

THERAPEUTIC INTERVENTION

# Riluzole and motor neurone disease

'The best is the enemy of the good'

Voltaire 1694–1778

'Hope, in reality, is the worst of all evils because it  
prolongs the torments of man'

Nietzsche 1844–1900

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### INTRODUCTION

Riluzole is the only agent approved as a disease-modifying treatment for motor neurone disease (MND). It may, or may not (depending on how one views the evidence), modify the rate of disease progression. We will examine the use of this drug that is generally viewed to have at best only a limited impact on survival in a miserable disease. With the general neurologist in mind, we hope to present a balanced view of the available evidence, with thoughts for future research and what we do in our own practice. We will highlight some of the scientific and ethical issues posed by disorders like MND, and the constraints imposed by the priorities of the pharmaceutical industry and state-sponsored research bodies.

### WHAT IS THE IDEAL?

What then are the desirable features of a disease-modifying therapy for MND? We propose the following:

- significant increase in survival – at least 4 months (i.e. > 10%, taking an overall median survival of about 40 months from presentation as in our own series) (Turner *et al.* 2002);
- survival gain throughout all stages of disease;
- quality of life should be maintained throughout;
- no significant adverse effects;
- favourable cost.

### WHAT IS RILUZOLE?

The benzothiazole riluzole was originally used in a photographic developing solution, and later as an industrial bleach (Fig. 1). Two scientists, working in separate laboratories on the same floor, apparently swapped chemicals so that riluzole was screened in an in-vitro assay of glutamate inhibition and found to be effective. It was then developed as a potential anti-convulsant designed to exhibit broadly anti-excitatory activity. With the emergence of excitotoxicity as a possible mechanism involved in cell dysfunction and death in a variety of neurological

conditions (Doble 1999), attention was turned to the potential of riluzole as a neuroprotective agent. The precise mechanism of action is unproven, although several theories have been proposed from blockade of presynaptic glutamate release to inhibition of glutamate-evoked  $Ca^{2+}$  entry into cells, NMDA receptor antagonism, inhibition of apoptosis and inhibition of protein aggregation (Doble 1996).

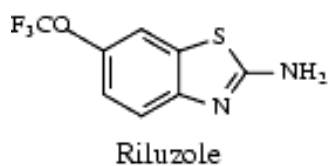
The benzothiazoles have a broad potential in neurodegenerative diseases. Riluzole has recently been tested in Huntington's disease patients, where treatment has had positive effects on chorea (Rosas *et al.* 1999), and it has also been reported to extend the lifespan in a Huntington's mouse model (Schiefer *et al.* 2002).

### THE EVIDENCE IN MOTOR NEURONE DISEASE

#### The randomized trials

Two large randomized, placebo-controlled trials provide most of the evidence for riluzole's efficacy (Bensimon *et al.* 1994; Lacomblez *et al.* 1996). In the first study, 155 patients received 100 mg/day for up to 21 months using death and tracheostomy as the primary outcome measure. Secondary outcomes included manual muscle testing, the rate of decline of a functional score including limb and bulbar components, forced vital capacity (FVC) and various subjective assessments. A significant advantage in survival was found at 12 and 21 months, with significantly slower deterioration in muscle strength. The median survival was 449 days for placebo and 532 days for the riluzole treated groups. Overall, riluzole therapy reduced mortality by 39% at 12 months (relative risk 0.61; 95% CI 0.39 to 0.97;  $P = 0.014$ ) and by 19% at 21 months ( $P = 0.046$ ). The effect of riluzole on survival appeared to be greater in the bulbar-onset group but, in retrospect, this was an artefact of the small overall sample size and the even smaller size of this subgroup.

The second study involved 959 patients randomized to four treatment arms: 50, 100 or 200 mg/day riluzole and placebo. 100 mg/day was taken as the optimum dose in terms of benefit-to-risk. At the end of the double-blind phase (18 months) there was a trend towards significant improvement in tracheostomy-free survival. Fifty percent of the placebo-treated patients and 57% of those who received 100 mg/day riluzole were alive without trache-



**Figure 1** The chemical structure of riluzole.

ostomy (unadjusted relative risk 0.79,  $P = 0.08$ ), equivalent to an estimated gain in survival of about three months. Adjusting for the differences in prognostic factors at baseline between the patients, the relative risk reduction was greater: 0.65 (95% CI 0.50 to 0.85;  $P = 0.002$ ). At 12 months, the difference in survival was significant with a hazard ratio of 0.66 (95% CI 0.48 to 0.91;  $P = 0.019$ ).

