

Assessment of Therapeutic Response of Edaravone and Riluzole Combination Therapy in Amyotrophic Lateral Sclerosis Patients

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a progressive disease characterized by chronic degeneration of upper and lower motor neurons and finally death within 3–5 years usually because of respiratory failure. Riluzole and edaravone are presently available treatments. It may be better to try combination therapy rather than taking individual medications. **Objectives:** To compare the effectiveness of (edaravone + riluzole) combination therapy versus riluzole therapy alone in slowing down the progression of ALS and to evaluate the role of serum creatinine as a marker of disease progression. **Materials and Methods:** Observational, randomized, parallel assignment, open label study. Thirty patients with definite and probable ALS were randomly assigned to two treatment groups. The case group received (riluzole + edaravone) for the initial 6 months, followed by riluzole for the next 6 months. The control group received riluzole for 12 months. After 6 and 12 months, changes in ALS functional rating scale (ALSFRS-R), mRS, and Japanese ALS scores were determined. *P* value <.05 was considered significant. **Results:** An increase in mRS at 6 months in the case group versus control group was 0.07 versus 0.20, respectively (*p* = 0.02). At 12 months, it was 0.47 versus 0.53, respectively (*p* = 0.17). A decrease in serum creatinine at 6 months in case group versus control group was 0.08 versus 0.09, respectively (*p* = .82). There was no change in ALS FRS for bulbar symptoms (salivation), 3.46 versus 3.46 in the case group (*p* = .018) for the first 6 months. **Conclusions:** Combined with riluzole, edaravone slows disease progression and is safe, but the effect is short-term. Bulbar symptoms respond better to combination therapy. The serum creatinine is helpful in monitoring disease progression.

Keywords: ALSFRS, edaravone, mRS, riluzole

Context: Amyotrophic Lateral Sclerosis

INTRODUCTION

In the year 1974, amyotrophic lateral sclerosis (ALS) was first described by Charcot.^[1] ALS is a progressive, fatal disease in which death occurs within 3–5 years usually because of respiratory failure. ALS has an incidence of 1.5 to 2.7/100,000/year and a prevalence of 3 to 5/100,000.^[2] In the Indian population, the average age of onset is between 45 and 55 years, with male predominance (M:F: 1.5:1).^[3,4] The limb onset type is most common (70%), followed by bulbar onset (25%) and isolated respiratory involvement (8%).^[5]

Glutamate is an excitatory neurotransmitter implicated in pathophysiology of ALS which acts on NMDA (N-methyl-D-aspartic acid) and AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors, resulting in neurodegeneration.^[6] Increased 3-NT immunoreactivity in motor neurons also suggests the role of oxidative stress.^[7] Plasma creatinine levels are an ideal biomarker correlating with strength and functional disability. Also, it is simple, inexpensive, and widely available.^[8]

There is a dearth of effective disease-modifying therapies in ALS. For many years, riluzole, a glutamate inhibitor, was the only choice available. It got US Food and Drug

Administration (FDA) approval in the year 1995 for having a modest benefit in survival. A controlled trial of riluzole (100 mg/day) in ALS by Bensimon G, *et al.*^[9] (1994) ALS/Riluzole Study Group concluded that it has a significant difference in survival after 12 (*p* = 0.014) and 21 months (*p* = 0.046). Similar findings were also obtained in a multi-center international study by Lacomblez L, *et al.* (1996).^[10]

Later in the year 2017, US FDA approved edaravone, a free-radical scavenger. A randomized, double-blind, placebo-controlled trial by Edaravone (MCI-186) ALS 19 Study Group (2017) showed a significantly smaller decline of ALS functional rating scale (ALSFRS-R) score compared with placebo. The literature on the use of these agents is sparse in

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India. Therefore, we planned this study to assess outcomes of combination therapy in Indian patients.

