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Safety and efficacy of edaravone compared to historical controls in patients with amyotrophic lateral sclerosis from North-Eastern Italy

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ABSTRACT

Objective: To test efficacy and tolerability of edaravone in patients with amyotrophic lateral sclerosis (ALS) originating from North-Eastern Italy.
Methods: We compared 3-month and 6-month changes of ALSFRS-R score, FVC value, and MRC score of 31 consecutive patients with ALS who were treated with edaravone to those of 50 historical ALS patients who were not treated with edaravone.
Results: No significant difference for any functional measures was found between the two groups at each time point as compared to baseline. In treated patients, we also observed creatinine values to significantly decrease at 3 and 6 months ($p = 0.0078$ and 0.030, respectively) and ALSAQ5 score to significantly increase (i.e. worse quality of life) at 3 and 6 months ($p = 0.0005$ and 0.0078, respectively). Yet, we observed an overall safety of the medication over the 6-month period of observation.
Conclusions: Our retrospective study suggests no benefit of edaravone on ALS in populations of Caucasian ancestry.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease characterized by progressive loss of upper and lower motor neurons leading to death within 2–5 years after diagnosis [1,2]. Cognitive dysfunctions occur in 20%–50% of cases, whereas 5%–15% of patients develop overt frontotemporal dementia (FTD) [3,4]. Approximately 5% to 10% of ALS cases are familial [5–7]. The cause of ALS still remains unknown, except for familial forms [2,6,8].

Several pathogenic mechanisms have been postulated in ALS, including oxidative stress due to oxygen radicals [9,10]. In 2006, an open-label phase 2 study conducted in a small group of Japanese patients with ALS demonstrated that edaravone, a free radical scavenger [11], could safely slow motor decline with a concurrent cerebrospinal fluid (CSF) reduction of 3-nytrothirosine (3-NT), a marker of oxidative cellular damage [12,13] Then, a confirmatory double-blind, parallel-group, placebo-controlled study enrolling 199 ALS patients was set up. The study consisted of a 12-week pre-observation period followed by a 24-week treatment period. Treated patients (100) received 60 mg intravenous edaravone with a monthly dosing scheme including two weeks on and two weeks off. Unfortunately, at the end of the study no significant difference in functional disability progression, as measured by changes in the revised ALS Functional Rating Scale (ALSFRS-R) score, was observed between patients treated with edaravone and those on placebo. Yet, adverse events were limited and similar between the two study groups [14]. A subsequent post-hoc analysis of this study data suggested a potential benefit of edaravone in early-stage patients with scores of 2 or more on all items of ALSFRS-R, forced vital capacity (FVC) of at least 80% at baseline, and disease duration of 2 years or less. To substantiate these findings, 137 Japanese ALS patients meeting the above criteria were further randomized (1:1) to receive edaravone or placebo for 24 weeks, according to the same dosing scheme of the previous trial. The final results confirmed a significant reduction of ALSFRS-R decline, although without any effect on measures such as

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[2] G.S., E.P., and A.M. designed the research; A.F., M.G. and I.M. performed evaluations; L.B. conducted statistical analysis; G.S., C.B. and L.B. performed data analysis.; Medical Doctors belonging to EDARAVONE STUDY GROUP performed pre-starting evaluations and strict patients' follow up. All authors wrote and reviewed the article.

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strength or FVC, in this subset of patients compared to placebo group [15]. These positive outcomes, along with the overall safety of the drug, paved the way to edaravone approval as a therapeutic option for ALS in Japan (2015) [16], United States (2017) [17], and Italy (2017) [18].

Although relevant ethnic differences in the pharmacokinetic profiles of edaravone have been ruled out [19], no clinical data is available on the use of edaravone in populations other than Japanese, including Caucasians. Therefore, we compared the clinical outcome of ALS patients from the Northeastern area of Italy, treated with edaravone at our Motor Neuron Disease Clinic of the University of Padova (Italy), with natural history data from the same Center.

