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Review paper

Edaravone, a new therapeutic option in amyotrophic lateral sclerosis: Evaluation of challenges in the drug accessibility

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Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, with about 3–4 years median survival from the onset of symptoms. Only two therapies for ALS have been proven effective in slowing down this condition, riluzole and edaravone. Recently approved edaravone, either original or generic, is not registered in Poland. It can only be used after special approval of Polish Ministry of Health. The costs of payment have to be covered by patient in full.

Aim: In this article we will describe the public demand of edaravone in Poland for ALS treatment and problems related to prescribing the drug, like procedures and prices.

Material and methods: This article is based on the available literature and on data obtained from Polish Ministry of Health.

Results and discussion: The high cost of therapy affects the relatively widespread use of generic medicines not registered in Europe. We identify mechanisms of the demand and supply for various formulations of edaravone in Poland. These information should be of relevance to many other countries, especially within the European Union.

Conclusions: Medicines available from licensed manufacturer are more expensive than offers available on-line. Although original chain of distribution presents with unrivaled warranty to avoid purchasing of adulterated drug we report the challenges of the edaravone treatment initiation in ALS patients in Poland.

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1. INTRODUCTION

Amyotrophic lateral sclerosis (ALS), known as Charcot's disease or Lou Gehrig's disease, is a fatal neurodegenerative disease, which affects central and peripheral motor neurons leading to progressive muscle weakness, dysphagia and dysarthria. In the last phase of the disease, respiratory muscle weakness leads to respiratory failure. What is also important, ALS is a rare disease with unclear pathophysiology. The incidence of ALS is approximately 2 cases per 100 000 population, which varies in the range from 1 case per 100 000 up to 8 cases per 100 000 in some parts of Europe.[1] In 2015 in the European Union, about 30 000 to 50 000 people suffered from this disease and the number of patients is gradually increasing.[2, 3] According to data released by polish authorities, there is approximately 586 new ALS patients in Poland yearly.[4] The median survival from the onset of symptoms is about 3–4 years, however, population studies show that it is difficult to clearly predict what the time course of the disease will be for individual people. The disease affects significantly more often men than women, predominatingly aged 40–70 with the peak of illness in the seventh decade of life.[5] There are also two basic types of ALS: sporadic ALS (sALS) and family ALS (fALS).[6] However, only about 5%–10% of all cases are hereditary, and the majority of cases are sporadic.[7]

Despite the extensive work on possible treatment, so far apart from the only available drug riluzole[8,9] and experimental therapies,[10] among others associated with the administration of stem cells,[11–13] there have been no major advances in the treatment of this tragic disease. The edaravone, approved by the Food and Drug Administration (FDA, USA) in 2017 (Radicava, Mitsubishi Tanabe Pharma America), was light in the tunnel for ALS patients around the world. Main goal of pharmaceuticals therapies is slowing down progress of disability and decrease natural course of ALS. The registered and experimental therapies try to affect one of diseases pathological mechanisms, because effectiveness strictly depends on understanding the primary cause of the disease.[14] There is long list of potential triggers that may contribute to motor neuron degeneration in ALS: oxidative damage, glutamate toxicity, impaired axonal transport, mitochondrial malfunction, apoptotic death of neurons, growth factor deficiency, glial cell pathology and abnormal RNA metabolism. Difficulty in attempting to treat spontaneous ALS is that its causes remain unclear. A way to treatment the genetic causes of ALS could be gene therapy.[15] Symptomatic treatment in ALS includes therapies for spasticity, muscle cramps, pain, sialorrhea signs, insomnia and depression.[16] Except pharmaceutical therapies, rehabilitation tailored to the individual's needs,[17] speech therapy, mechanical ventilation and enteral tube feeding are integral to optimal, multidisciplinary care for ALS patients.

Despite the numerous clinical trials, until now, only two disease-modifying therapies (DMT) for ALS have confirmed to show an improvement of the selected clinical parameters of the patient. First was riluzole, a glutamate release inhibitor approved for the treatment of ALS in 1995. A survival benefit of approximately 3 months was noted in clinical trials with no effect on function or quality of life was discernible.[18,19] More recently, in 2017, another drug was found to be effective in altering ALS progression: edaravone.[20] Edaravone is a putative antioxidant but a direct mechanism of its in vivo effect in ALS is not fully understood.[21] With these two compounds only available as DMT the major part of ALS treatment has to be limited to the supportive care and symptomatic treatments.[22]

Early clinical trials conducted from 2001 have indicated that edaravone shows promising efficacy in terms of inhibiting the deterioration of motor function in ALS patients. Although the first 3rd phase randomised clinical trial (RCT) for edaravone failed to demonstrate the efficacy of this drug in the treatment of ALS (MCI186-16). Post hoc analysis revealed the efficacy of edaravone for the early stage and typical features in ALS patient who have a duration of illness up to 2 years, a percentage forced vital capacity over 80%, scores 2 or more points for each item of the ALSFRS-R scale, no abnormal breathing symptoms, and a diagnosis of either definite or probable ALS according to the revised El Escorial criteria.[23] The second 3rd phase study (MCI186-19) confirmed the distinct efficacy of edaravone in this group of ALS patients.[4] This study prospectively documented a 33% reduction in rate of progression of ALS. Recently two meta-analyses and post-hoc analyses of the MCI186-16 and MCI186-19 have been published. Luo et al. have concluded that intravenous edaravone was efficacious in ALS patients, with no severe adverse effects.[24] However, a need for the more well-designed RCTs with a larger sample size was emphasized in order to explore the long-term efficacy and safety of edaravone. Similarly, Palumbo et al. have supported detection of a treatment effect in published RCTs of edaravone in ALS,[25] and as in the Luo's et al. study, there is also a need of a larger RCT. Additionally a call for a real-world analysis and experience has been made to further support the role of edaravone in ALS treatment. Indeed, a first post-marketing studies with edaravone in an non-selected group of patients with ALS start to emerge and support the need of a real-life setting evaluation of edaravone effect in ALS patients.[26]

