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July 2017 ENCALS statement on edaravone

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REPORT

ENCALS

European Network for the Cure of ALS

July 2017

ENCALS statement on edaravone

AMMAR AL-CHALABI¹ , PETER M. ANDERSEN², SIDDHARTHAN CHANDRAN³, ADRIANO CHIO⁴, PHILIPPE CORCIA⁵, PHILIPPE COURATIER⁶, OLOF DANIELSSON⁷, MAMEDE DE CARVALHO^{8,9}, CLAUDE DESNUELLE¹⁰, TORSTEN GREHL¹¹, JULIAN GROSSKREUTZ¹², TRYGVE HOLMØY¹³, CAROLINE INGRE¹⁴, MERETE KARLSBORG¹⁵, GRETHE KLEVELAND¹⁶, JAN CHRISTOPH KOCH¹⁷, BLAZ KORITNIK¹⁸, MAGDALENA KUZMAKOZAKIEWICZ¹⁹, HANNU LAAKSOVIRTA²⁰, ALBERT LUDOLPH²¹, CHRISTOPHER MCDERMOTT²² , THOMAS MEYER²³, BERNARDO MITRE ROPERO²⁴, JESUS MORA PARDINA²⁵, INGELA NYGREN²⁶, SUSANNE PETRI²⁷, MÓNICA POVEDANO PANADES²⁸, FRANCOIS SALACHAS²⁹, PAMELA SHAW²² , VINCENZO SILANI³⁰, GERT STAAF³¹, KIRSTEN SVENSTRUP¹⁵, KEVIN TALBOT³², OLE-BJØRN TYSNES³³, PHILIP VAN DAMME^{34,35,36}, ANNEKE VAN DER KOOIJ³⁷, MARKUS WEBER³⁸, PATRICK WEYDT³⁹, JOACHIM WOLF⁴⁰, ORLA HARDIMAN^{41*}  & LEONARD H. VAN DEN BERG^{42*} 

¹Maurice Wohl Clinical Neuroscience Institute, Department of Basic and Clinical Neuroscience, King's College London, London, UK; ²Department of Pharmacology and Clinical Neuroscience, Umeå University, Umeå, Sweden; ³University of Edinburgh, Scotland, UK; ⁴Rita Levi Montalcini' Department of Neuroscience, ALS Center, University of Torino, Torino, Italy; ⁵Centre de compétence SLA-fédération Tours-Limoges, CHU de Tours, Tours, France; ⁶Centre de compétence SLA-fédération Tours-Limoges, CHU de Limoges, Limoges, France; ⁷Department of Neurology, and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden; ⁸Institute of Physiology-Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Lisbon, Portugal; ⁹Department of Neurosciences And Mental Health, H Santa Maria-CHLN, Lisbon, Portugal; ¹⁰Hôpital Pasteur 2 – CHU de Nice, Nice, France; ¹¹Alfried Krupp Krankenhaus, Rüttenscheid, Essen, Germany; ¹²Hans-Berger Department of Neurology, Jena University Hospital, Jena, Germany; ¹³Kershus Universitetssykehus Lørenskog, Lørenskog, Norway; ¹⁴Karolinska Institutet, Stockholm, Sweden; ¹⁵Department of Neurology, Bispebjerg Hospital, Copenhagen, Denmark; ¹⁶Avdeling for nevrologi og klinisk nevrofysiologi, Sykehuset Innlandet, Lillehammer, Norway; ¹⁷Department of Neurology, University Medicine Göttingen, Göttingen, Germany; ¹⁸Institute of Clinical Neurophysiology, University Medical Centre Ljubljana, Ljubljana, Slovenia; ¹⁹Department of Neurology, Medical University of Warsaw, Warsaw, Poland; ²⁰Helsinki University Central Hospital, Helsinki, Finland; ²¹Department of Neurology, University of Ulm, Ulm, Germany; ²²Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, UK; ²³ALS Outpatient Department, Charité – Universitätsmedizin Berlin, Berlin, Germany; ²⁴Sahlgrenska Universitetssjukhuset, Gothenburg, Sweden; ²⁵ALS Unit, Hospital San Rafael, Madrid, Spain; ²⁶Uppsala University, Uppsala, Sweden;

*Dr Hardiman and Van den Berg are shared last authors.