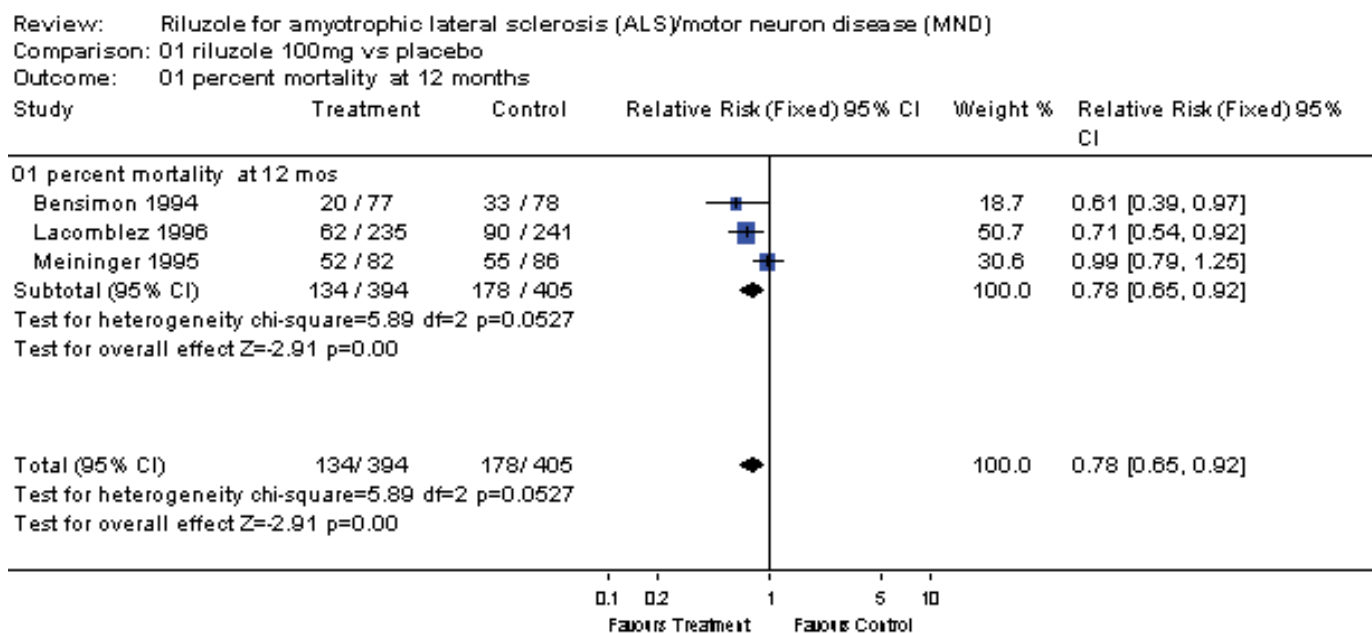
### The meta-analysis

Other trials of riluzole have been undertaken (Yanagisawa *et al.* 1997; Sojka *et al.* 1997; Riviere *et al.* 1998; Kalra *et al.* 1998; Desiato *et al.* 1999; Arriada-Mendicoa *et al.* 1999; Pongratz *et al.* 2000; Couratier *et al.* 2000; Debove C *et al.* 2001; Lacomblez *et al.* 2002), but the only trial to qualify for the Cochrane Review (Miller *et al.* 2002), in addition to the two above, was of 168 patients outside the inclusion criteria for the Lacomblez and colleagues dose-ranging study (Bensimon *et al.* 2002). For the primary outcome measure (mortality or tracheostomy), at all time points at a dose of 100 mg/day, there was a 16% relative hazard reduction which did not quite reach statistical significance ( $P = 0.056$ ). This represented a 9% absolute

increase in surviving free of tracheostomy at one year (66% vs. 57%), corresponding to an increase in the median survival of about two months. For the secondary outcome measure of mortality at 12 months at a dose of 100 mg daily vs. placebo, there was a significant effect on survival with a relative risk reduction of 22% (95% CI 35% to 8%;  $P = 0.004$ ) (Fig. 2). The number needed to treat to delay one death until after 12 months was calculated as 11. Although clearly a very modest effect, the authors of the review made the point that the inclusion of patients with more advanced disease, through the addition of the third trial, was likely to have diluted the benefit to some extent. A small beneficial effect was noted in both bulbar and limb function, but not in muscle strength. Significant adverse effects included nausea and asthenia, and there was nearly a three times excess risk of a threefold or greater increase of serum alanine transferase.