2. Methods

After edaravone formal authorization as an ALS therapy by the Italian Medicines Agency (AIFA, public institution responsible for the regulatory activity of drugs in Italy) in July 2017 [18], 31 consecutive ALS patients were admitted to the treatment at the Motor Neuron Disease Clinic of the Department of Neurosciences, University of Padova (Italy) until May 2018. They all met the following inclusion criteria issued by AIFA in line with previous evidence from the literature: [15] 1. Age between 18 and 75 years; 2. a defined or probable diagnosis of ALS according to the revised El Escorial criteria; 2.a score of at least ≥2 per item of ALSFRS-R; 3. a Forced Vital Capacity (FVC) ≥ 80% of predicted; 4. disease duration ≤2 years; 5. a decrease of 1–4 points in ALSFRS-R score during the previous 12 week-period.

The presence of other neurological disorders (including cognitive impairment), creatinine clearance ≤50 ml/min, severe systemic diseases contraindicating the drug in the physician's opinion, ongoing pregnancy and inability to give an adequate informed consent were considered exclusion criteria. Patients on riluzole had to continue the drug at the same daily posology; those who were not on riluzole were asked not to start this medication.

Sixty mg edaravone (Avone®, a commercially available edaravone bioequivalent of Radicut®) was initially administered for 14 consecutive days followed by a 2-week drug-free period (first cycle). Subsequently, edavarone was administered for 5 days a week for 2 weeks each month followed by a 2-week drug-free period (subsequent cycles) according to the standard protocol [18].

Before starting edaravone and every three months thereafter, each patient underwent the following evaluations: 1. Vital signs; 2. Complete physical exam; 3. Blood chemistry including blood cells count, routine coagulation parameters, transaminases, direct and indirect bilirubin, BUN, creatinine, creatine-kinase, potassium, sodium, chloride, magnesium; 4. Functional assessment using the ALSFRS-R scale and manual muscle strength testing according to the Medical Research Council (MRC): score from 0 (absence of movement) to 5 (full strength). Muscles evaluated were: deltoid, triceps and biceps brachii, finger and carpi extensors, thumb adductor, thigh flexor, knee extensor, ankle extensor and allucis extensor. All muscles were tested bilaterally. We considered the total MRC score ranging from 0 to 100. Each functional test was performed by a Neurologist with expertise in neuromuscular diseases; 5. Respiratory function evaluation by standard spirometry and recording FVC expressed as a percentage of predicted; 6. Quality of Life assessment by the Amyotrophic Lateral Sclerosis Quality of Life Scale-5 (ALSAQ-5); 6. Recording of adverse events. To further monitor edaravone safety, patients received a check-up phone call by the treating Neurologist every week. A treatment-period of 6 months was considered.

For comparison, we generated a historical control cohort based on our Motor Neuron Disease Clinic database established since 2005, considering all ALS patients who fulfilled the above inclusion and exclusion criteria for edaravone treatment. We selected patients for whom at least three consecutive quarterly visits, including ALSFRS-R score, FVC value, MRC score, were available. Patients who participated in other interventional programs (with the exception of riluzole) were excluded.

This study was approved by the local Institutional Ethics Committee (authorization code AOP1619).

2.1. Statistical analysis

Quantitative variables were summarized as mean ± standard deviation and/or median and ranges. Baseline evaluation was defined as start of edaravone for treated patients, and first evaluation after diagnosis for controls. Quantitative variable distributions were compared between groups by Mann-Whitney tests for independent groups, while categorical variables were compared by χ^2 or Fisher exact test as appropriate. Outcomes changes at 3 and 6 months were compared between groups by ANCOVA models, including covariates for: sex, age, disease duration, spinal vs. bulbar onset, and riluzole treatment (on vs off). Six-month changes of ALSAQ5 score and creatinine values within the treated group was evaluated by paired Wilcoxon-Mann-Whitney test. Statistical significance was set at $p < 0.05$, and a formal correction for multiple testing was not applied, considered that multiple disease outcomes are inter-correlated, rather than independent.

3. Results

Table 1 summarizes baseline characteristics of the 31 patients included in the edaravone protocol and 50 selected controls from our Motor Neuron Disease database. As shown, the two groups did not differ for any demographic and clinical features except for age and disease duration, both higher in edaravone group.

To evaluate edaravone efficacy, we compared 3-month and 6-month

Table 1
Demographics and baseline characteristics of treated and control patients.

