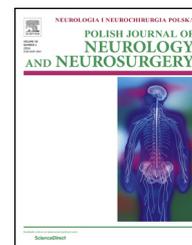


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Editorial

Edaravone in the treatment of amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is the most frequent adult-onset motor neuron disease. It involves damage of the upper motor neuron within the motor cortex and the lower motor neuron in the nuclei of the cranial nerves and alpha motor neurons of the spinal cord. The disease mechanism is complex and involves disturbed mRNA metabolism, glutamate excitotoxicity, cytoskeletal defects and altered axonal transport, hyperactivation of microglia, disturbance of protein quality control and oxidative stress [1]. In approximately 70% of cases the disease starts in limbs (impaired manual skills or foot drop), while in 30% of patients it first involves bulbar muscles leading to dysarthria and dysphagia. In rare cases (<1%) the first symptoms are head drop or respiratory distress. Along with disease progression, ALS leads to respiratory insufficiency, quadriplegia with muscle wasting, loss of useful speech and swallowing. Death, mainly due to the respiratory insufficiency, follows after 3–5 years from the first symptoms' onset. In 10% of cases the disease lasts for over 10 years or less than 1 year [2,3].

Although ALS is a rare disease with the overall incidence of 1.75 in 100 000 population/year, and prevalence of approximately 6 cases per 100 000, there are nearly 450 000 people living with ALS worldwide [4,5]. In 1995 the Food and Drug Administration (FDA) approved riluzole for the treatment of ALS. The drug was registered in Europe in 1996, but in some countries it became refunded as late as in 2010. Riluzole blocks the NMDA receptors, decreases glutamate concentration in the synaptic cleft, increases its reuptake what leads to decreased influx of calcium ions and exaggerated activation of the cell metabolism, called excitotoxicity [6]. Unlike hundreds of other compounds studied throughout the years, riluzole was the only drug able to modify ALS clinical outcome. The treatment has not however fulfilled the patients' needs. Riluzole neither improves the clinical state, nor affects the muscle strength or stops disease progression. It only modestly prolongs mechanical ventilation-free survival by 2–3 months if taken for the first 18 months of disease duration [7]. For these reasons, an approval of edaravone, a new drug modifying ALS progression, caused enthusiasm among ALS patients.

Considering the serious nature of the disease, which inevitably leads to death in a short time-period, and a

prolonged lack of effective treatment, edaravone (Radicava, Mitsubishi Tanabe Pharma America) was approved by FDA for the treatment of ALS in May 2017, after only one small positive clinical trial of short duration [8]. The drug had earlier been registered in Japan and South Korea (under a brand name of Radicut) for the treatment of acute stroke (2001), and ALS (2015) [9]. Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a neuroprotective compound. Its mechanism of action in the treatment of ALS is not clear but most probably based on radical scavenging properties [10].

In physiological conditions, edaravone is present in both dissociated (anionic) hydrophilic form and non-dissociated, neutral lipophilic form [11]. It is therefore active in the cytoplasm, where it neutralizes free oxygen species by adding a spare electron. The lipophilic properties, on their turn, enable diffusion through the cell membranes [9,11]. In preclinical studies edaravone was effective against lipophilic radical oxygen species (similarly to vitamin E), as well as the hydrophilic ones (like in the case of ascorbic acid). It has shown neuroprotective properties toward neurons, as well as the ability to suppress inflammatory response of the activated microglia [11].

In serum 90% of edaravone binds to proteins and its half-life ranges from 4.5 to 6 h [10]. The drug is metabolized in liver and kidneys. In doses used in humans, edaravone and its metabolites do not influence the metabolism of CYP450 [12]. The pharmacokinetics of edaravone does not depend on age, gender and body mass. A study performed in a group of 86 healthy volunteers showed no clinically significant differences in the pharmacokinetics and pharmacodynamics between the population of Caucasian and Japanese origin [13]. Pharmacokinetic data on individuals with renal or liver insufficiency are however lacking [12].

The safety and efficacy of edaravone in ALS was studied in 206 patients in a randomized, double-blind, placebo-controlled trial (MCI186-16) [14]. After 3 months of clinical observation, patients received either edaravone or placebo for 6 months. The studied compounds were infused intravenously once a day: for 14 days in the first cycle, followed by a 14-day-wash out period, and for 10 out of 14 days of the month followed by a 14-day long drug-holiday in cycles 2–6. The

Table 1 – Summary of clinical trials with edaravone in patients with amyotrophic lateral sclerosis (ALS).