SUBJECTS AND METHODS

Clearance is taken from the institutional ethical committee. This study was conducted in the Department of Neurology, Government Medical College, Kota. Definite and probable ALS patients attending Neurology Out-patient Department and In-patient Department were included in the study after written informed consent. Study design [Figure 1]: Observational, randomized, parallel assignment, open label study. Sample size: The sample size consists of 30 patients of definite and probable ALS after ruling out secondary causes. Inclusion Criteria: Definite/probable ALS patients according to Revised EL Escorial criteria having a disease duration of 2 years or less and a forced vital capacity of 80% or more. Exclusion Criteria: Patients with severe ALS in which functional assessment not possible, ALS FRS ≤ 3 for dyspnea, orthopnea, and respiratory insufficiency, and possible ALS according to EL Escorial criteria. Patients were classified after randomization into two groups (15 each). One group (case) received (riluzole + edaravone) therapy, and the other group (control) received riluzole therapy alone. Edaravone was administered once a day via 60-min intravenous infusion in normal saline. As approved by US FDA, 60 mg of edaravone was initially administered for 14 consecutive days, followed by a 2-week drug-free period and subsequently administered for 10 days within a 2-week period; then, the same cycle was repeated two more times in total 24 weeks duration. The tablet Riluzole 50 mg twice daily was continued in both groups until the end of the study at 12 months follow-up.

Patients were categorized into the limb-onset and bulbar-onset types on the basis of clinical features. Differences in average ALS FRS from the baseline to 6 and 12 months in the (edaravone + riluzole) group were compared to those

from the baseline to 6 and 12 months in the control (riluzole) group. Changes in biochemical data from the baseline to 6 and 12 months were examined in the both groups. Safety endpoints included the incidence of adverse events, adverse drug reactions, and abnormal biochemical data. Statistical Analysis: Differences in clinical characteristics between groups were analyzed using the Chi-square test and/or Fisher’s exact test. Differences in averages of ALS FRS, mRS, and Japanese ALS score were analyzed by two-way analysis of variance.

RESULTS

Table 1. At the baseline, both groups were comparable. The average age of disease onset for the combination therapy group was (52.8 ± 6.87) years, and that for the riluzole group was (54.2 ± 3.59) years. The percentage and number of males were (73%, 11) in the combination therapy group and (60%, 9) in the riluzole group. The average duration of illness in months was (bulbar 7.83 ± 2.13 , limb 14.88 ± 2.60) in the combination therapy group and (bulbar 8.71 ± 0.94 , limb 15.125 ± 1.31) in the riluzole group. The percentage and number of patients with bulbar onset were (40%, 6) in the combination therapy group and (46%, 7) in the riluzole group. The percentage and number of definite and probable ALS patients were (definite 80%, $n = 12$ and probable 20%, $n = 3$) in the combination therapy group and (definite 73%, $n = 11$ and probable 27%, $n = 4$) in the riluzole group. There was no statistically significant difference in age of presentation, sex distribution, duration of illness, onset (bulbar/limb), and category of ALS (definite/probable) between the two groups. In the group receiving combination therapy, the average of mRS worsened [Figure 2] from 2.33 to 2.40, whereas in the riluzole group, it worsened from 1.73 to 1.93 ($p = 0.02$). Later in the following 6 months, the worsening in average of mRS for the combination therapy group was from 2.40 to 2.87, and for the riluzole therapy group, it was from 1.93 to 2.46 at 6 and 12 months ($p = 0.17$). The average

