Edaravone: a new treatment for ALS on the horizon?

Despite the urgent, unmet clinical and economic need for treatment of neurodegenerative diseases, trials of disease modifying drugs have produced little success. Amyotrophic lateral sclerosis (ALS), an exemplar of neurodegeneration, is primarily characterised by rapid-onset loss of upper and lower motor neurons that results in patient death from respiratory failure. As with other neurodegenerative diseases, the pathobiology of ALS is not well understood. At least 30 genes of major effect have been reported, and disease models suggest that a number of different but interacting pathogenic processes contribute to disruption of neuronal cell machinery, oxidative stress, and activation of a neuroinflammatory response by microglia and astrocytes. The relative contribution of various pathogenic processes within individual patients has not been well characterised, and disease heterogeneity is likely to account in part for the failure of over 50 major phase 2 and 3 clinical trials in patients with ALS, despite positive studies in animal models.

Edaravone, a neuroprotective drug that has properties of a free radical scavenger, could potentially reduce oxidative stress, and was initially developed as an intravenous treatment of acute ischemic stroke. A previous study showed that edaravone attenuated motor symptoms or motor neuron degeneration in mice with the mutant SOD1 gene (a rodent model of ALS), and results of an open label phase 2 study in patients with ALS provided evidence of reduced oxidative stress as measured by 3-nitrotyrosine levels in the treated group. However, a double-blind, placebo-controlled phase 2 study using intravenous edaravone therapy in patients with ALS failed to show a significant difference between treated and control patients. Post-hoc analysis of this study suggested the presence of a subgroup of patients who might have experienced a positive effect of the compound, and based on stringent criteria, a second phase 3 trial was designed, comprising 69 patients in the treatment group and 68 in the control group. In The Lancet Neurology, Makoto Akimoto and colleagues now report that the edaravone-treated group showed a change in ALSFRS-R score of −5.01 (SE 0.64) compared with −7.50 (0.66) in the placebo group (p=0.0013), which suggests a beneficial effect of the drug over a period of 24 weeks.

Despite the positive outcome of this trial and recent approval of edaravone by the US Food and Drug Administration for treatment of ALS, there are limitations which could make it difficult for clinicians to prescribe the drug with an expectation of efficacy. First, the inclusion criteria were stringent, as the investigators sought to reflect the clinical characteristics of the apparent responders identified by post-hoc analysis. 137 patients were enrolled from 31 Japanese ALS centres over a 34 month period. This relatively long enrolment period and the large number of sites are not surprising. Using the stated criteria and applying them to population-based registers in Ireland and The Netherlands, we estimate that less than 7% of patients with ALS would be eligible for enrolment.

Second, the study duration was short, comprising 24 weeks in total, preceded by a 12-week observation period. Most trial guidelines of the European Medicines Agency propose a duration of at least 12–18 months. While the data suggest that the slope of ALSFRS-R decline was reduced in the treatment group, we do not have information relating to the longer term effect on safety, function, or overall survival. Moreover, the clinical meaningfulness of a change in overall ALSFRS-R slope is unclear. Recent data suggest that the slope of the subscales of the ALSFRS-R differs between patients with bulbar and spinal onset, and subscale analysis would be limited by power in this study.

Third, while it is biologically plausible that subcohorts of patients might respond differentially to targeted therapies, how to select such patients remains a conundrum, as at present there are no reliable markers of pathobiology. Akimoto and colleagues have provided enrolment criteria based on a post-hoc analysis of clinical characteristics. In doing so, they appear to have selected patients most likely to progress, and thus most susceptible to measuring a possible response to treatment. However, it is not possible to determine whether this selected cohort also represents a biological subgroup of patients characterised by high levels of oxidative stress. Measurement of CSF 3-nitrotyrosine, which showed a convincing decrease after edaravone treatment in the phase 2 trial, was not incorporated in either of the subsequent trials.
Finally, although the side-effect profile does not suggest toxicity, the treatment regimen of intravenous infusions for 10–14 days each month is inconvenient and potentially costly, and the longer term efficacy of the drug and patient adherence to the intravenous treatment has not been established. Otherwise, this study is a positive indication of a potentially useful therapeutic agent in a disease for which there is only one disease modifying drug. Future studies of edaravone are eagerly anticipated. The challenge, as in all clinical trials for patients with ALS, will be to identify biological markers that can truly anticipate treatment responders.

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