N		Treated group	Control group	p-Value[a]
		31	50	
Age (years)	Mean	65.0 ± 11.7	60.5 ± 10.3	p = 0.047
	Median	67	62, 5	
	Range	(26; 81)	(23; 80)	
Year of birth	Mean	1953 ± 12	1950 ± 10	p = n.s.
	Median	1951	1948	
	Range	(1937; 1992)	(1934; 1987)	
Disease duration (months)	Mean	17.8 ± 6.0	11.7 ± 5.8	p < 0.001
	Median	20	12	
	Range	(6; 24)	(3; 24)	
Sex	F	15 (48%)	19 (38%)	p = n.s.
	M	16 (52%)	31 (62%)	
Riluzole	On	31 (100%)	46 (92%)	p = n.s.
	Off	0 (0%)	4 (8%)	
Onset	Bulbar	13 (42%)	14 (28%)	p = n.s.
	Spinal	18 (58%)	36 (72%)	
ALSFRS-R total score	Mean	40.94 ± 3.63	42.47 ± 2.34	p = n.s.
	Median	41	43	
	Range	(34; 46)	(35; 46)	
FVC (%)	Mean	1.02 ± 0.13	0.99 ± 0.17	p = n.s.
	Median	1.02	0.93	
	Range	(0.80; 1.25)	(0.82; 1.60)	
MRC score	Mean	96.41 ± 12.42	99.94 ± 9.16	p = n.s.
	Median	100.00	102	
	Range	(60.75; 110.00)	(77.00; 110.00)	
Creatinine (mg/dl)	Mean	31	–	–
	Median	0.77 ± 0.20	–	
	Range	0.71 (0.27; 1.34)	–	
ALSAQ-5	Mean	31	–	–
	Median	6.16 ± 3.34	–	
	Range	6 (0; 12)	–	

N: numbers; ALSFRSR: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; FVC: forced vital capacity; MRC: Medical Research Council; ALSAQ-5: Amyotrophic Lateral Sclerosis Assessment Questionnaire.

[a] Wilcoxon-Mann-Whitney for comparison of quantitative variant distributions; Fisher exact test for comparison of categorical distributions.

