Edaravone: a baby in the bathwater?

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Communication in today's world is fast and ever accelerating. Until May 2017, however, it remained largely unnoticed on both sides of the North Atlantic that a new drug, edaravone (Radicava®, Mitsubishi Tanabe, Japan), for treating amyotrophic lateral sclerosis (ALS) was approved by the Pharmaceutical and Medical Device Agency in Japan on 26 June 2015. This delay is remarkable because pharmaceutically active compounds are viewed as having only a modest effect on the natural history of ALS, and therapeutic innovations are absolutely necessary.

The only drug that has been repeatedly shown to favorably influence the disease course is riluzole, a glutamate release blocker, which slowed the disease course by 3 months in patients with a mean life expectation of approximately 12 months.[1] The mechanistic concept of a successful antiglutamatergic mode of action is complementary to the results of recent neuroanatomical studies and their interpretation.[2]

What is edaravone and what kind of data support the claim for its efficacy in this dreadful disease? The reportedly neuroprotective effect of edaravone has been attributed to its antioxidative properties, and in Japan, the drug has been approved for treating patients with acute ischemic strokes. Edaravone was then tested in animal models of ALS and shown to have a limited impact. These animal models have been critically discussed[3] and, since they are rodent models, are not ideal for testing therapies in a disease of phylogenetically young anatomical structures of the human brain.[2]

Although the results in animal models were not convincing, the company developing edaravone moved forward to human studies[4] and found in a *post hoc* analysis that a subgroup of patients with ALS experienced beneficial effects from edaravone treatment. This subgroup consisted of patients with early-stage ALS in whom disease progression was rapid rather than gradual. Then, a second randomized, double-blind, parallel-group trial was performed, in which the inclusion criteria were restricted to this group of early patients. This trial used a dosage of 60 mg edaravone, included 137 patients, and confirmed the results of the *post hoc* analysis by showing that the decrease of the established clinical score, the ALS Functional Rating Scale (ALS-FRS), was statistically significantly reduced during the disease.[5] Reported adverse effects were minor.

Do we now have a second successful ALS drug? This issue will be hotly debated, similarly to the discussions surrounding riluzole studies in the 90s. In my view, the following aspects are relevant:

1. **Is the published effect of edaravone treatment relevant for ALS patients?**
   I believe that the effect of slowing down the ALS-FRS score by one-third in 24 weeks for the subgroup of ALS patients included in the trial is a significant one. This, in turn, has immediate practical implications for treatment since the patients treated were only affected by the disease in a minor way. Can we diagnose these patients with early ALS? The answer is yes: in our Schwabia Registry (capture/recapture rate $> 80\%$), we calculated a time to diagnosis of 6 months[6] using the old El Escorial criteria.[7] Recently, new El Escorial criteria were recommended by the World Federation of Neurology.[8] These will accelerate diagnosis and were developed for drugs with an efficacy profile resembling that of edaravone.
   What about a survival benefit similar to the one shown for riluzole? In the most recently published studies, survival was not chosen as an endpoint. This aspect definitely needs to be addressed, and the ALS field should use the opportunity to include measurements of long-term survival effects of drugs, which oncologists have been doing for decades.

2. **Is an intravenous infusion of a drug administered by health care professionals in cycles a practical way for treating ALS patients?**
   In my view, this method of application can only be justified by the historical use of the drug (i.e. in stroke medicine), and an oral drug that can be administered on a daily basis must be developed soon. This is particularly true for a drug with antioxidative properties.
3. **Was the trial dosage chosen the right one?**
   The answer is that we have no firm knowledge about the dose–response relationship of edaravone in ALS.
4. **Should we prescribe edaravone for all patients with ALS?**
   Once again, we do not know. It is not unlikely that, provided a longer study period and different endpoints are chosen, other patient groups could experience a disease-modifying effect as well.

Clearly, heated discussions on the potential effects of edaravone are foreseeable, among them the price of the drug. The debates will not provide answers; answers will emerge by the willingness to act. This means a new trial must be performed that includes survival (ideally, long-term survival) as an endpoint and tests multiple doses. Moreover, an oral form of the drug needs to be developed.

Discussions are unavoidable (and necessary) in a pluralistic world; but the ALS community should avoid throwing the baby out with the bathwater!

Author's Note

AL is on an advisory board of Biogen, Treeway and Hoffmann-La Roche, has signed contracts for clinical studies with AB Science, Biogen Idec, Cytokinetics, GSK, Orion Pharma, Novartis, TauRx Therapeutics Ltd. and TEVA Pharmaceuticals, and as a consultant for Mitsubishi, Orion Pharma, Novartis, and TEVA.

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Conflict of interest statement

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