The newly approved antioxidant drug edaravone, beyond riluzole, is a force multiplier for ALS treatment.[27] Edaravone is recommended to treat early phase of probably and definitely ALS. This therapy inhibits motor function deterioration[28] and shows a significantly smaller decline of ALSFRS-R score compared with placebo, with a safety profile comparable to placebo in reported side effects.[21]

According to selected registers from the USA, approximately 25% of registered patients with ALS started edaravone treatment. Among them, about 17% have discontinued this therapy, typically about 2.6 months after starting treatment.[29]

2. AIM

Important issue to consider is the problem of the availability of various preparations of the edaravone on the free market, mainly on the internet, but distributed outside the official

supply chain. Such drugs are much cheaper, but their effectiveness is not certain. In this article we will outline how, 2 years after registration of the drug, it is evaluated by doctors and patients and how it is used in Poland for ALS treatment.

3. MATERIAL AND METHODS

This research was based on the information obtained from Polish Ministry of Health, and own analysis of edaravone formulation availability in online pharmacies.

4. RESULTS AND DISCUSSION

Currently there are no edaravone preparations available in Poland and edaravone treatment is not recovered/refund by Polish health care system, according to lack of positive approval of proper authorities (Rada Przejrzystości). In general, negative opinion about this treatment is caused by unknown price, and lack of possibility to calculate cost and effectiveness ratio, and non-appropriate evidence about efficacy of the drug.[4] Nonetheless, Polish national health care system allows to use unregistered medicines under special agreement given by the Ministry of Health, and this procedure seems to be working properly. Application, prepared by patient's neurologist, is passed to voivodeship consultant for neurology and then to ministry for final approval. Procedure takes up to about 20 days and after it, patient is able to buy medicine with full payment in commune pharmacies. The medicine can be administered to a patient in a public hospital, but in some cases, administration is private and patient must cover full cost of it.

From March 15, 2017 to the beginning of June 2019, 114 needs for medicinal products with an active substance of the international name edaravon/edaravone were submitted to the Polish Ministry of Health (in accordance to procedure of 'importing a medicinal product necessary to save the life or health of a patient admitted to trading without having to bring medicine from abroad. obtaining a permit'). In total, 97 consents were issued for 54 patients (Table 1).

As a new medication, original formulation of edaravone (Radicava) is expensive for polish patients, and according to information obtained from neurologists dealing with the procedure of obtaining a medicine, 'generic' formulations, mainly produced in India, are widely used. For example, price of original Radicava (from internet pharmacy) is about 200 euro per day of treatment,[30] meanwhile price of generic drug from India is about 16 euro per day of treatment,[31] so it's more than 10 times cheaper.

The very high cost of therapy using the original drug prevents access to this therapeutic option for a patients in many European countries, including Poland, combined with the lack of effective alternatives, causes a high interest in the use of a generic drug. Furthermore the original preparation containing edaravone is registered only in the USA, Canada, South Korea, Japan and Switzerland.[32] A situation of a high demand from an ALS patients for a novel treatment, a supply of a various preparations which none of them is officially registered as well as extreme differences in the treatment financial burden complicates treatment decisions for a neurologist beyond purely medical aspects. Therefore the situation of edaravone availability for ALS patients treatment needs to be properly. A situation observed in Poland indicates a problem that exists in all European Union countries, as well as many other locations, affecting the therapeutic choices for an ALS patients.

However, emerging doubts about quality of drug, calls into question preparations produced as generic formulation in general. Especially in new clinical situations for neurologists, when patient bring his own and 'suspiciously looking' medicine to the hospital ward, to start very specialist treatment. Additional abnormality is lack of proper documentation for 'generic' formulations, as proper drug characteristics, available for any drug registered in Europe.

It is worth to underline that official chain of distribution (producer–distributor–pharmacy) allows physicians to expect that medicines are non-falsified, produced correctly, properly stored and transported due to rigorously respected and controlled rules of Good Manufacturing Practice and Good Distribution Practice.

5. CONCLUSIONS

Drug demand, its price and numerous formulations available in on-line pharmacies and shops, seems to be source of potential problem. Edaravone formulations available on official market are circa 10 times more expensive than numerous offers available on-line. It is technically possible to buy any medicines by Internet and get it by parcel post. Such procedure is always connected with risk of purchasing of adulterated drug. That fact should be taken into account when prescribing edaravone. It seems to be easier, quicker and cheaper than following official way, awaiting official approval, etc. It must to be firmly underlined, that official chain of distribution is unique warranty to avoid purchasing of adulterated drug. Nevertheless as it is seen in Poland, cost burden of the treatment for ALS patient could present as a dominating factor further influencing therapeutic decisions.

Table 1. Demand for edaravone according to the data of the Polish Ministry of Health (own study).

Date range	Number of applications submitted to the ministry	Number (%) of consents issued	Number of patients for whom consent has been granted
March 2017 – June 2019	114	97(85)	54

Data obtained from the Department of Accessibility and Safety of Medicinal Products in the Department of Pharmaceutical Policy and Pharmacy of the Ministry of Health in Poland at June 3, 2019.

Conflict of interest
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