MND/ALS: Therapeutic Options

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Learning Objectives:

1. Multidisciplinary Care
2. Disease modifying therapy
3. New Horizons

Key Message:
The therapeutic landscape is transforming
Treatment - beginnings:

• 1993: Glutamate toxicity mediated via redox system

• ↑ CSF glutamate

• 'excitotoxicity' theory

Amyotrophic lateral sclerosis

Matthew C Kiernan, Steve Vucic, Benjamin C Cheah, Martin R Turner, Andrew Eisen, Orla Hardiman, James R Burrell, Margaret C Zwing

The Lancet 2011
1. International clinical trials
2. Early access to Riluzole
3. Expand the safety profile
Threshold Tracking TMS

Normal short intracortical inhibition

Reduced short intracortical inhibition

On riluzole

Off riluzole

Riluzole exerts central and peripheral modulating effects in amyotrophic lateral sclerosis

Steve Vucic,1,2 Cindy Shin-Yi Lin,2,3 Benjamin C. Cheah,2 Jenna Murray,2 Parvathi Menon,1 Arun V. Krishnan2,3 and Matthew C. Kiemer1,4

doi:10.1093/brain/aaq086

BRAIN
A journal of neuroscience

interstimulus interval (ms)

threshold change (%)
Riluzole – how and when?

Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study

Ton Fang, Ahmad Al Khleifat, Jacques-Henri Meurgey, Ashley Jones, P Nigel Leigh, Gilbert Bensimon, Ammar Al-Chalabi

Summary
Background Riluzole is the only drug to prolong survival for amyotrophic lateral sclerosis (ALS) and, at a dose of 100 mg, was associated with a 35% reduction in mortality in a clinical trial. A key question is whether the survival benefit occurs at an early stage of disease, late stage, or is spread throughout the course of the disease. To address this question, we used the King’s clinical staging system to do a retrospective analysis of data from the original dose-ranging clinical trial of riluzole.

Riluzole, disease stage and survival in ALS

Following pivotal clinical trials in amyotrophic lateral sclerosis (ALS), approval of riluzole by the US Food and Drug Administration in 1995 was met with optimism. The argument for earlier efficacy might seem more conceptually feasible than later effects, given the lower likelihood that any treatment could confer a significant
Intrinsic Membrane Hyperexcitability of Amyotrophic Lateral Sclerosis Patient-Derived Motor Neurons

Brian J. Wainger,1,4* Evangelos Kiskinis,3,6 Cassidy Mellin,1 Ole Wiskow,3 Steve S.W. Han,3,4 Jackson Sandoe,3 Numa P. Perez,1 Luis A. Williams,3 Seungkyu Lee,1 Gabriella Bouling,1 James D. Berry,7 Robert H. Brown, Jr.,4 Merit E. Cudkowicz,4 Bruce P. Bean,6 Kevin Eggan,3,4,7* and Clifford J. Woolf1,2*

A Phase 2 Pharmacodynamic Trial of Ezogabine on Neuronal Excitability in Amyotrophic Lateral Sclerosis
Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996–2000

B J Traynor, M Alexander, B Corr, E Frost, O Hardiman

J Neurol Neurosurg Psychiatry 2003;74:1258–1261
Respiratory support

- NIV compared to standard care
- Improved survival
- Maintenance or improved quality of life
- Unresolved – when to institute?

Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial

Stephen C Bourke, Mark Tomlinson, Tim L Williams, Robert E Bullock, Pamela J Shaw, G John Gibson

Summary

Background Few patients with amyotrophic lateral sclerosis currently receive non-invasive ventilation (NIV), reflecting clinical uncertainty about the role of this intervention. We aimed to assess the effect of NIV on quality of life and survival in amyotrophic lateral sclerosis in a randomised controlled trial.
Exercise Therapy: Sydney Hydrotherapy Study

- Goals – relaxation, strength & mobility
- 80% reported improved function out of the water
- Mood impact 60%; ↑ QoL; ‘makes me happier’
- 80% achieved goals; keep coming!
- None experienced difficulties
Inspiratory Muscle Training

- INSPIRATionAL (Inspiratory Training for Amyotrophic Lateral Sclerosis)
- Threshold IMT
- Commence training at 2\textsuperscript{nd} visit
- 12 weeks
- 10 minutes 3x/day
- Threshold load is gradually increased over time
- Strengthened respiratory muscles
- 2 INSPIRATionAL underway

ORIGINAL ARTICLE

INSPIRATionAL – INSPIRAitory muscle Training In Amyotrophic Lateral sclerosis

BENJAMIN C. CHEAH\textsuperscript{1,2}, ROBERT A. BOLAND\textsuperscript{1}, NINA E. BRODATY\textsuperscript{2}, MARGIE C. ZOING\textsuperscript{1,2}, SANDRA E. JEFFERY\textsuperscript{2}, DAVID K. MCKENZIE\textsuperscript{1,2} & MATTHEW C. KIERNAN\textsuperscript{1,2}

