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The first exploratory clinical trial using Batroxobin combined with Edaravone to treat ALS

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Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by permanent degeneration of both lower and upper motor neurons. The main symptoms of ALS are muscle atrophy, fasciculations, spasticity and loss of muscle strength. Loss of muscle strength in the respiratory system eventually leads to death. Without artificial ventilation, death occurs within 2 to 4 years after the onset of symptoms. Five to ten percent of ALS patients have contracted ALS due to genetic causes, having relatives with ALS [1]. Mutations in *SOD1* (superoxide dismutase 1) and several other genes have been identified as genetic causes of ALS. The remaining 90% of patients are classified as sporadic ALS patients [2]. The cause of the disease in these cases remains unclear. At present, since no curable treatment of ALS exists, current treatment methods focus on managing symptoms. Gastrostomy is used to counter dysphagia and artificial ventilation is used to provide respiratory support.

The first pharmaceutical treatment for ALS was riluzole, an antiglutamatergic drug, approved for therapeutic use in Japan in 1999. Edaravone, a radical scavenger, was approved in 2015 in Japan and in 2017 in USA for ALS. Riluzole has been reported to prolong life expectancy and edaravone has been reported to prolong the duration of a better quality of life [3-4]. However, as these drugs have limited effectiveness, more effective treatment is necessary. Several treatment agent candidates such as methylcobalamin, masitinib and levosimendan are currently being developed [5-7]. Also, mesenchymal stem cell therapy is being studied [8].

Batroxobin is a thrombin-like enzyme extracted from the venom of the snake species *Bothrops moojeni*. A single-chain glycopeptide, batroxobin has a molecular weight of approx. 36,000 Da. Batroxobin promotes the hydrolysis of fibrinogens and causes separation of fibrinopeptide A. Increasing the dosage of batroxobin causes a decrease in blood stream fibrinogen concentration, a decrease in blood viscosity, and the likelihood of blood coagulation. In Japan, batroxobin was approved in 1989 with the name Defibrase®. Batroxobin has been used to treat Burger's disease, vibration disease, and sudden deafness in Japan [9]. In China, it is also used for cerebral infarction [10].

It is widely known that oxidative stress is one of the main mechanisms of ALS. ALS patients benefit from edaravone due to its protective effect on motor neurons against free radicals. Edaravone neutralizes a wide range of free radicals and supposedly protects neurons, glial cells, and endothelium cells. Several studies have demonstrated that ALS patients have increased numbers of inflammatory biomarkers in their brains and spinal cords [11]. Keizman et al. reported that ALS patients have low-grade inflammation and elevated fibrinogen levels [12]. In recent years, neuroinflammation has been considered to be one of the mechanisms of ALS.

Inoue et al. conducted an animal experiment on demyelination, showing that batroxobin was effective in inhibiting neuropathy caused by the activation of microglia and astrocytes [13]. Furthermore, Yang et al. demonstrated possible preventive and curative effects of batroxobin with their experimental autoimmune encephalomyelitis (EAE) mouse model [14]. Zhang et al. used an ischemia-reperfusion model to measure changes in superoxide dismutase and malondialdehyde in the hippocampi and demonstrated the effectiveness of batroxobin in neutralizing free radicals [15]. In China, edaravone and batroxobin are commonly used together in treating cerebral infarction patients, and it has been reported that this combination of drugs has been effective [16].

Based on the above studies, we consider batroxobin as a candidate drug for treating ALS. We conducted a clinical trial of batroxobin to evaluate the safety and efficacy in the treatment of ALS. Precautions should be taken when using batroxobin owing to an increased susceptibility to hemorrhage due to decreased fibrinogen concentration and delayed hemostasis. For safety reasons, the fibrinogen concentration of each patient was monitored, and each patient was given a warning regarding hemorrhage, prior to the trial. The study protocols were approved by the Institutional Review Board of Asai Dermatology Clinic.

Participants in this trial were definite and probable ALS patients, who had experienced ALS symptoms for 2 years or less, were being administered edaravone, were capable of living independently, and had forced vital capacity (FVC) of 80% or higher.

In this trial, the DF-521-15 study, during a 2-week course in which edaravone was administered, batroxobin was first administered at a dose of 10 batroxobin units (10 BUs) and then (from the 2nd to the 6th time) at a dosage of 5 BUs, on alternate days, six times in total. This was followed by a two-week rest period. The sequence of a two-week medication period and two-week rest period was considered a single cycle. This study consisted of three cycles; therefore the total duration was 12 weeks. The total number of participants was five.

During the course of the study, no adverse events were found regarding increased susceptibility to hemorrhage, or any other negative effects. Clinical test values showed a single instance of the following: increased white blood cell count, increased ALT, and increased γ-GTP.

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However, each of these was clinically no significant. As for effectiveness, one participant demonstrated a 6-point decrease in ALSFRS-R (ALS Functional Rating Scale-Revised), and the remaining four showed a 1-point decrease. As for secondary effects, participants demonstrated an average 1.6% decrease in FVC.

In conclusion, we suggest that DF-521-15 demonstrated the safety of batroxobin in treating ALS patients. Further studies are required to determine the optimal dosage and duration of batroxobin treatment.

Conflicts of interest

H. Yoshino receives research funding from Tobishi Pharmacertical Co., Ltd. and is a consultant for Tobishi Pharmaceutical Co., Ltd.,

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