### Evidence from retrospective and database studies

As a result of controversies over the original trials, and with future placebo-controlled trials now widely regarded as unethical, attention has



**Figure 2** Forest plot showing combined effect on mortality of 100 mg daily riluzole vs. placebo at 12 months. Result favours treatment with a relative risk of 0.78. Figure 01.01.00 Miller RG, Mitchell JD, Lyon M and Moore DH, Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND) (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software. MetalView © Update Software, Oxford. Cochrane Reviews are regularly updated as new information becomes available and in response to comments and criticisms. The reader should consult The Cochrane Library for the latest version of a Cochrane Review. Information on the Cochrane Library can be found at <http://www.updatesoftware.com>.

turned to other ways of looking at the long-term effects of riluzole. One controversial method is to use databases of MND patients to compare those treated with riluzole at any time with those known definitely never to have received the drug. For example, in our King's Database of 841 patients presenting over a 10-year period (Turner *et al.* 2002), the results compared reasonably well with those of the randomized trials – an increase in survival of about 4 months in the riluzole-treated group at 12 months (Fig. 3a). The benefit appeared to increase over an extended period so that at 60 months there was about a 24% absolute improvement in survival (Fig. 3b). It is very difficult to control for all potential confounding factors but other groups have carried out similar analyses with similar results despite different health care systems and study designs (Couratier *et al.* 2000; Meininger *et al.* 2000; Traynor *et al.* 2003; Brooks *et al.* 2001; Chio *et al.* 2002).

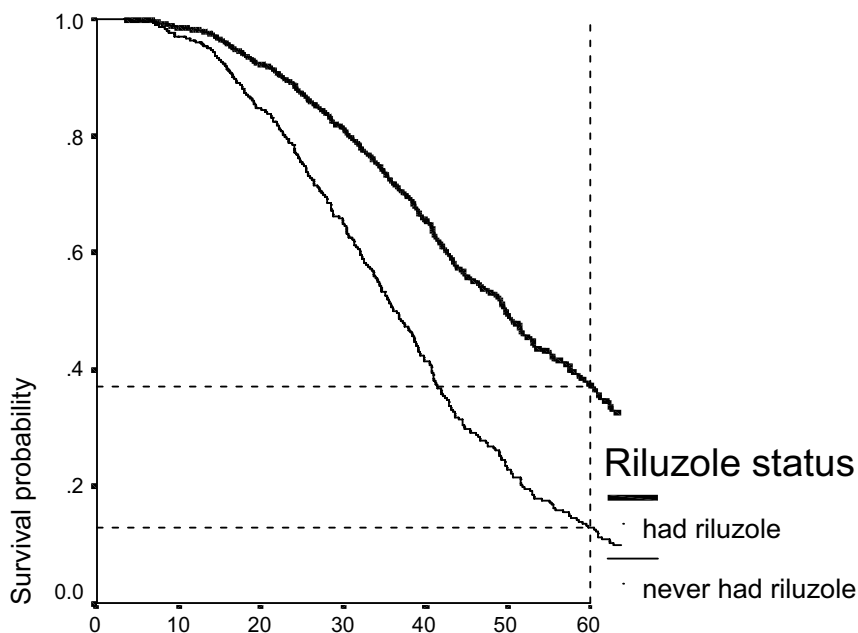
**COST-EFFECTIVENESS OF RILUZOLE**

One year of Riluzole treatment costs approximately £4000. Coupled with the modest benefits in terms of survival, several studies have attempted to assess cost-effectiveness (Chilcott *et al.* 1997; Munsat *et al.* 1998). A report to the Development and Evaluation Committee of the Wessex Institute for Health Research and Development calculated that for every six patients treated with riluzole, at a total estimated cost of £33 500, one death or tracheostomy at 18 months was delayed (Booth-Clibborn *et al.* 1997). A study in Israel concluded that the additional 3 months of survival provided by riluzole was justified in terms of cost (Ginsberg & Lev 1997). One UK study conceded that the estimated cost of £45 000 per life year gained with riluzole was beyond that normally accepted

