were treated with edaravone (Table 1). Most of them were male ($n=14$, 87.5%), with a mean age of 53.5 years (SD 14.87) at first treatment infusion. There were only two patients with bulbar onset (12.5%) and the majority ($n=11$, 68.8%) had a definite ALS diagnosis according to El Escorial criteria. Mean time since the onset of symptoms to the diagnosis was 10.88 months (SD 9.47). All but one patient were also treated with riluzole. Mean time since diagnosis to starting treatment was 3.7 months (SD 2.8) for riluzole and 19.8 months (SD 19.8) for edaravone. The initial infusion of edaravone was usually received at a health care facility (75%) and was followed by domiciliary cycles (87.5%). Most patients received the medication through a peripheral venous catheter with only one of them (0.06%) needing a port-a-cath for treatment infusion. Half the patients received five or more cycles of edaravone. With regards to mild adverse effects, one patient suffered from thrombophlebitis, another experienced a brief flu-like syndrome after every infusion and a third one had lower limb pain during infusion, which was alleviated in the following cycles with pre-treatment with antihistamines. Three patients underwent tracheostomy (18.8%), one of which died shortly after and accounts for one of the three deaths (18.8%) in this cohort. Two patients stopped treatment due to drug ineffectiveness. Nine patients received edaravone though donations or private funding (56.2%) while seven patients (43.8%) did through their health insurance.

Discussion

Since the 1980s, more than 50 trials have failed in their quest for a disease modifying drug for ALS treatment [7, 16]. Until recently, riluzole was the only available medication, providing a mild benefit in survival. It was initially described for a subset of patients without severe respiratory impairment [3, 5] but a recent analysis also showed benefit for more affected patients [17]. More than 20 years elapsed since a second medication emerged from a phase III trial. Nevertheless, edaravone seems to only benefit a subset of patients [4] which is estimated to represent 7% of ALS cases [16]. Moreover, its beneficial effect in the reduction of the decline in ALSFRS-R in the mentioned subgroup needs to be confirmed in larger trials [18] and there is still controversy with regards to its impact in FVC, time to tracheostomy or survival [19–21]. Nonetheless, it is already being used as standard ALS treatment in several countries and few reports have been published notifying the real-life experience.

In one of them, Fortuna et al. [12] reported the efficacy and safety in 31 treated patients compared to historical records. Outcomes were similar in both populations and there were two patients with deep venous thrombosis and one with sudden death in the edaravone group. Abrahams et al. [22] reported their experience with 22 unselected ALS patients treated with edaravone. No clinical benefit was observed either but one third of the patients suffered respiratory complications during or shortly after the drug's infusion. In the series of Jackson et al. [14] in which several specialized centers in ALS were asked about the prescription of edaravone to ALS patients, only 53% of the physicians had ever indicated this medication. They also analyzed the post-marketing safety reports of 3000 patients who had received it. Among them, 1006 had discontinued the medication due to disease progression. Adverse effects attributable to the drug were hypersensitivity, infection at the infusion site and deep vein thrombosis. Park et al. [13] also reported adverse events with the use of edaravone in 22 ALS patients. Although there were no major complications, two patients had minor allergic reactions during the infusion, three insomnia, two headache and one transient leukopenia.

Our experience is limited since the local regulatory authorities have not yet approved its commercialization in our country and the drug must be imported through a special procedure. Ethical issues of access to non-registered treatments in Argentina are in continuous debate. The Compassive treatment access program allows the importation and use of a determinate medication by a patient under certain circumstances but does not provide the economical means for it. In our series, the patients that received the medication through donation or personal savings were those without health insurance.

As reported in the USA study [14], riluzole treatment was started earlier than edaravone. However, unlike in their series, 94% of our patients received both medications. We believe the treatment delay in our case was mainly due to treatment-access difficulties. Unlike Jackson et al. [14], although the first infusion was received at a health care facility, the following

Table 1 Patients' demographics and experience with edaravone

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13	Pt 14	Pt 15	Pt 16
Sex	M	M	M	M	M	M	M	M	F	M	M	M	F	M	M	M
Age at edaravone infusion	66	48	58	74	78	52	64	32	45	49	56	29	42	35	56	72
Escorial criteria	D	P	D	D	P	P	D	D	D	D	P	D	D	D	P	D
Time between the onset of symptoms and diagnosis (months)	6	9	7	12	6	4	18	12	5	11	42	14	1	15	5	7
Riluzole use	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time between diagnosis and starting treatment with riluzole (months)	0	1	12	2	2	3	3	2	2	6	2	1	2	2	5	1
Time between diagnosis and starting treatment with edaravone (months)	32	3	12	24	15	3	8	10	24	39	83	14	6	25	5	14
First edaravone infusion at health care facility	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes
Follow up infusions at heath care facility	No	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No	No	Yes	No
Use of peripheral venous catheter for edaravone infusion	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total infusions of edaravone	3	4	2	2	6	3	4	6	3	6	12	3	18	6	5	6
Edaravone side effects	No	Flu-like	No	No	No	No	No	No	Limb pain	No	No	No	No	No	No	Thrombophlebitis
Tracheostomy	No	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	No
Death	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Edaravone treatment through health insurance	No	No	Yes	No	No	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes

Pt Patient, *M* male, *F* female, *D* definite, *P* probable

cycles were performed at the patient's home. As in the Italian publication [12] and once again unlike the USA report [14], most of our patients received edaravone though a peripheral access. We presume these differences are probably due to local regulations or even to the optimization of the process when involving a larger number of people. Our average of cycles per patient is similar to that reported by Jackson et al. [14]. We had the largest percentage of deaths (18.8%) since the other cohorts reported 0% [13], 3% [12], 5% [14] and 14% [22]. We initially presumed that the high incidence in the cohort from Israel was a consequence of their unselected population, hence including patients with more advanced disease. However, Park et al. also had broader inclusion criteria and after the same period of observation (a mean of 6 months), they did not report any deaths. It is likely then that genetic variables (that can contribute to more aggressive diseases) and not only the severity of disease when starting edaravone are associated with this outcome. It can also be a sampling peculiarity since our cohort was a small one. We believe larger studies are needed to accurately interpret this finding. Finally, side effects were infrequent and included infusion site mild infection such as in the American cohort [14] and hypersensibility reactions like in the Italian, American and Korean cohorts [12–14].

In sum, a total of 16 patients with ALS meeting the edaravone indication criteria were able to receive the medication. This was financially limited since less than half of them received treatment through their health insurance. After the first supervised infusion, most patients were treated at their home and through a peripheral catheter. In this group of patients, edaravone was well tolerated with mild and infrequent side effects.

Author contributions GR conceived the presented idea. CQ, MB, RR and GR treated and registered the patients. All authors discussed the results and contributed to the final manuscript.

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Compliance with ethical standards

Conflict of interest None.

Ethics approval This study was approved by the Ethics committee of the three ALS clinics involved.

Consent to participate All patients signed an informed consent.

Consent for publication All patients signed an informed consent.

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