The effectiveness of riluzole for motor neurone disease

Rapid review

The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review

A Stewart
J Sandercock*
S Bryan
C Hyde
PM Barton
A Fry-Smith
A Burls

West Midlands Development and Evaluation Service,
The University of Birmingham, Birmingham, UK

* Corresponding author

Executive summary

Health Technology Assessment 2001; Vol. 5: No. 2

Health Technology Assessment
NHS R&D HTA Programme

Executive summary

Update

After this review had been completed, the manufacturers of riluzole provided some additional information, which had been requested whilst the report was in preparation. These additional materials are addressed in an update section appended to this report. This summary reflects the information contained in the update.

Background

Riluzole (trade name Rilutek®) is a drug used to treat people with the amyotrophic lateral sclerosis (ALS) form of motor neurone disease (MND). Its licensed indication is to extend life or the time to mechanical ventilation, and it costs about £3700 per year. The prevalence of MND is approximately seven per 100,000, and ALS constitutes 65–85% of this. Incidence rises with age. At any one time, about 3000 people in the UK have ALS, and a district of 500,000 residents could expect to have about 20–25 ALS sufferers.

ALS is a progressive disorder that causes degeneration of the motor neurones of the brain and spinal cord. Symptoms include spasticity, muscle weakness and paralysis and impaired speaking, swallowing and breathing. The disease is extremely distressing for patients and their carers, and is relentlessly progressive with death usually occurring within 3–5 years. Survival time is significantly reduced when the disease starts with bulbar symptoms or at an older age. Death usually occurs from respiratory infection and failure, and complications of immobility. There is no cure and treatment consists mostly of symptomatic, supportive and palliative care.

Objective

To assess the clinical effectiveness and cost-effectiveness of riluzole for the treatment of MND.

Methods

A systematic review of randomised controlled trials (RCTs) and economic studies addressing the clinical effectiveness and cost-effectiveness of riluzole in MND was undertaken. Electronic databases, reference lists from publications, conference abstracts and the Aventis Pharma submission to the National Institute for Clinical Excellence were searched. Clinical experts and specialist organisations were also contacted. Studies were included if they had investigated either clinical effectiveness, cost-effectiveness or safety of riluzole, or quality of life/patient satisfaction associated with its use in MND patients, with no restrictions on age or sex. The review adhered to the guidance of the West Midlands Development and Evaluation Service Handbook and the York Centre for Reviews and Dissemination guidelines, and a model of the cost-effectiveness was developed. An existing economic model was also reviewed in detail; revised estimates from this model are provided in the update section of this report.

Results

RCTs found

Four studies met the inclusion criteria for the clinical effectiveness review. All compared riluzole to placebo; three trials used riluzole at 100 mg daily and one used dosages of 50, 100 and 200 mg daily. Three of the trials had broadly similar eligibility criteria, whereas the fourth recruited patients who were ineligible for one of the other trials and thus used patients who were older or more ill or with a forced vital capacity < 60%. All four trials reported tracheostomy-free survival as a main outcome. Most patients were prevalent, rather than incident, cases.

Evidence on clinical effectiveness

Median follow-up in all trials was 18 months with most patients having follow-up of between 16 and 21 months. Combined results favoured riluzole with a hazard ratio for tracheostomy-free survival of 0.88 (95% confidence interval (CI), 0.75 to 1.02). There was no evidence that the effectiveness of the treatment differed by site of onset. There was also no significant difference in effectiveness in daily dosages of between 50 and 200 mg. There was, however, some evidence of statistical heterogeneity ($p = 0.09$) and, if this

is not due to chance, there is no clear explanation as to why this may have arisen.

Riluzole does not improve symptoms. When data on functional status were combined, a small reduction in the rate of deterioration of functional status was observed, although it was not clear whether this was clinically significant. A large proportion of patients in both groups reported adverse events, but there was little overall difference between riluzole and placebo.

There was no evidence available on treatment outcomes beyond 18 months. All placebo patients were offered riluzole at the end of follow-up, and no longer-term comparative data will thus be available from any of these trials.

Costs and economic analysis

The evidence suggests that current published estimates of the cost-effectiveness of riluzole must be viewed cautiously. Some of the key remaining uncertainties concerning the benefits within the economic analysis are the disease stage(s) in which any survival gain is experienced, the quality-of-life utility weights for ALS health states and the mean gain in life expectancy for patients taking riluzole. It is clear that riluzole is associated with a net increase in costs to the health service, although the magnitude of the increase is difficult to predict accurately.

A more robust estimate of the riluzole-induced gain in life expectancy over the whole disease duration is required to diminish current uncertainties relating to methods of extrapolation beyond observed survival in trials. In our model, base-case incremental cost-effectiveness ratio (ICER) produced a cost per life-year of £39,000 and a cost per quality-adjusted life-year (QALY) of £58,000. A sensitivity analysis indicated that the most optimistic ICER (cost per QALY) is £20,000 and the most pessimistic has riluzole dominated by placebo.

A review of the model presented by the manufacturers of riluzole (based on previously published work) is detailed in the update section of this report. This model was derived from a subset of data from one of the four trials identified in this review. In common with the model we developed, this model is sensitive to the methods used to extrapolate benefit over time. The approach presented by the company produced a base-case ICER of £21,000. An alternative approach, presented in the update section of this report, produced a base-case ICER of £31,500. It was not possible with the information provided to perform a full sensitivity analysis or to empirically address sensitivity to alternative means of deriving model parameters from the clinical data.

Conclusions

There is limited evidence of a modest benefit in tracheostomy-free survival for patients taking riluzole. However, the evidence is restricted and uncertainty remains as to the true benefit of riluzole; the CI is wide and compatible with little or no difference between riluzole and placebo. When costs and the health economic impact are considered when extrapolating survival beyond that observed in trials, the uncertainty about whether the benefits are worth the costs is magnified. Even under the most optimistic assumptions, riluzole at best only postpones death for a few months, and does not preclude the need for supportive care and practical help.

If riluzole were to be made available to all patients in whom it is not contraindicated, the annual cost to the NHS would be about £8.4 million, assuming all these patients wish to take it. Many patients, given accurate information about the benefits and effects of riluzole, may choose not to. Patients should be made aware that riluzole does not cure ALS; accurate patient information is essential.

Recommendations for research

Ideally, reliable evidence from further trials is necessary to answer the many uncertainties that exist. These should include a substantial incident population, with long-term (5-year) survival follow-up, and collection of health economic and quality-of-life data. Further analysis of existing trial data and information from ALS databases may provide additional useful data in the short term.

Publication

Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al.* The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review. *Health Technol Assess* 2001;**5**(2).

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources.

The research reported in this monograph was funded as project number 00/01/01.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA Programme Director: Professor Kent Woods
Series Editors: Professor Andrew Stevens, Dr Ken Stein, Professor John Gabbay and Dr Ruairidh Milne
Monograph Editorial Manager: Melanie Corris

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org ISSN 1366-5278