July 2017 ENCALS statement on edaravone

Citation for published version:

Digital Object Identifier (DOI):
10.1080/21678421.2017.1369125

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher’s PDF, also known as Version of record

Published In:
Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

Publisher Rights Statement:
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 13. Nov. 2018
July 2017 ENCaLS statement on edaravone


To link to this article: https://doi.org/10.1080/21678421.2017.1369125

© 2017 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

Published online: 04 Oct 2017.

Submit your article to this journal

Article views: 836

View related articles
REPORT

July 2017

ENCALS statement on edaravone

AMMAR AL-CHALABI1, PETER M. ANDERSEN2, SIDDHARTHAN CHANDRAN3, ADRIANO CHIO4, PHILIPPE CORCIA5, PHILIPPE COURATIER6, OLOF DANIELSSON7, MAMEDE DE CARVALHO8,9, CLAUDE DESNUELLE10, TORSTEN GREHL11, JULIAN GROSSKREUTZ12, TRYGVE HOLMØY13, CAROLINE INGRE14, MERETE KARLSBOG15, 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 STAAR31, KIRSTEN SVENSTRUP15, KEVIN TALBOT32, OLE-BJØRN TYSNES33, PHILIP VAN DAMME34,35,36, ANNEKE VAN DER KOOI37, MARKUS WEBER38, PATRICK WEYDT39, JOACHIM WOLF40, ORLA HARDIMAN41, & LEONARD H. VAN DEN BERG42, 43

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 Turin, Turin, 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; 16Afdeling for neurologi og klinisk neurofysiologi, Sykehuset Innlandet, Lillehammer, Norway; 17Department of Neurology, University Medicine Göteborg, Göteborg, Sweden; 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.

(Received 11 August 2017; accepted 15 August 2017)

ISSN 2167-8421 print/ISSN 2167-9223 online © 2017 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

DOI: 10.1080/21678421.2017.1369125
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 (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 Staafl, 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, Kidron 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.
Vincenzo Silani received consulting fees from Mitsubishi and Cytokinetics.
Philip Van Damme received consulting fees from Mitsubishi, Cytokinetics, Biogen Idec.
Anneke van der Kooi received research grant from Behring for investigator initiated study.
Markus Weber received consulting fees from Mitsubishi, Biogen Idec, Merz Parma Schweiz, consultant without compensation to Treeway.
Leonard H. van den Berg is consultant without compensation to Treeway, LHvdb declares personal fees from Baxalta, and is a member of the Scientific Advisory Boards for Biogen Idec, Cytokinetics and Orion.
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