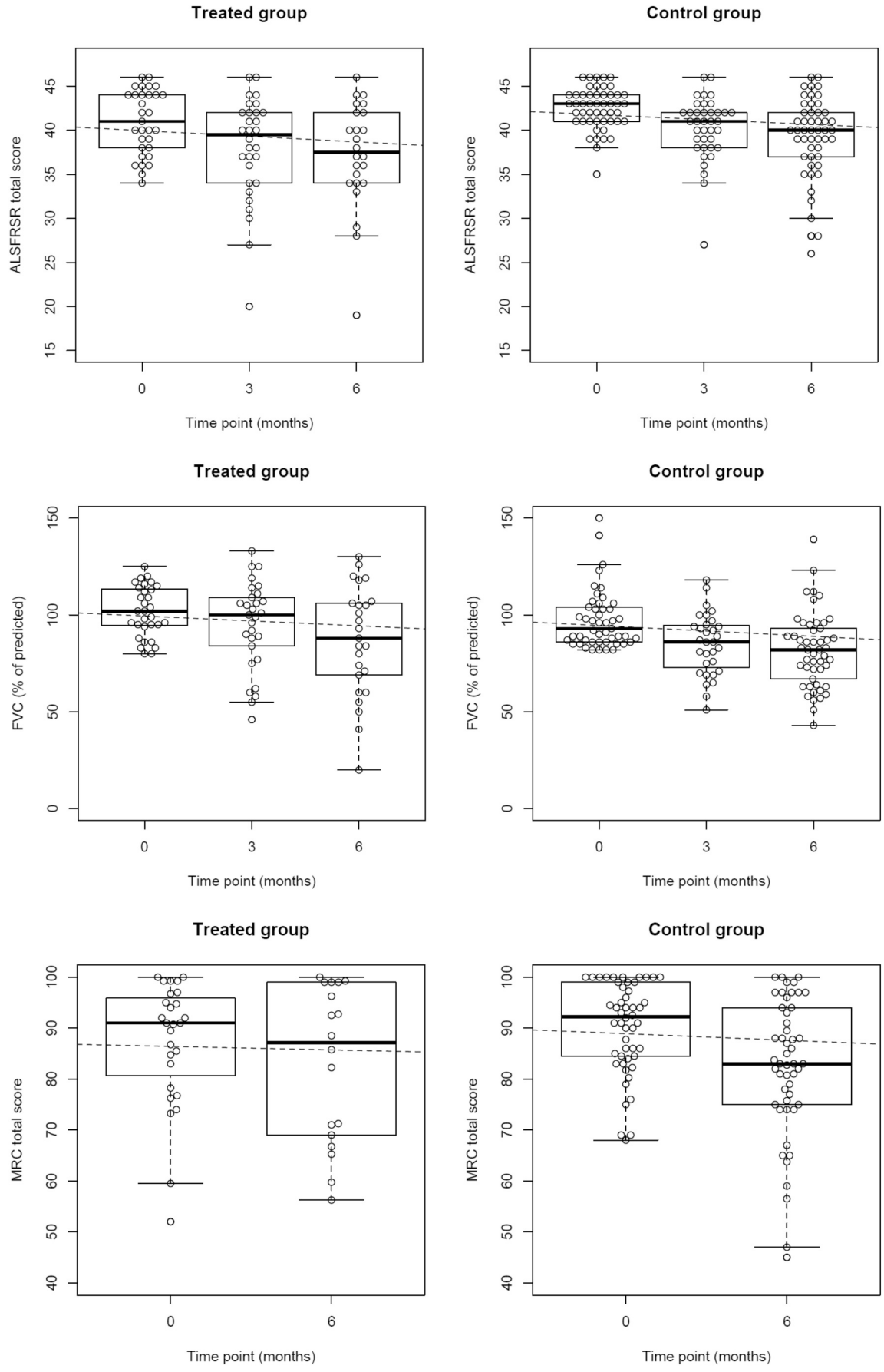

Fig. 1. Functional changes from baseline to 3 and 6 months in treated and control patients.
ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; FVC: forced vital capacity; MRC: Medical Research Council; ALSAQ-5: Amyotrophic Lateral Sclerosis.

changes of ALSFRS-R score, FVC value, MRC score between the two groups. No significant difference for any of these functional measures was found at each time point (Fig. 1) (Full data in Supplementary Table 2). For some outcomes and time points, specific covariates showed statistically significant effects or non-significant trends within the corresponding ANCOVA models. In particular, female sex showed a trend of association with greater negative changes of total ALSFRS-R score and bulbar subscore at 3 months (approximately −2.1 and −0.48 points respectively relative to males, p = 0.058 and 0.058), and with a greater FVC worsening at 6 months (−11% relative to males, p = 0.074). Moreover, older age was significantly associated with faster progression of bulbar impairment at 6 months (−0.024 per year of age at baseline, p = 0.046). Furthermore, longer disease duration showed strong associations with higher total and upper/lower limb ALSFRS-R scores at 3 and 6 months (+0.22, +0.11 and +0.06 points per month of disease duration, p = 0.004, 0.009 and 0.02) and at 6 months (+0.20, +0.10 and +0.05 points per month, p = 0.02, 0.03 and 0.07), and with higher FVC and MRC total score at 6 months (respectively +1% and +0.8 points per month, p = 0.02 and 0.002). Finally, a bulbar onset was strongly associated with faster ALSFRS-R score worsening at 6 months (−2.9 points relative to spinal onset, p = 0.0006), and, unsurprisingly, with faster bulbar subscore worsening (−0.8 at 3 months and −1.4 at 6 months relative to spinal, p = 0.001 and < 0.0001, respectively). However, there was a trend of association between a bulbar onset and better MRC outcomes at 6 months (+5.9 p = 0.053), as may be expected for a measure of spinal impairment. Riluzole treatment did not show significant effects in the ANCOVA model, probably because very few patients were off riluzole.

Creatinine values significantly decreased in treated patients at 3 and 6 months (−0.04 mg/dl both at 3 and 6 months as compared to baseline, p = 0.0078 and 0.030 respectively). Higher p-values for the latter time point reflect lower sample size because of drop-outs. In parallel, ALSAQ5 values showed significant increases (i.e. worse quality of life) at 3 and 6 months (+1.77 and +1.50 points at 3 and 6 months as compared to baseline, p = 0.0005 and 0.0078 respectively).