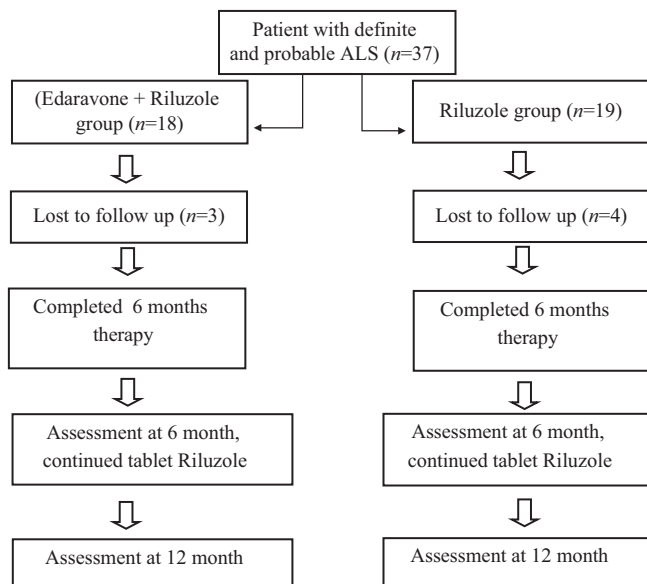


Figure 1: Flowchart of study

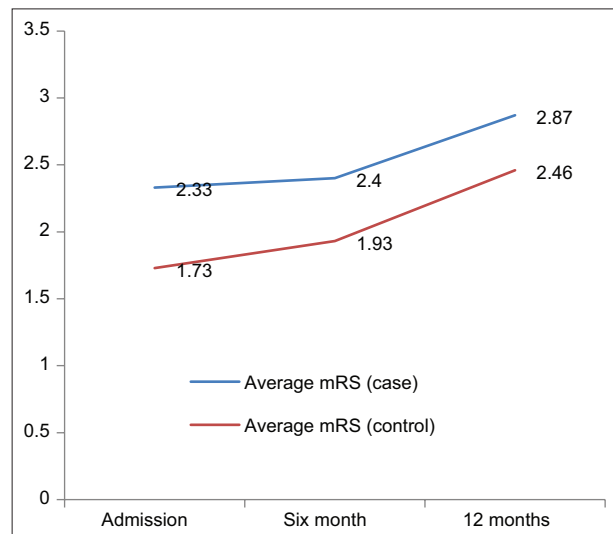


Figure 2: Average of mRS at admission, 6 months, and 12 months between the case and control

of Japanese ALS severity score [Figure 3] in the combination therapy group at admission, 6 months, and 12 months was 1.93, 2.00, and 2.46, and in the riluzole therapy group, it was 1.67, 1.87, and 2.00 ($p = 0.10$ at 6 months, $p = 0.17$ at 12 months). The decline in average of serum creatinine level [Figure 4] in the combination therapy group was 0.08 (0.77 to 0.69) in the first 6 months and 0.13 (0.69 to 0.56) in the following 6 months. The decline in the riluzole group was 0.09 at 6 months and 0.08 at 12 months (0.79 to 0.70 to 0.62). At 6 months, $p = 0.82$, and at 12 months, $p = 0.42$ [Tables 2 and 3]. The decline in average of ALS FRS for bulbar symptoms was not seen in the combination therapy group. For salivation in the combination therapy group at admission, 6 months, and 12 months, the value was 3.46 to 3, and in the riluzole therapy group, it was 2.93 to 2.67 at 6 months, $p = 0.018$, and at 12 months, $p = 0.06$.

Table 1: Characteristic between the case and control

CHARACTERISTICS	CASE (n=15)	CONTROL (n=15)	P
Age (mean with 2 SD years)	52.8±6.87	54.2±3.59	0.49
Sex			
Male	11	9	0.70
Female	4	6	
Onset			
Bulbar	6	7	0.71
Limb	9	8	
Duration of illness at adm. (mean±2 SD months)			
Bulbar	7.83±2.13	8.71±0.94	0.15
Limb	14.88±2.60	15.125±1.31	0.74
ALS			
Definite	12	11	0.66
Probable	3	4	
mRS (avg. of 15 patients)			
Adm	2.33	1.73	
6 months	2.40	1.93	0.02
mRS (avg. of 15 patients)			
6 months	2.40	1.93	0.17
1 year	2.87	2.46	
Japanese ALS severity scale (avg. of 15 patients)			
Adm	1.93	1.67	
6 months	2.00	1.87	0.10
Japanese ALS severity scale (avg. of 15 patients)			
6 months	2.00	1.87	0.17
1 year	2.46	2.00	
Serum creatinine (avg. of 15 patients, mg/dl)			
Adm.	0.77	0.79	0.82
6 months	0.69	0.70	
Serum creatinine (avg. of 15 patients, mg/dl)			
6 months	0.69	0.70	0.42
12 months	0.56	0.62	
Complications (Adverse Effects/Death)	No significant	No significant	

