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Clinical Efficacy and Safety of Edaravone a New Molecule as a Ray of Hope for Motor Neuron Disease (An Incurable Illness) a Mini Review

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Abstract

The etiology of Amyotrophic Lateral Sclerosis (ALS) is unknown. Oxidative stress may be one of the major mechanisms involved. *In vitro* and *in vivo* data of edaravone suggest that it may possess broad free radical scavenging activity and protect neurons, glia, and vascular endothelial cells against oxidative stress. This paper describes and reviews data pertinent to the potential mechanism of action of edaravone, and reviews the development history of edaravone for the treatment of ALS.

Introduction

Edaravone, originally developed by Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan, is a potent radical scavenger and was approved for treating acute cerebral embolism. It removes oxygen radicals, including nitric oxide. The reaction between edaravone and peroxynitrite is approximately 30-fold greater than uric acid (physiological scavenger for peroxynitrite). Nagase et al. reported that plasma uric acid was lower in ALS patients than in age-matched healthy controls and edaravone-elevated plasma uric acid, a possible scavenger for peroxynitrite anion. The antioxidant mechanisms of edaravone include enhancement of prostacyclin production, hydroxyl radical trapping, and quenching of active oxygen, suggesting that it may provide neuroprotection against oxidative stress in motor neurons [1,2]. It is a member of the substituted 2-pyrazolin-5-one class, has the chemical name 3-methyl-1-2-pyrazolin-5-one. It is a white crystalline powder with a melting point of 129.7°C and is freely soluble in acetic acid, methanol, or ethanol as well as slightly soluble in water. The molecular formula of edaravone is C10H1ON2O and the molecular weight is 174.20 [3].

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Mechanism of Action

Edaravone is understood to be a free radical scavenger. It was approved in Japan in 2001 for the improvement of neurological symptoms, disruption of daily living, and functional impairment associated with acute ischemic stroke [4,5]. This article will describe the properties of edaravone and how clinical studies in stroke were followed by phase II and III studies performed during its clinical development for ALS.

Edaravone has shown anti-oxidative effects against water-soluble peroxyl radicals like vitamin C and lipid-soluble peroxyl radicals like vitamin E and has been shown to scavenge free radicals, including lipid peroxyl radical (LOO.), as well as peroxynitrite (ONOO) another form of reactive oxygen species through its electron donating properties. Edaravone has shown protective effects on neurons, glia (microglia, astrocytes, and oligodendrocytes), and vascular endothelial cells against oxidative stress and has been shown to suppress the inflammatory response of activated microglial cells. In ALS patients in an open-label phase II study with six cycles of edaravone (24-weekstudy MCI18612), levels of the oxidative stress marker 3NT in Cerebrospinal Fluid (CSF) were diminished after the first treatment cycle of 60 mg edaravone once a day (2 week administration) and were undetectably low in most patients after the sixth treatment cycle. Reduction of 3NT might be are result from reduction of peroxynitrite (ONOO) by edaravone because the formation of nitrotyrosine represents a specific peroxynitrite-mediated protein modification [1].

Pharmacokinetics

After IV infusion in human subjects, edaravone is metabolized into sulfate and glucuronide conjugates mainly in the liver, and is rapidly eliminated primarily by renal excretion. There is no accumulation in plasma concentration after repeated doses. Neither the sulfate nor the glucuronide has free radical scavenging activities. Edaravone and its metabolites are not expected to inhibit or

induce CYP450 isozymes at the clinical dose level [1].

Clinical Experience with Edaravone in Stroke

Five phase I studies of edaravone were conducted in healthy volunteers (47 Japanese and 50 Caucasian). A phase III study was conducted in acute ischemic stroke in Japanese patients with treatment initiated within 72 h of the onset of symptoms. The study drug edaravone 30 mg (or placebo) was administered intravenously over 30 min twice daily for 14 consecutive days. The study demonstrated a significant improvement in functional outcome in the edaravone group compared with the placebo group as evaluated by the modified Rankin Scale at 3 months. When a subset analysis was performed for the patients in whom edaravone was initiated within 24 h of stroke onset (according to an instruction by the Japanese health authority during their data review), the difference between the two groups was greater. The study result led to the approval of edaravone in Japan in 2001 for the improvement of neurological symptoms, disruption of daily activities, and functional impairment associated with acute ischemic stroke. The approved dosing regimen for acute ischemic stroke in Japan is the same as investigated in the study (30 mg intravenously over 30 min, twice daily, up to 14 days) with the recommendation that it should be initiated within 24 h of the onset of symptoms. Since 2001, approximately 1.7 million acute ischemic stroke patients have received edaravone in Japan [1].

Clinical Studies of Edaravone in ALS

The dosage regimen in all phase III studies was 60 mg by infusion over 60 min once a day for 14 days, followed by a 2-week break without infusions in the initial cycle. Repeating treatment cycles were comprised as 10 days of treatment out of 14 days, followed by a 2-week break without infusions. The 14- day treatment duration in each cycle was based on the regimen established in stroke patients in Japan. The 60 mg dose was selected based on the findings of a 24-week phase II study in ALS. This phase II study (Study MCI186-12) compared the disease course of enrolled patients "on drug" relative to their pre-treatment rates of decline. The 60 mg/d dose showed a statistically significant reduction in decline in ALSFRS-R, in addition to the reduction of 3NT in CSF after the 60 mg/d treatment [1,6,7].

Adverse Effects

They include gait disturbance, confusion dermatitis, respiratory failure, glycosuria, tinea infections [6].

Conclusion

ALS clinical trials have faced challenges in handling large variability in disease progression among patients. In the series of clinical trials of edaravone in ALS, the ALSFRS-R, as a well-validated scale, was used as the primary endpoint to measure the rate of disease progression during a 24-week double blind period, Edaravone has been approved for ALS in Japan and South Korea in 2015, and in the United States in 2017. Our study about clinical efficacy and safety of edaravone in ALS is underway.

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