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Advanced Treatment of Amyotrophic Lateral Sclerosis (ALS)

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neuromuscular disease that affects approximately 5 of every 100,000 individuals, Approximately half of ALS patients die within 30 mo of symptom onset and the majority do not survive beyond 5 years, Currently, riluzole and edaravone are the only United States Food and Drug Administration (FDA)–approved treatment options

Methods: Outcome (the change in ALS Functional Rating Scale–Revised, ALSFRSR, from baseline) was projected for placebo patients through 48 weeks and compared with 48-week edaravone or 24-week edaravone after switching from placebo.

Results: A total of 123 patients received open-label treatment (65 edaravoneedaravone; 58 placebo-edaravone). The projected ALSFRS-R decline for placebo from baseline through week 48 was greater than for 48-week edaravone ($P < .0001$). For patients switching from placebo to edaravone, ALSFRS-R slope approached that of continued edaravone for 48 weeks. ALSFRS-R decline did not differ between actual and projected edaravone through week 48.

Conclusions: Compared with placebo, these analyses suggest that edaravone is beneficial in ALS patients even after 6 mo of receiving placebo, and efficacy is maintained for up to 1 year.

Introduction :

Amyotrophic lateral sclerosis (ALS) is the most common form of the neurodegeneration , is progressive and fatal neuromuscular disease , the disease characterized by the degeneration of motor neurons in the brain and spinal cord , when the motor neurons die , the ability of the brain to control muscle movement lost, the people loss the ability to speak , move , eat , breath .

Approximately half of (ALS) patients die within 3-5 years of symptoms onset , the (ALS) usually strikes people between the age 40-70 , the disease is discovered by French doctor named (jean-martin charcot) , “ Amyotrophy “ refers to the atrophy of the muscle fibers , which are denervated as their corresponding anterior horn cell degenerate , “ Lateral sclerosis” refers to hardening of the anterior and lateral corticospinal tracts as motor neurons in these areas degenerate and are replaced by gliosis .

, riluzole and edaravone are the only united states food and drug administration (FDA) approved treatment options . there are other therapeutic agents for symptoms agents , and devices and multidisciplinary care strategies are used with the goals of providing palliative care , prolonging survival , improving equality of life , and maintaining the patient’s independence for as long as possible .

The aim of this review is to discuss the pathogenesis of the disease and M.O.A and dosing ,Administration , side affects of edaravone and riluzole.

Materials and Method

First study design

was a randomized, double-blind, parallel-group, placebocontrolled study. The details of study methodology, ethical study conduct, patient selection (inclusion and exclusion criteria), Briefly, patients were randomized to either edaravone (60 mg) or placebo for 24 weeks followed by a 24-week open-label extension period. The primary efficacy end point was the change in ALSFRS-R score from baseline to the end of week 24.

Second Post-hoc assessment

Multiple linear regression analysis was performed to project the results from the placebo-controlled, double-blind phase from baselin through week 48 for all treatment groups. Progression rate in the treatment group originally randomized to edaravone was estimated for the first 24 weeks and was used to predict progression for the next 24 weeks; this was compared with actual change in ALSFRS-R in patients who initially received edaravone for 24 weeks and continued on open-label edaravone from weeks 24 to 48 (edaravone-edaravone group). For the group originally randomized to placebo, rate of progression for the first 24 weeks was used to predict progression for the following 24 weeks; this was compared with the actual progression in this group, who were switched to edaravone from weeks 24 to 48 (placebo-edaravone group). Thus, at the 48-week time point, projected placebo progression rate could be compared with the actual progression in the placebo-edaravone group as well as the edaravoneedaravone group, and the projected progression in the edaravoneedaravone group compared with actual progression.

Third Post-hoc analysis statistics

The relationship between the change in ALSFRS-R and time was visualized with linear regression analysis for each treatment group. A linear mixed model with covariates of linear slope of time, treatment, baseline value, and interaction of time and treatment, and random intercept, was used to estimate the treatment difference in the change in ALSFRS-R at week 48.