**Figure 3** (a) Survival probability plot by riluzole therapy status from the King's MND database of over 800 patients. Other prognostic factors are fixed at their covariate means by Cox regression and so 'controlled' for. At 12 months the riluzole treated group survival is on average about 4 months longer than the untreated group (permission requested). (b) Expansion of (a), showing about a 24% absolute difference in cumulative survival between riluzole-treated and untreated groups for a theoretical average individual at five years (reprinted with permission from Turner *et al.* 2002, <http://www.tandf.no/als>).



(a) Actual survival in months



(b) Actual survival in months

(Gray 1998), however an Italian study estimated the cost at a more favourable £27 000 (Messori *et al.* 1999). Using a disease burden stratification method, Tavakoli and colleagues estimated a cost per quality-adjusted life year of approximately £20 000 (Tavakoli & Malek 2001).

Whilst acknowledging the burden of these costs, it is worth considering that, despite comparable financial implications, chemotherapy has become an accepted part of the treatment of non-small cell carcinoma of the lung – a disease with a 5-year survival across all stages of only 12%. A Cochrane meta-analysis comparing supportive care only with supportive care plus all forms of chemotherapy, gave a hazard ratio of 0.73 (27% relative reduction in the risk of death, equivalent to a 10% improvement in survival at one year) (Non-small Cell Lung Cancer Collaborative Group 2003) – a result comparable to riluzole in MND.

### OFFICIAL GUIDANCE

In the USA, where cost issues do not have the same impact as they do in the UK National Health Service (NHS), riluzole is an accepted part of 'best practice' in the care of MND patients. In Canada, riluzole is approved pending the results of a phase IV study. The UK National Institute for Clinical Excellence (NICE) reviewed the evidence in support of funding riluzole therapy within the NHS (National Institute of Clinical Excellence 2001). The initial cost per quality-adjusted life year was estimated at £34 000 to £43,500, however, this was revised to nearer £20 000 following submission of a report by Bryan and colleagues containing long-term data. The cost of making riluzole available to all MND patients in England and Wales was estimated at £5 million/year. NICE ruled in favour of riluzole therapy within certain guidelines (Table 1).

### THE ARGUMENTS AGAINST USING RILUZOLE

As Rowland warned in the opening line of an editorial written in response to the original trial of riluzole, 'when it comes to announcing an effective treatment for a currently untreatable disease, investigators have a grave responsibility' (Rowland 1994). The temptation to grasp at any drug with potential benefits in MND is understandable. There are several legitimate concerns about the state of the evidence for the use of riluzole:

In the USA, where cost issues do not have the same impact as they do in the UK National Health Service, riluzole is an accepted part of 'best practice' in the care of MND patients

- flaws in trial design;
- the value of a small increase in survival, especially in the absence of demonstrable effects on disability and/or quality of life;
- the value of a small increase in survival, if it is only at the end of the disease;
- the adverse effect profile.

For some neurologists the evidence from the randomized trials is simply not persuasive enough. After all, a difference in median survival of 83 days in the first study is not huge by any standards. Australia has not approved the use of riluzole on the present evidence.

More worrying is the apparent lack of consistent efficacy in terms of disability measures in the meta-analysis, despite the improved survival. As well as raising questions about trial methodology, there is also concern that prolonging survival as disability worsens is futile. It may be that the explanation for this apparent paradox is a beneficial effect on forced vital capacity, but these data were not included in the original trial. Any future studies will need to incorporate more rigorous measures of respiratory muscle weakness to answer this crucial question.

The adjusted Cox analysis employed by Lacomblez and colleagues in the dose-ranging study has been challenged (Guilloff *et al.* 1996). Randomization should balance important

**Table 1** Summary of National Institute for Clinical Excellence (NICE) guidance on the use of riluzole for the treatment of motor neurone disease in the UK National Health Service (NHS)

### Guidance

Riluzole is recommended for the ALS form of MND.

Therapy should be initiated by a neurologist with MND expertise with routine supervision through locally agreed shared care protocols.

### Clinical need

Definition of MND.