Edaravone was overall well tolerated. However, one patient died before the second treatment cycle due to unexplained causes (sudden death), and 6 discontinued therapy after < 6 months. Reasons for discontinuation included two cases of deep venous thrombosis and a suspected acute lung injury with minor X-ray abnormalities in one. Three patients voluntarily suspended the treatment due to lack of effects. Moreover, a peripheral venous catheter (Midline) was placed in two patients to overcome venous access issues. Other minor adverse events included complain of mild and transient dizziness in one patient, and burning sensation at the injection site in a few cases. No remarkable events were observed after interruption of treatment.

4. Discussion

Our retrospective, single-centre analysis does not confirm the positive effects of edaravone on ALS progression. Indeed, the trend of ALSFRS-R, FVC and MRC score changes of treated and control patients did not differ over a 6-month-time-period, also taking into account the unbalanced clinical features of the two groups at baseline (i.e. older age and longer disease duration of treated group), which were considered as covariates in the statistical model. Furthermore, the analyses of covariate effects in the overall multivariate model indicated that a longer disease duration was associated with higher functional scores at 6 months, probably because of a more stable disease. Therefore, the longer disease duration in the treated group would have represented an “advantage”, rather than a disadvantage, in evaluating edaravone efficacy in the setting of our study. Older age, on the other hand, might have negatively influenced the outcome in treated patients, especially regarding bulbar symptoms which resulted to be significantly influenced by age in the multivariate analysis. All this considered, the two groups compared here seem adequately balanced, despite the obvious limits of a non-randomized study design.

The apparent lack of edaravone efficacy was further confirmed by the lowering of creatinine levels, that are associated with poorer prognosis [21], and the worsening of patient-reported quality of life throughout the 6-month study period. Yet, we observed an overall safety of the medication. Among 7 patients who discontinued edaravone, only three developed relevant side effects. In two cases it was due to deep venous thrombosis which is still a relatively common event in ALS patients, expecially when lower limb function is impaired [22]. The decision to suspend therapy relied on the reported risk of haematologic alterations secondary to edaravone assumption [20]. One patient showed an acute respiratory event evocative of acute lung injury. Acute lung injury is characterized by cough, pyrexia, dyspnea and X-ray alterations and it is a potential side effect of edaravone therapy [20]. Along with the clinical picture, such a diagnosis was further supported by the lack of response to antibiotic treatment and the detection of normal levels of inflammation indexes [23,24]. In addition to these cases, one patient of our cohort suddenly died after completing the first edaravone cycle. Although the precise causes of death remain obscure (autopsy was refused by patient's family), we argued a cardiac death representing about 10% of causes of exitus in ALS patients [25,26].

The discrepancies between our findings and the Japanese studies are hard to explain univocally. The main limitation of our study lies in the historical nature of the control group, which is inherently prone to confounding and bias compared to a longitudinal randomized control. However, the stringent inclusion and exclusion criteria along with the accurate record-keeping indicated by AIFA are supposed to have reduced selection errors. Moreover, we considered ALS control patients back up to 2005, so that patients in the control group may have been exposed to different environmental risk factors or experienced lower standards of care. Anyhow, such risk factors may hardly have had substantial effects on disease course within a time as short as 6 months, and therapeutic/assistance care has not significantly changed in the last 20 years [27,28]. Last but not least, the number of patients in our single-centre study is insufficient to conclusively proof the effect of edaravone. Indeed, according to previous results of efficacy (approximately 2.5 score difference between control and treated group at 6 months) (16) we had to include at least 70 patients per arm. Yet, our findings still provide noteworthy information from a “real world” point of view. As a further matter, clinical evaluations have been carried out by the same neuromuscular team, which certainly ensured a greater consistency of data.

The negative findings of our study could also rely on patient-related mechanisms rather than study protocol limits or drug inefficacy. In particular, despite a similar edaravone pharmacokinetic profile, the genetic architecture of ALS in Japanese vs. European is likely to be different, as confirmed by more prevalent SOD1 mutations in the former and C9Orf72 expansions in the latter [29]. (genetic assessment of this study patients, both controls and treated, are shown in Supplementary Table 3). This might lead to a different pathogenetic role of oxidative stress and eventually to a variable response to anti-oxidative agents such as edaravone. We argue that future clinical trials, if any, should also consider the genetic background of patients.

In conclusion, our retrospective study suggests no benefit of edaravone on ALS in populations of Caucasian ancestry. Further investigations, including prospective multicenter analysis, is warranted to confirm the usefulness of edaravone for a better prognosis of ALS.

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Competing interests

The authors declare no competing interests.

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