The decline in average of ALS FRS during first 6 months in the riluzole group and combination therapy group was as follows: for speech, it was (0.26 vs 0); for swallowing, it was (0.33 vs 0); for handwriting, it was (0.33 vs 0.07); for cutting food and handling utensils, it was (0.47 vs 0.26); for dressing and hygiene, it was (0.27 vs 0); for turning in bed and adjusting bed clothes, walking, climbing stairs, orthopnea, and respiratory insufficiency, it was (0 vs 0); and for dyspnea, it was (0.14 vs 0). The changes were statistically insignificant ($p > 0.05$) [Table 2].

The decline in average of ALS FRS between 6 and 12 months in the riluzole group and combination therapy group was as follows: for speech, it was (0.33 vs 0.8); for salivation, it was (0.07 vs 0.46); for swallowing, it was (0.40 vs 0.93); for handwriting, it was (0.53 vs 0.46); for cutting food and handling utensils, it was (0.20 vs 0.14); for dressing and hygiene, it was (0.13 vs 0.20); for turning in bed and adjusting bed clothes, it was (0.20 vs 0.20); for walking, it was (0.27 vs 0); for climbing stairs, it was (0.27 vs 0.27); for dyspnea, it was (0.13 vs 0.07); for orthopnea, it was (0.27 vs 0.26); and for respiratory insufficiency, it was (0.13 vs 0.42). The changes were statistically insignificant ($p > 0.05$) [Table 3].

DISCUSSION

Our observational, randomized, parallel assignment, single-center analysis evaluating the efficacy of combination therapy (edaravone + riluzole) versus riluzole alone suggests that the rate of worsening in mRS and ALS FRS (salivation) was slower in the combination therapy group. Changes in mRS were used to determine functional abilities^[11] and changes in the Japanese ALS severity scoring scale and ALS FRS score to measure ALS progression.

For the combination therapy group, there was a change in mRS of 0.07 versus 0.20 for the riluzole group during the

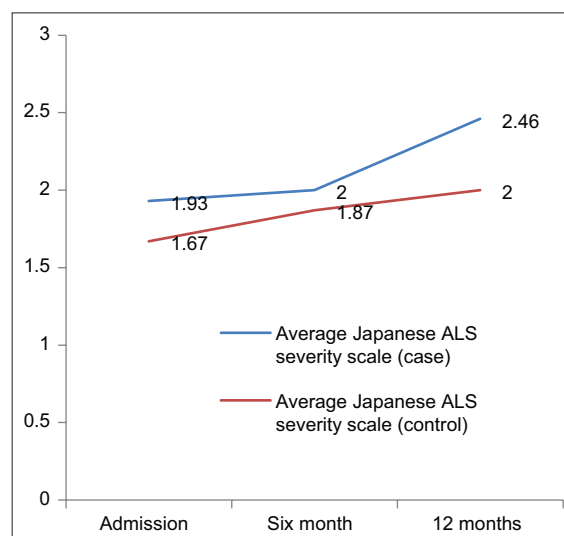
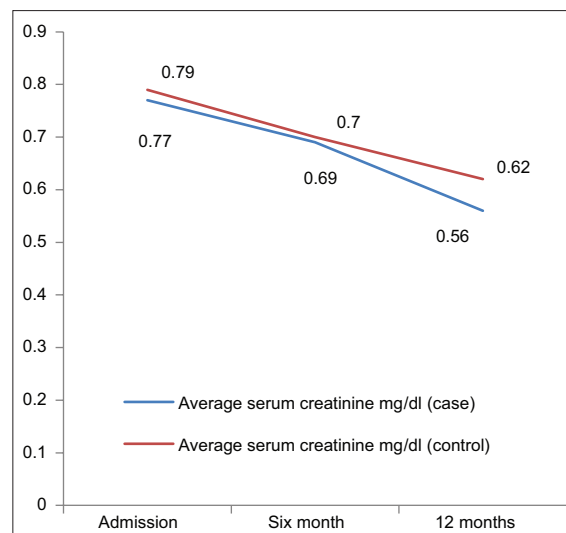