MND is clinically heterogeneous.

Specific MND variants include amyotrophic lateral sclerosis, progressive muscular atrophy and progressive bulbar palsy.

Riluzole has been used to treat all of the above.

There is no test for MND and often diagnostic delay.

The prevalence of amyotrophic lateral sclerosis in England and Wales is about 2000.

There are numerous options, both medical and surgical (e.g. PEG), for symptomatic treatment.

There is a need for multidisciplinary care, community services, including palliative care in the later stages.

### The technology

Riluzole is currently the only licensed drug for amyotrophic lateral sclerosis, designed to delay time to mechanical ventilation. The summary of Product Characteristics recommends riluzole should not be used for any other form of MND.

Riluzole inhibits the release of glutamate thought to be toxic to motor neurones.

The major side-effect of riluzole is abnormal hepatic function and blood should be checked monthly for the first 3 months then every 3 months for a further 9 months, then annually thereafter.

Dosage is 50 mg twice daily. The total annual cost of treatment is estimated as £3742.

### Evidence

Four randomized controlled trials (1477 patients).

All trials used tracheostomy-free survival as the primary outcome.

Overall hazard ratio 0.88 (95% CI 0.75 to 1.02) with heterogeneity across trials.

Small reduction in rate of deterioration of functional status observed, but statistical methods 'questionable'.

Few adverse events.

Strong clinical support for riluzole use in forms of MND other than amyotrophic lateral sclerosis (ALS) but trials used ALS only.

Current estimates of cost-effectiveness must be viewed cautiously.

Key uncertainties about which stage of disease the survival gain is experienced. Mean gain in survival estimated at 2–4 months.

Conservative estimate of cost per QALY £34 000 to £43,500.

The Committee took short life span of amyotrophic lateral sclerosis patients into consideration when assessing cost effectiveness.

### Implications for the NHS

Estimated additional cost to NHS for provision of riluzole to all amyotrophic lateral sclerosis patients in England and Wales about £5 million.

Diagnosis of MND to be made by a specialist, and monitoring of therapy to be either by the specialist or general practitioner.

In latter stages of disease, patients may wish to review continued use of riluzole.

### Further research

Further trials of riluzole at different dosing regimes are needed.

Methods for earlier diagnosis, and so treatment, are needed.

### Implementation

NHS Trusts with MND patients should enable neurologists to consider option of riluzole.

Neurologists' practice should be reviewed in light of NICE guidance.

Patient information leaflet provided.

### Clinical audit advice

Treatment plans to be recorded for each patient.

Information to be incorporated into local audit systems.

Multi-disciplinary care protocols to be reviewed in light of NICE guidance.

Prospective clinical audit programmes should be initiated to record adherence to guidelines.

### Review of guidance

January 2004



prognostic factors, but this may not always be achieved as was the case here. Although the Cox model can allow this imbalance to be adjusted for, this does assume proportional hazards throughout the course of the disease. This is unlikely to be true for all relevant prognostic factors (Armon *et al.* 2002). Thus, we should rely primarily on the non-adjusted analyses of survival, using the Cox analysis as supplementary corroboration. It remains the case that riluzole significantly prolongs survival at 12 months.

As stated already, databases cannot substitute for randomized evidence and are therefore subject to potential bias, even if multiple prognostic factors are allowed for (Armon *et al.* 2002). However, we would argue that such an approach may be used to generate hypotheses as well as to test the consistency of possible drug effects in different MND populations – data that will never be acquired through randomized trials.

Despite the NICE ruling, debate continues as to whether the National Health Service's limited resources could be better used to fund other areas of neurology, not least the multi-disciplinary care, symptomatic treatments and community support that is undoubtedly lacking in the UK, and yet is vital to MND patients and their carers. The debate in the UK has been particularly charged by the initial refusal by NICE to approve the use of interferon therapy for the treatment of multiple sclerosis (MS). Could the relatively small number of patients with MND compared to the many with MS have influenced the NICE decision?

### ADVERSE EFFECTS

The open-label study by Lacomblez and colleagues concluded that riluzole was well-tolerated for at least 7 years (Lacomblez *et al.* 2002). Although the raised liver enzymes are often mentioned by colleagues as a reason not to prescribe riluzole, the reality is that with monthly monitoring for the first 3 months, 3-monthly for the next 9 months, and annually thereafter, significant and irreversible hepatic damage is extremely rare. Nausea and asthenia are often more significant in terms of quality of life. Whatever one thinks of the efficacy of riluzole, toxicity is not an adequate reason not to use it.