Results

First Patient disposition and baseline Characteristics

A total of 137 patients were initially randomized to receive either edaravone (n = 69) or placebo (n = 68) in the double-blind phase. The demographics and baseline characteristics were well balanced between treatment groups at baseline, except for

male gender and Japan ALS Severity Classification.10,11 Briefly, the mean age was approximately 60 years, and the mean duration of disease at study enrollment was 1 year. The mean (SD) ALSFRS-R score for patients in the edaravone and placebo groups, respectively, was 41.9 (2.4) and 41.8 (2.2) at baseline. A total of 127 patients completed the doubleblind period, and 123 patients (65 patients from the edaravone group [edaravone-edaravone] and 58 patients from the placebo group [placebo-edaravone]) continued into the active-treatment period. From these groups, 53 edaravone-edaravone and 40 placebo-edaravone patients completed the open-label treatment period.11 Six patients died in the study; all were considered "not reasonably possible" with regard to a relationship to study drug.

Second Post-hoc analysis

The projected change in ALSFRS-R score from baseline through week 48 was significantly greater for placebo than edaravone .This was also evident when measuring the rate of decline in ALSFRS-R score through week 48 (slope of the graphs), which was significantly greater for the projected placebo than for the projected edaravone group . The projected placebo group also showed significantly greater change (decline) in ALSFRS-R score from baseline through week 48 than the actual edaravone-edaravone treatment group (patients originally randomized to edaravone and participating in the open-label period). The corresponding rates of decline in ALSFRS-R. The rate of decline in ALSFRS-R score for placebo-edaravone (originally randomized to placebo and received open-label, 24-week edaravone) was significantly less than that of projected placebo while appearing similar to that of edaravone patients .Comparing the actual edaravone-edaravone group with the projected edaravone estimate, there was no difference in either the change in ALSFRS-R scores from baseline through week 48 or the rate of ALSFRS-R decline (1).

Discussion

The exact molecular pathway causing motor neuron degeneration in ALS is unknown, but as with other neurodegenerative diseases, is likely to be a complex interplay between multiple pathogenic cellular mechanisms which may not be mutually exclusive . These include: Genetic factors : 20% of cases with autosomal dominant FALS and 2% of patients with SALS show mutations in the Copper-Zinc superoxide dismutase (SOD1) gene ,Mutations in the gene are though to cause disease through a toxic gain of function rather than causing impairment of the antioxidant function of the SOD1 enzyme.

Oxidative stress : has longed been linked to neurodegeneration and it is known that accumulation of reactive oxygen species (ROS) cause cell death. As mutations in the anti-oxidant enzyme superoxide dismutase 1 (SOD1) gene can cause familial ALS. Excitotoxicity : This is the term for neuronal injury induced by excessive glutamate induced stimulation of the postsynaptic glutamate receptors such as cell surface NMDA receptors and AMPA receptors .This over stimulation of glutamate receptors is thought to result in massive calcium influx into the neurons, leading to increased nitric oxide formation and thereby neuronal death.

Mitochondrial Dysfunction : Abnormalities in mitochondrial morphology and biochemistry have been reported in sporadic ALS patients Mitochondria from ALS patients show elevated calcium levels and decreased activity of respiratory chain complexes I and IV Mitochondrial DNA mutations have been described in ALS patients.Oxidative stress, reactive oxygen species (ROS), and glutamate excitotoxicity are considered to be the main contributing factors in ALS.[2]