Figure 3: Average of Japanese ALS severity score at admission, 6 months, and 12 months between the case and control

Table 2: ALS FRS (avg. of 15 patients) at admission and 6 months between the case and control

ALS FRS (avg. of 15 patients)	CONTROL (n=15)	CASE (n=15)	P
Speech			
Adm	(2.26)	(2.4)	0.08
6 months	(2)	(2.4)	
Salivation			
Adm	(2.93)	(3.46)	0.018
6 months	(2.67)	(3.46)	
Swallowing			
Adm	(2.8)	(2.73)	0.31
6 months	(2.47)	(2.73)	
Handwriting			
Adm	(2.2)	(1.87)	0.17
6 months	(1.87)	(1.8)	
Cutting food and handling utensils (without gastrostomy)			
Adm	(2.54)	(2)	0.12
6 months	(2.07)	(1.74)	
Dressing and hygiene			
Adm	(2.47)	(2.4)	0.33
6 months	(2.2)	(2.4)	
Turning in bed and adjusting bed clothes			
Adm	(2.6)	(2.33)	Nil
6 months	(2.6)	(2.33)	
Walking			
Adm	(3)	(2.87)	Nil
6 months	(3)	(2.87)	
Climbing stairs			
Adm	(2.87)	(2.6)	Nil
6 months	(2.87)	(2.6)	
Dyspnea (new)			
Adm	(3.47)	(3.2)	0.052
6 months	(3.33)	(3.2)	
Orthopnea (new)			
Adm	(3.87)	(3.53)	Nil
6 months	(3.87)	(3.53)	
Respiratory insufficiency (new)			
Adm	(4)	(4)	Nil
6 months	(4)	(4)	

first 6 months of therapy. This was found to be statistically significant ($p = 0.02$), suggesting that less disease progression occurred during this period and edaravone + riluzole prevented early functional disability. Edaravone was found to act as a force multiplier in ALS therapy.^[12] From this, it can be hypothesized that both have different mechanisms of action, with edaravone^[13,14] involved as a free-radical scavenger and riluzole^[15] involved in anti-glutamatergic modulation of excitotoxic pathways, mitochondrial functions, changes to fat metabolism, peripheral axonal effects on persistent sodium channel functions, and potentiation of calcium-dependent potassium currents, which helped to slow down disease progression from multiple targets. Therefore, a combination therapy is more advantageous.

**Figure 4:** Average of decline in serum creatinine (mg/dl) between the case and control

The Japanese ALS severity scale^[16-19] was used to assess the slowing of disease progression, but no statistically significant difference was seen at 6 months ($p = 0.10$) and 12 months ($p = 0.17$) between the case and control. It may be because severe ALS cases were not considered in our study, and the Japanese severity scale has a very narrow difference between scoring cases and their clinical correlates, which leads to the failure to capture fine details and changes. Therefore, it appears to be of limited value in predicting early disease progression.