Study	Treatment duration	Number of participants	Inclusion criteria	Primary end-points	Secondary end-points	Result	Adverse effects
MCI186-16 randomized, double blind, placebo-controlled study [14]	6 months	n = 104 edaravone, n = 102 placebo	Definite/probable/probably laboratory supported ALS, disease duration ≤ 36 months, FVC ≥ 70%, 4 points at all ALSFRS-R respiratory items	ALSFRS-R at 6 months from baseline	%FVC, grip/pinch strength, Modified Norris Scale, ALSAQ-40, time till death or till reaching milestones of disease progression (loss of unassisted walking/upper limb functions, artificial ventilation of gastrostomy) as above	Negative (positive result in post-hoc analysis in a subgroup of patients [17])	Equal frequency in edaravone and placebo group
MCI186-17 double-blind randomized, prolongation of MCI186-16 study [15]	6 months (12 months including the double-blind M186-16 study period) followed by a 3-month open-label edaravone phase	n = 48 edaravone (from MCI186-16)-edaravone group, n = 45 edaravone-placebo group, n = 88 placebo-edaravone group	As above	As above	as above	Negative	Higher frequency in edaravone group
Open label extension study of MCI-186 [16]	6 months (12 months including the double-blind M186-16 study period)	n = 65 edaravone (from MCI-186 group)-edaravone, n = 58 placebo-edaravone, n = 0 placebo-placebo	Definite/probable ALS, disease duration ≤ 24 months, FVC ≥ 80%, ≥2 points on all 12 ALSFRS-R items	ALSFRS-R, %FVC, Modified Norris Scale score, ALSAQ-40, time to death or till reaching milestones of disease progression (loss of unassisted walking/upper limb functions, artificial ventilation of gastrostomy)	Negative	Equal frequency in edaravone and placebo group	
MCI186-18 randomized, double-blind, placebo-controlled study [18]	6 months	n = 13 edaravone, n = 12 placebo	Definite/probable/probably laboratory supported ALS, FVC ≥ 60%, disease duration ≤ 36 months	ALSFRS-R, %FVC, Modified Norris Scale score, ALSAQ-40, grip/pinch strength and time to death or till reaching milestones of disease progression (loss of unassisted walking/upper limb functions, artificial ventilation of gastrostomy)	Negative	Equal frequency in edaravone and placebo group	

Table 1 (Continued)

Study	Treatment duration	Number of participants	Inclusion criteria	Primary end-points	Secondary end-points	Result	Adverse effects
MCI186-19 randomized, double blind, placebo-controlled study [8]	6 months	n = 69 edaravone, n = 65 placebo	Definite/probable ALS, ALSFRS-R ≥ 2 points on each item, FVC ≥ 80% disease duration ≤ 24 months	ALSFRS-R at 6 months from baseline	%FVC, grip/pinch strength, modified Norris scale, ALSAQ-40, time till death or till reaching milestones of disease progression (loss of unassisted walking/upper limb functions, artificial ventilation of gastrostomy)	Positive for Δ ALSFRS-R, QoL and Modified Norris Scale at 6 month	Equal frequency in edaravone and placebo group

Legend: The edaravone dose was equal in all studies: 60 mg iv once daily iv for 14 days in the first cycle, followed by a 14-day wash-out period, and for 10 of the first 14 days of the month followed by a 14-day drug holiday in the subsequent cycles. ALSFRS-R – ALS functional rating scale-revised, ALSAQ40 – ALS assessment questionnaire, QoL – quality of life.

primary end-point was a change of ALSFRS-R at 6 months from baseline. The secondary end-points are summarized in Table 1. The overall result of the study was negative. A prolongation study (MCI186-17), in which after 6 months of treatment with edaravone the patients were again randomized to receive either edaravone or placebo for 6 months followed by a 3-month open-label edaravone phase, did not show drug-induced benefit [15]. The study showed more serious adverse effects associated with ALS progression in the edaravone group possibly due to asymmetric randomization (a higher percentage of older patients in the edaravone group).

However a post-hoc analysis of the data from the MCI186-16 study revealed that edaravone might have a positive effect on subgroup of patients in an early stage of ALS and definite or probable diagnosis [17]. The patients who could potentially profit from the treatment had disease duration of less than 24 months, FVC ≥ 80% and obtained ≥ 2 points in every item of ALSFRS-R (subtle speech and swallowing problems, able to self-feed, and self-dressing, walking without assistance, no indications for gastrostomy and ventilation support).

Based on this analysis, in 2011 a new smaller phase 3 study was launched, which enrolled exclusively patients fulfilling the above-mentioned criteria [8]. Indeed, edaravone showed a benefit after 6 months of treatment. There was a significantly smaller decline of ALSFRS-R score compared with placebo (-5.01 ± 0.64 vs. -7.50 ± 0.66 , $p = 0.0013$), better outcome on the modified Norris scale and ALSAQ-40. In their conclusions the authors pointed out there was no indication that edaravone might be effective in a wider population of patients with ALS who did not meet the criteria [8]. There was also a randomized, double-blind placebo-controlled study in a group of 25 patients with advanced ALS. It enrolled patients with clinically definite, probable or probable-laboratory supported ALS, FVC > 60% and disease duration < 36 months. Although there were no differences in the frequency of adverse events between the groups, the study failed to reach statistical power and did not show clinical benefits after 6 months [18].

For this reason, a very fast approval of edaravone for the treatment of the entire population of ALS patients raised serious considerations among the neurologist involved in the ALS care.

