Safety and Efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled trial

Lancet Neurology 2017 May 15; 16: 505-512

Oxidative stress is considered as a potential pathophysiological mechanism in ALS disease progression. Indeed, prior to this trial, the free-radical scavenger edaravone had been shown to reduce motor neuron death in animal models of ALS and other CNS disease, by reducing oxidative stress. This pre-clinical data led to an open-label, phase 2 study of edaravone in ALS patients, and data from this initial study showed some benefit of edaravone, in terms of disease progression. Shortly after, a placebo-controlled, phase 3 study of edaravone was conducted in ALS patients, though data from this subsequent trial revealed no significant differences in ALSFRS-R scores between edaravone and placebo-treated patients. However, sub-group analyses did suggest a potential benefit in a very select group of ALS patients, namely those with $\geq$2 on all scores of the ALSFRS-R and FVC values $\geq$80%. As such, this follow-up phase 3 study assessed the efficacy of edaravone in ALS patients meeting those select clinical criteria.

Experimental design and statistical analysis: This was a randomized, double-blind, parallel-group, placebo-controlled trial conducted in Japan. Eligibility included 1) 20-75yrs old w/an independent living status, 2) scores of $\geq$2 on all parts of the ALSFRS-R AND an FVC $\geq$ 80%, 3) definite or probable ALS, and 4) disease duration $\leq$2yrs. Exclusion criteria is below.[1] Prior to randomization, eligible participants were observed for 12wks, and any patient with an ALSFRS-R decline by >4pts during this period was excluded. All other eligible patients were then randomized (1:1) to either edaravone (60mg via a 60-min IV infusion) or placebo (saline), stratified by age, probable vs. definite ALS, and ALSFRS-R score change during the 12wk observation. Treatment lasted for 24wks, with 6 cycles. Cycle 1 consisted of daily study drug for 14d, then a 2wk drug-free period. Cycles 2-6 consisted of 10d of study drug over 14d, with 2wk drug-free periods between each cycle. All patients could continue, but not start, Riluzole. The primary efficacy outcome was the change in ALSFRS-R from baseline to cycle 6, with assessments completed before cycle 1, and after each subsequent cycle. Secondary efficacy endpoints included the change in FVC, changes in Modified Norris Scale scores (assessing limb and bulbar function), QOL scores, ALS severity, grip/pinch strength, and time to death or disease progression. Safety endpoints included adverse events, drug reactions, lab abnormalities, and sensory tests. Primary outcomes were compared between groups using ANOVAs w/mixed effect models, adjusting for patients with missing values (i.e, those who did not complete all cycles). Secondary endpoints were analyzed similarly, with Kaplan Meier curves used for time to death/disease progression.

Results: From Nov 2011 to Sept 2014, N = 137 patients were randomized, with a total of 134 (N = 68 in edaravone, N = 66 in placebo) included in the primary analyses. Baseline characteristics were generally similar between treatment groups (**Table 1**). In terms of the primary outcome, the decline in ALSFRS-R scores from baseline to the end of cycle 6 was LOWER with edaravone: the mean treatment group difference by the end of cycle 6 was 2.49 ($p<0.01$, **Table 2 and Figure 2**). Primary outcome data remained significant after accounting for missing patient data. In addition, total scores on the Modified Norris Scale also favored edaravone (mean group difference: 4.89, $p<0.05$, **Table 2**), as did scores of QOL (**Table 2**). There were no group differences in terms of the change in FVC scores over the study period, and the numbers of patients with disease progression also did not differ between treatment groups (N = 2, edaravone; N = 6, placebo; p = 0.13 via log-rank test). Finally, the numbers of patients reporting at least one adverse event were similar between treatment groups, with rates of contusion, constipation,

[1]ALSFRS-R scores of $\geq$3 for orthopnea, dyspnea, or respiratory insufficiency, a h/o spinal stenosis surgery, CrCl <50mL/min

and dysphagia being the highest in both groups (**Table 3**); no serious adverse drug reactions occurred in either treatment group.

Conclusions: Overall, data from this phase 3 study showed that edaravone reduces functional decline in a well-defined population of patients with early stage, definite or probable ALS. Specifically, the differences in mean ALSFRS-R scores between the two treatment groups amounted to 33%, which is considered as clinically significant. The study authors did note that despite these positive outcomes, there were limitations to the study related to the generalizability of the results, as only a very select population of ALS patients were included (based on the clinical variables noted above). As such, use of edaravone can only be readily applied to this patient population. Further, the long-term benefit of edaravone was not addressed here, so the authors highlight that future work should evaluate the utility of edaravone with respect to survival in ALS, perhaps also in a broader subset of ALS patients.

Additional reading, if interested:

1. Abe, K, et al., *Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients*. Amyotroph Lateral Scler Frontotemporal Degener (2014), 15: 610–17.

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