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What is edaravone?

Edaravone is a free radical scavenger originally developed for treatment of stroke, and is administered intravenously (IV). Patients receive the drug every day for 2 weeks, then take a break (‘drug holiday’) for 2 weeks, followed by 10-d sessions of treatment every month. Ideally, the first 2 treatment courses should be administered in a hospital for safety reasons, including potential side-effects and reactions to the drug.

What is known about the effectiveness of edaravone?

Japanese clinicians working with Mitsubishi Tanabe Pharma ran a 9-month study of edaravone, which included a 3-month observational period followed by a 6-month test period. This double-blind placebo controlled trial involved over 200 people with ALS, half of whom were randomized to receiving the drug, and half to a placebo treatment. This trial did not show any statistically significant benefit in favor of the drug, although there was a trend towards slower disease progression in the people taking the drug. This hint of an effect led the investigators to analyze the data more thoroughly, and they identified a subgroup of people that appeared to obtain some benefit. Subsequently, the investigators carried out an additional smaller study focused on patients with clinical characteristics of this subgroup only. These were people who had mild to moderate involvement of swallowing, fine motor function and gross motor function measured using the ALS functional rating scale (ALSFRS-R), with symptoms in 3 of 4 body regions (arms, legs, bulbar and thorax, as inclusion was restricted to definite ALS according to the El Escorial criteria), within 2 years of symptom onset, and with normal respiratory function. Enrolment took place across many sites in Japan over a 2-year period, and a total of 130 people were recruited. This trial showed a statistically significant slowing of disease progression as assessed using the ALSFRS-R over the 24-week treatment period in those taking edaravone.

The facts about edaravone

- The positive study was based on a small group of people with ALS who fulfilled very specific criteria before they could be enrolled in the trial. Within this group, those who received edaravone as part of the study experienced a
reduction in the rate of disease progression. Those taking edaravone declined by 5.1 points on the ALSFRS-R scale over 6 months, compared with those on placebo, who declined by 7.5 points. Previous studies have shown that most people with ALS decline by about 5.6 points over 6 months.

- The effect of edaravone on muscle strength and respiratory function is not clear.
- There is no known effect of edaravone on quality of life.
- No studies of the effect of edaravone after 6 months have been published yet.
- Due to the short study period (6 months) no survival data were collected.
- Treatment with edaravone is cost- and labor-intensive, with daily infusions for at least 10 d in the first 2 weeks of every month although in some countries, doctors can arrange drug administration off site from hospital settings.
- Intravenous (IV) injection of edaravone can be via a PICC line, Port-A-Cath, cannula (eg venflon) or butterfly, and it can take up to an hour for each daily infusion to be completed.
- It is recommended that at least the first 2 sets of infusion courses are administered in a hospital because of possible side-effects and the risk of a reaction to the drug.
- The costs of edaravone are more than €1000 per patient per month plus the cost of giving the infusions. Reimbursement of these costs by health services will depend on the health structure within each country. In some countries, the drug will not be funded by the existing health system, and the person with ALS will be required to pay for the treatment.

**Decision making on edaravone treatment**

Weighing up the pros and cons of edaravone treatment should be made on an individual basis, taking into account how closely the patient matches the trial clinical criteria, the therapeutic goals of the affected person, and their personal resources. Given the mode of drug application with frequent intravenous infusions, treatment with edaravone is associated with considerable time expenditure for patients and their care givers. The therapeutic benefits of edaravone treatment must be balanced against the potential burden of an intravenous route for the application of the drug.

**The opinion of ENCALS**

While the results of the studies are encouraging, questions regarding the effectiveness of edaravone remain:

1. Is edaravone beneficial to patients who are more severely affected than those who participated in the study?
2. Is the effect maintained if taken for more than 6 months?
3. Does edaravone affect survival?

The consensus view of the ENCALS neurologists is that an extended clinical trial with at least 12 months followup, including analysis of effects on survival, is indicated to resolve these questions, and to ensure that appropriately selected patients with ALS have maximum opportunities to avail themselves of a potentially beneficial therapeutic agent.

**ENCALS invites MT Pharma to conduct a trial in Europe**

**Declaration of interest**

The following author do not have conflict of interest: Siddharthan Chandran, Philippe Couratier, Olof Danielsson, Torsten Grehl, Caroline Ingre, Merete Karlsborg, Grethe Kleveland, Blaz Koritnik, Magdalena KuzmaKozakiewicz, Hannu Laaksovirta, Bernardo Mitre Ropero, Ingela Nygren, Mónica Povedano Panades, Francois Salachas, Gert Staal, Kirsten Svenstrup, Kevin Talbot, Ole-Bjørn Tysnes, Patrick Weydt, and Joachim Wolf.

Ammar Al-Chalabi is consultant for Mitsubishi-Tanabe Pharma, Cytokinetics, OrionPharma, Chronos Therapeutics, Treeway, GSK, Lilly, Biogen Idec; Chief Investigator for clinical trials run by Cytokinetics, OrionPharma; speaking honoraria from Cytokinetics Inc and Lilly.

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Adriano Chio served on an advisory panel on MITOS and KING’S for Mitsubishi Tanabe, consultant without compensation to Treeway, consultant for Biogen Idec and Italfarmaco.

Philippe Corcia is an investigator for clinical trials led by Cytokinetics, Consulting fees from Roche.

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Claude Desnuelle is a consultant for EFFIK SA France, Sanofi–Genzyme Co, NanoMedSyn.

Julian Grosskreutz is consulted for Biogen.

Trygve Holmøy received consulting fees from Biogen, Merck, Genzyme and run studies without compensation for Merck and Biogen, not related to ALS.

Jan Christoph Koch is Co-PI of IIT ROCK-ALS.

Albert Ludolph is on an advisory board of Biogen, Treeway, Hoffmann-La Roche, has signed contracts for clinical Studies with AB Science, Biogen Idec, Cytokinetics, GSK, Orion Pharmar,
Novartis, TauRx Therapeutics Ltd. and TEVA Pharmaceuticals, consulted for Mitsubishi, Orion Pharma, Novartis, Teva.

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