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Symptomatic therapies

- Muscle cramps
- Spasticity
- Sialorrhea
- Dyspnea
- Weight loss; dysphagia
- Emotional lability

Motor neurone disease: progress and challenges

Thanuja Dharmadasa¹, Robert D Henderson², Paul S Talman³, Richard AL Macdonell⁴, Susan Mathers⁵, David W Schultz⁶, Merrillie Needham⁷, Margaret Zoing¹, Steve Vucic⁸, Matthew C Kiernan¹
Current Clinical Trials

**JAMA Neurology | Original Investigation**

Association of Regulatory T-Cell Expansion With Progression of Amyotrophic Lateral Sclerosis: A Study of Humans and a Transgenic Mouse Model

Rebecca X. Shearer, PhD, Elisa C. McKay, PhD, Eliska Centeney, PhD, Christopher R. Bue, PhD, Nora D. Peere, PhD, Denis Yamashita, BSc, Richard A. Wexler, MD, Chtit Karine J. Scheller, PhD, Enam Dinamar, PhD, Narasimha Murugan, PhD, Stephen D. Schlessel, MD, Najia Mannal, BSc, Justin J. Yeh, PhD, Brendan L. Nunn, PhD, David R. Booth, PhD, Guereme J. Stewart, MD, Mathew C. Dorman, BSc, Steve Volic, PhD, Bradley J. Turner, PhD

**Importance**
Neuroinflammation appears to be a key modulator of disease progression in amyotrophic lateral sclerosis (ALS) and thereby a promising therapeutic target. The CD4+Foxp3+ regulatory T-cells (Tregs) infiltrating into the central nervous system suppress neuroinflammation and promote the activation of neuroprotective microglia in mouse models of ALS. To our knowledge, the therapeutic association of host Treg expansion with ALS progression has not been studied in vivo.

**Phase 2 Randomised Placebo-Controlled Double-Blind Study to Assess the Efficacy and Safety of Tecfidera in Patients with Amyotrophic Lateral Sclerosis – TEALS Study**

**Study Overview and Timelines**

- **First Patient Randomized (FPR)** 15Apr2018
- **First Patient Screened (FPS)**
- **Last Patient Screened (LPS)**
- **Last Patient Out (LPO)**
- **Database Lock (DBL)**
- **6 Sites**
- **120 Subjects across all sites**
- **9 Months**

**EDITORIAL**

The Role of Regulatory T Lymphocytes in Amyotrophic Lateral Sclerosis

David R. Beers, PhD; Weihua Zhao, MD, PhD; Stanley H. Appel, MD
ALS – new horizons

➢ Masitinib – tyrosine kinase inhibitor

Paris, 20 March 2017, 8am

AB Science announces positive top-line results of final analysis from study AB10015 of masitinib in amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease

Primary analysis is a success and confirms interim analysis

Company to host webcast on masitinib in ALS

AB Science SA (NYSE Euronext - FR0010557264 - AB), a pharmaceutical company specializing in the research, development and commercialization of protein kinase inhibitors (PKIs), today announced that the phase 2/3 study AB10015 of masitinib in amyotrophic lateral sclerosis (ALS) has met its pre-specified primary endpoint. This is the first successful phase 3 trial of a tyrosine kinase inhibitor in the treatment of ALS, signifying masitinib as first-in-class for ALS, with a unique mechanism of action against microglia cells.

➢ AB14008 – contacted to incorporate global sites
ALS – new horizons

- Edaravone (Mitsubishi Pharma) – free radical scavenger
- Phase 3; younger onset, FVC >80%
- Recent FDA approval

3.5. Edaravone, a free radical scavenger

Edaravone was developed as a free radical scavenger that has been used to treat patients with acute cerebral infarction in Japan, in addition to several other neurological diseases [82–84]. Edaravone appears to remove lipid peroxides and hydroxyl radicals during cerebral ischemia and protects neurons.
ALS – promising studies

- Cytokinetics CK 2017357 Fortitude
- Mexilitene/Flecainide/membrane stabilizers
- Neural Stem and Brainstorm; gene therapy

NEALS consortium: The network of clinical sites and patients exist, so trials can be done well throughout the US, Canada, Europe and Australia. And there is a growing pipeline of therapeutic targets and agents under development for ALS.
• Hypermetabolism
• Hyperlipidemia
• Insulin resistance
• Low BMI: Higher BMI - prognosis
• Eating behaviour and survival
ALS – problems with designing trials

- Biomarkers
- Clinical heterogeneity
- Genotype/phenotype
- Phase 2 – unlikely to predict effect size
- Natural History
MND the future: when did it begin?

Amyotrophic lateral sclerosis: a long preclinical period?

Andrew Eisen, Matthew Kiernan, Hiroshi Mitsumoto, Michael Swash
ALS – future approaches

- If ALS truly focal → regional therapy to contain spread
Conclusions

- Understanding of MND is evolving
- New therapeutic interventions in a multi-disciplinary care setting
- New diagnostic approaches → earlier Rx, more likely success
- Neuronal spread?
- Better outcomes
MND – References