European Network for the Cure of ALS (ENCALS) published a statement addressing some crucial issues considering the available information on the potential benefit of edaravone [19]. The authors emphasized that edaravone registration was based on a single clinical trial performed in a small ($n = 137$) group of patients in one population. A short trial duration (6 months) did not allow for analysis of survival. Despite the fact the treatment significantly reduced disease progression and positively influenced the quality of life in a subgroup of ALS patients fulfilling specific criteria, the authors pointed out at a very fast disease progression in the ALS placebo group (-7.5 points in ALSFRS-R/6 months) compared to earlier studies, which showed ALSFRS-R decrease at -5.6 points/6 months on average. It might again suggest an asymmetric randomization, which could have influenced the study outcome. The same issue was brought up in the correspondence to Lancet Neurology [20]. ENCALs encouraged Mitsubishi Tanabe Pharma (MT Pharma) to conduct a longer trial in Europe.

In response to the ENCALS statement, the company performed a study, which compared demographic and clinical data of Japanese, US and European ALS patients who participated in 12 clinical trials published since 2000 [21]. No significant differences were found between the familial/ sporadic cases, bulbar/limb onset, diagnosis delay, or disease progression. As compared to European and US studies ($n = 10$), the patients participating in 2 Japanese (edaravone) clinical trials had a lower BMI, higher use of riluzole and shorter disease duration. The progression rate in patients who received placebo, as assessed by slope changes in the ALSFRS-R score ranged from -6.2 to $-7.3/6$ months in the Japanese patients as compared to -5.3 – $9.6/6$ months in the European and US patients. Based on the above comparison the authors concluded that there was evidence to support the generalizability of data from the Japanese ALS trial experience to the US and Europe populations in early to mid-stage of ALS [21].

The MT Pharma performed an indirect analysis of the effect of edaravone on the function of muscle groups (bulbar, arms, legs, respiratory) based on the ALSFRS-R outcome. The analysis concerned the change in the ALSFRS-R items and domains at the end of the positive phase 3 study compared to baseline [8,22]. It showed that edaravone slowed functional decline across all 4 anatomical regions. The favorable effect was present in patients with either bulbar or limb onset [21]. After completion of the 6-month double-blind study, patients from edaravone ($n = 65$) and placebo ($n = 58$) groups received edaravone for further 6 months in an open-label trial [23]. The analysis showed a better clinical outcome of patients who received edaravone treatment for 12 months as compared to a 6-month-treatment.

A combined analysis of adverse events was performed based on the results of three phase 3 studies, which included the total of 368 ALS patients ($n = 184$ in the edaravone and placebo group each) [17,24]. The frequency of adverse effects requiring treatment was equal in both groups (87.5 vs. 87.0%, respectively) and it was stable throughout the treatment period. Serious adverse events included disease-attributed respiratory disorders and dysphagia (17.4% vs. 22.3%). Only 2.2% patients discontinued treatment in the edaravone and 5.4% in the placebo group, while 3.3% patients died during the study due to respiratory insufficiency (2.2% and 1.1%, respectively). Commonly reported adverse events that were more frequent in the edaravone group included contusion, gait disturbance, headache, skin changes, respiratory disorder and glucosuria [24]. Since hypersensitivity reactions and anaphylactic reactions were reported in spontaneous postmarketing reports, the drug is contraindicated in patients with a history of hypersensitivity to edaravone or any of the inactive ingredients of the product. The sodium bisulfite present in the solution may cause allergic type-reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people, more probably in patients suffering from asthma [12].

Based on the data published to date we can summarize that edaravone is a drug, which decreases disease progression in early-stage of ALS in self-dependent patients with no respiratory involvement and indications for gastrostomy. It can be safely used for 12 months provided precautions considering allergic-type reactions in predisposed patients.

Treatment decisions should however be taken after a careful consideration of organization and administrative issues. Intensive as it is, the edaravone treatment requires careful time planning. The drug is given intravenously once daily for 14 days followed by a two-week break. In consecutive cycles it may be administered for 10 out of the first 14 days of the month again followed by a fortnight break. Each infusion lasts for approximately 60 min and for safety reasons at least the first two cycles should be administered at hospital settings [19]. Therefore the patients should be prepared to spend half of every month on treatment. Not only do they have to consider the primary need for hospitalization, but also the localization and commute to the infusion center or logistics of home infusions. The costs of the drug range from 220 to 1000 USD/infusion, excluding the hospitalization expenditure, commute, work-absence days, involvement of the care-giver, etc [25]. Altogether, despite the fact edaravone was proved to increase the quality of life, its costs and way of administration may negatively influence the compliance of some patients. On the other hand, there are patients who may profit from certain regularity in treatment, which gives them a feeling of an active launch against the disease [25].

With all the pros and cons, edaravone has brought a new treatment strategy into the ALS field [26]. For the first time in the history of drug research in ALS, the study reagent has been used in a group of patients with predefined clinical features [27]. It might be the first step toward tailoring treatments for prospectively stratified patients with the scope to identify patients' groups who will most likely profit from given therapeutic agents.

Conflict of interest

The author is a member of the Executive board of the European Network for the Cure of ALS (ENCALS).

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