As measured by the ALSFRS-R,^[20-22] the average scores for bulbar symptoms did not vary between admission and at 6 months after therapy in the combination therapy group. As for speech (2.4, 2.4), salivation (3.46, 3.46), and swallowing (2.73, 2.73), they remained unchanged. In the riluzole group, there was a decline in average score between admission and at 6 months. For speech, it was (2.26, 2); for salivation, it was (2.93, 2.67); and for swallowing, it was (2.8, 2.47). Although the data clearly support the advantage of combination therapy, the only statistically significant change was found in salivation ($p = 0.018$). Thus, combination therapy seems to have the upper hand in slowing down the progression of bulbar symptoms [Table 3]. In the later part of the study between 6 months and 12 months when both groups were on riluzole for a period of 6 months, there was a consistent decline in ALSFRS-R in both the groups. No statistically significant difference was observed during this period. Other symptoms also showed a slower decline when on combination therapy, but none had any statistically significant slowing [Tables 2 and 3]. A multi-center study performed by Wintzel *et al.*^[23] (2022) evaluated the long-term safety and effectiveness of combination therapy. They concluded that combination therapy did not offer any clinically relevant additional long-term benefits. Although they have given edaravone for at least four cycles, different patients received varying lengths of treatment,

Table 3: ALS FRS (avg. of 15 patients) at 6 months and 12 months between the case and control

ALS FRS (avg. of 15 patients)	CONTROL	CASE	P
Speech			
6 months	(2)	(2.4)	0.36
1 year	(1.67)	(1.6)	
Salivation			
6 months	(2.67)	(3.46)	0.06
1 year	(2.6)	(3)	
Swallowing			
6 months	(2.47)	(2.73)	0.49
1 year	(2.07)	(1.8)	
Handwriting			
6 months	(1.87)	(1.8)	0.46
1 year	(1.34)	(1.34)	
Cutting food and handling utensils (without gastrostomy)			
6 months	(2.07)	(1.74)	0.06
1 year	(1.87)	(1.6)	
Dressing and hygiene			
6 months	(2.2)	(2.4)	0.15
1 year	(2.07)	(2.2)	
Turning in bed and adjusting bed clothes			
6 months	(2.6)	(2.33)	0.09
1 year	(2.4)	(2.13)	
Walking			
6 months	(3)	(2.87)	0.48
1 year	(2.73)	(2.87)	
Climbing stairs			
6 months	(2.87)	(2.6)	0.14
1 year	(2.6)	(2.33)	
Dyspnea (new)			
6 months	(3.33)	(3.2)	0.15
1 year	(3.2)	(3.13)	
Orthopnea (new)			
6 months	(3.87)	(3.53)	0.08
1 year	(3.6)	(3.27)	
Respiratory insufficiency (new)			
6 months	(4)	(4)	0.29
1 year	(3.87)	(3.58)	

so uniformity was lacking. Additionally, there were no patients from the Indian subcontinent. In contrast, we had given each patient six treatment cycles and found short-term benefits while the patient was undergoing treatment. It is known that a decline in serum creatinine correlates with progressive muscle wasting, functional disability, and significant motor impairment.^[24] It serves as a surrogate marker [Table 1]. We also observed a progressive decline in serum creatinine levels in our study. In the combination therapy group, it was 0.08 (0.77 to 0.69) in the first 6 months and 0.13 (0.69 to 0.56) in the later 6 months when patients were on riluzole. This suggests that a rapid decline was there in the later part of therapy. The decline in creatinine levels in the riluzole group was consistent throughout, 0.09 in the initial 6 months and 0.08 in the later 6 months (0.79 to 0.70 to 0.62). Here, combination therapy was better at slowing

down the development of muscle atrophy, but the results were not statistically significant ($p = 0.82$ at 6 months, $P = 0.42$ at 12 months). Thus, both groups showed a delay in progression to severe motor impairment, but combination therapy was slightly superior.

No significant adverse events were observed during the course of therapy, that is, clinical, hematological, or biochemical, except for mild transient symptoms such as nausea, vomiting, headache, myalgia, dizziness, and decreased appetite, which were easily manageable with symptomatic therapy. One patient developed fever during admission; on evaluation, the cause was found to be urinary tract infection, which relieved with medication and had no recurrence.

Limitations of the study

- 1) A small sample size.
- 2) Short follow-up only for 1 year was performed because of the prevailing coronavirus disease 19 pandemic and repeated lockdowns. Many patients lost to follow-up after 1 year.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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