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²⁷Department of Neurology, Hannover Medical School, Hannover, Germany; ²⁸Neurology department Hospital Universitario de Bellvitge-IDIBELL, Barcelona, Spain; ²⁹Hôpital de la Salpêtrière, Paris, France; ³⁰Department of Neurology-Stroke Unit and Laboratory of Neuroscience, Department of Pathophysiology and Transplantation, Center for Neurotechnology and Brain Therapeutics, Università degli Studi di Milano, IRCCS Istituto Auxologico Italiano, Milan, Italy; ³¹Lund University, Lund, Sweden; ³²Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK; ³³Haukeland universitetssjukehus, Bergen, Norway; ³⁴KU Leuven – University of Leuven, Department of Neurosciences, Experimental Neurology, Leuven, Belgium; ³⁵VIB Center for Brain & Disease Research, Leuven, Belgium; ³⁶University Hospitals Leuven, Department of Neurology, Leuven, Belgium; ³⁷Department of Neurology, Academic Medical Centre, University of Amsterdam Center, Amsterdam, The Netherlands; ³⁸Neuromuscular Diseases Center/ALS Clinic, Kantonsspital St. Gallen, St. Gallen, Switzerland; ³⁹Department of Neurodegenerative Diseases and Gerontopsychiatry, Bonn University, Bonn, Germany; ⁴⁰Department of Neurology, Mannheim, Diakonissenkrankenhaus, Mannheim, Germany; ⁴¹Academic Unit of Neurology, Trinity Biomedical Sciences Institute, Trinity College, Dublin, Ireland; ⁴²Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands

Neurologists of the ENCALS centers throughout Europe have discussed the potential of edaravone as a new therapy for amyotrophic lateral sclerosis (ALS, Motor Neuron Disease, MND) at the ENCALS meeting, 18–20 May 2017, in Ljubljana, Slovenia.

In May 2017, the US Food and Drug Administration (FDA) granted a license for the drug known as edaravone (licensed in Japan in 2015 as Radicut®) for the treatment of ALS in the United States (to be marketed as Radicava®). We are not aware of any official request from Mitsubishi Tanabe Pharma, the manufacturer of edaravone, to the European Medicines Agency (EMA) to register the drug for use in ALS in Europe. However, edaravone can be imported to Europe from Japan or the United States.

The FDA approval of edaravone is based on a single positive clinical trial. The ENCALS neurologists were of the view that the outcome of this trial requires a balanced and considered interpretation when considering how best to advise those with ALS and their families. This study showed that edaravone may slow disease progression in ALS, but the disease-modifying effect was limited to a subgroup of ALS patients with distinct clinical characteristics. For ALS patients without those characteristics there is currently no evidence for a therapeutic benefit of edaravone.

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 (ALSFERS-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 ALSFERS-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 Roperio, Ingela Nygren, Mónica Povedano Panades, Francois Salachas, Gert Staaf, 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.

Peter M. Andersen received consulting fees from Biogen Idec and Orphazyme ApS on matters concerning clinical trials and ALS.

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.

Mamede de Carvalho received consulting fees from Biogen, Merck Idec, Kedrion and Cytokinetics.

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 Pharam,

Novartis, TauRx Therapeutics Ltd. and TEVA Pharmaceuticals, consulted for Mitsubishi, Orion Pharma, Novartis, Teva.

Christopher McDermott is consultant for OrionPharma; Investigator for studies run by Biogen Idec, cytokinetics.

Thomas Meyer is consultant for Cytokinetics, GSK and Desitin Arzneimittel GmbH, founder of the internet platform Ambulanzpartner and co-owner of Ambulanzpartner Soziotechnologie GmbH.

Jesus Mora Pardina is consultant for AB-Science.

Susanne Petri is consultant for Cytokinetics, Investigator for clinical trials led by Cytokinetics, Orion Pharma, Biogen Idec, GlaxoSmithKline; speaking honoraria from Teva.

Pamela Shaw is consultant without compensation for Treeway and is a member of scientific advisory boards for Biogen, and Orion.

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Orla Hardiman is consultant for Mitsubishi and for Treeway.

ORCID

Ammar Al-Chalabi  <http://orcid.org/0000-0002-4924-7712>

Christopher McDermott  <http://orcid.org/0000-0002-1269-9053>

Pamela Shaw  <http://orcid.org/0000-0002-8925-2567>

Orla Hardiman  <http://orcid.org/0000-0003-2610-1291>

Leonard H. van den Berg  <http://orcid.org/0000-0002-5203-9674>