A careful assessment of riluzole and edaravone reveals startling differences and few similarities in their mechanism of action, The exact cellular and molecular targets of edaravone are unknown. Edaravone acts as a ROS scavenger and inhibits peroxyl radical (LOO•) induced peroxidation systems. One of the most interesting findings suggests that edaravone scavenges H2O2 and protects cells against oxidative stress via upregulation of Peroxiredoxin-2, downregulation of protein disulfide isomerase A3, and inhibition of apoptosis. The reaction between edaravone and ONOO− is approximately 30-fold greater than uric acid (physiological scavenger for ONOO−). Edaravone traps •OH and inhibits OH−-dependent lipid peroxidation or tyrosine nitration induced by ONOO−. Under physiological states, 50% of edaravone is present as an anion form, and electrons released from edaravone anion exert radical scavenging. Afterward, edaravone radicals are generated, react readily with oxygen atoms, and form a peroxyl radical (LOO•) of edaravone, and eventually 2-oxo-3-(phenylhydrazone)- butanoic acid.

Riluzole belongs to the benzothiazole class, a glutamate antagonist, and it appears to block the excessive release of glutamate from MNs., Unrestrained secretion of glutamate at synaptic junction overstimulates the MNs receiving the signals, which leads to abnormally high levels of calcium in MNs soma and glial cells. High levels of intracellular calcium [Ca2+]i lead to peroxidation of membrane lipids, damage to RNA and DNA, and disruption of mitochondria, resulting in cell death. ROS, produced after the damage of mitochondria, leads to the formation of superoxide anion ($O^{\cdot-}2$) and hydrogen peroxide (H2O2). Reactions between $O^{\cdot-}2$ and nitric oxide (NO) lead to the formation of peroxynitrite anion (ONOO−), which causes nitration of protein tyrosine residues. H2O2 decomposes into hydroxyl radicals (•OH), and both ONOO− and •OH are highly reactive and react with lipids, proteins, and DNA. Riluzole may contribute to excitotoxic cell death by a) inhibiting glutamate presynaptic release (activation of glutamate reuptake), b) inactivating voltagedependent sodium channels (reducing hyperexcitability), c) slowing potassium channel inactivation, d) inhibiting protein kinase C, and e) interfering with intracellular events that follow transmitter binding at excitatory amino acid receptors.

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The recommended dose for riluzole is 50 mg/12 hours, which should be taken at least an hour before or two hours after a meal to avoid a food-related decrease in bioavailability. Nausea, asthenia, and elevated liver enzyme levels are some of the dose-related side effects of riluzole. Increased alanine transaminase usually appears within 3 months after the start of riluzole medication but returns to below twice the upper normal range after 2 to 6 months while treatment is continued. Riluzole can be stored in the dark at RT 15°C to 30°C.

The recommended dose of edaravone is 60 mg (IV; 60 minutes), which is administered in two consecutive 30 mg/100 ml IV infusions at a rate approximately 1 mg/min or 3.33 ml/min. During the initial treatment cycle, edaravone should be administered daily for 14 days followed by a 14-day drug-free period. For all subsequent cycles, the drug should be dosed daily for 10 days out of 14-day periods, followed by a 14-day drug free period. Edaravone can be stored in the dark at 25°C.[3]

Conclusion

Findings from these post-hoc analyses suggested a possible continued treatment effect of edaravone and maintenance of long-term efficacy for up to 1 year. Ongoing and planned studies will further our understanding of the long-term safety and efficacy of edaravone in patients with ALS.

References

1. Shefner J, Heiman-Patterson T, Pioro E, Wiedau-Pazos M, Liu S, Zhang J et al. Long-term edaravone efficacy in amyotrophic lateral sclerosis: Post-hoc analyses of Study 19 (MCI186-19). Muscle & Nerve. 2019;61(2):218-221.

2. 4. Lyon M, Wosiski-Kuhn M, Gillespie R, Caress J, Milligan C. Inflammation, Immunity, and amyotrophic lateral sclerosis: I. Etiology and pathology. Muscle & Nerve. 2018;59(1):10-22.

3. 5. Jaiswal M. Riluzole and edaravone: A tale of two amyotrophic lateral sclerosis drugs. Medicinal Research Reviews. 2018;39(2):733-748.