### FUTURE RESEARCH NEEDED

A number of key questions remain in the assessment of riluzole across the range of MND patients. Most clinicians in the field consider the effect of riluzole to be sufficient to remove

the possibility of carrying out trials of new agents vs. placebo. Will such agents therefore have to be tested on patients already stabilized on riluzole?

### More power

Many of the potential neuroprotective agents that have been tested in MND (Turner *et al.* 2001) and other neurodegenerative diseases, might have succeeded had the trials been adequately powered. Meininger and Salachas (2000) estimated that less than 50% of the MND trials have been powered to detect a clinically meaningful effect on function. The way forward therefore has to be to test better drugs (i.e. more precisely targeted to key mechanisms of neuronal damage) in adequately powered clinical trials.

### Quality of life

One of the greatest weaknesses of the earliest studies with riluzole was the lack of any quality of life data to support the limited benefit on survival. Adequate quality of life measures are now recommended for future phase III trials in MND (Miller *et al.* 1999).

### Efficacy in advanced disease

The argument that riluzole prolongs life by a few months during the phase of marked disability has been fuelled by lack of quality of life data and inconsistent evidence of efficacy in terms of disability, but this is clearly an oversimplification. Whatever the mechanism of action of riluzole, it is likely to act in a continuous manner rather than only becoming effective in the later stages of disease. Unfortunately the question of the benefit, if any, of the drug in older patients and/or those with more advanced disease has not been answered satisfactorily to date, however further randomized trials (except in conjunction with other agents) are unlikely to take place.

### Earlier, more inclusive, treatment

The NICE guidelines recommend riluzole only in patients with the typical amyotrophic lateral sclerosis (ALS) form of MND. This excludes the 15% of MND cases who have progressive muscular atrophy. These patients have somewhat slower progression and many will eventually develop upper motor neurone signs. Clinically and pathologically they have MND. Of course, great care must be taken to exclude other disorders such as multifocal motor neuropathy, Kennedy's syndrome and spinal muscular

atrophy. However, once excluded by thorough clinical evaluation, the evidence, including that from our own patient database, suggests that patients with lower motor neurone-only presentations do ultimately develop more classical ALS (Williams *et al.* 2001), and they should therefore be eligible for treatment with riluzole. Limited retrospective analyses also suggest that patients presenting before significant upper motor neurone signs emerge (classified by the original El Escorial criteria as 'suspected' or 'possible' ALS) do benefit from riluzole.

The NICE ruling is therefore arbitrary and should be revised; it is of course based on an inflexible interpretation of the data available from the randomized trials.

### STRIKING A BALANCE

At present the emphasis of management of MND focuses on maintaining quality of life.

Riluzole probably contributes little to this, though we cannot speak for patients. Nevertheless, while the field of neuroprotection has been profoundly dispiriting, riluzole remains the one agent that has been shown in reasonably well-designed randomized trials to have some impact on survival.

The process by which the neurologist and patient reach a decision on riluzole therapy is clearly influenced by a range of factors (Armon 1999). In the UK, the issue of cost often supersedes everything else. It is however, an interesting observation that despite the Irish government providing riluzole free of charge, only two-thirds of patients registered in their MND database reported taking the drug (Traynor *et al.* 2001). We favour the individual patient's right to choose. An outline approach to informing the patient about riluzole is shown in Table 2.

**Table 2** A suggested framework for explaining riluzole to allow MND patients to make an informed choice

1. MND unfortunately has no cure, although there are many drugs available to treat the symptoms as the disease progresses. A multidisciplinary approach, usually coordinated by your family doctor/local neurologist, is the most important aspect of care.
2. Riluzole is the only drug currently licensed that has been shown in clinical trials to slow the progression of MND.
3. Riluzole is not a cure and its effect is modest. In the clinical trials, patients given the drug survived approximately 3 months longer at the 18 month cut-off point chosen by the investigators, than those who received placebo.
4. It is not possible to tell what the benefit for an individual patient will be – it may be longer than that shown overall in the trial. This is partly because of the significant variability in progression of MND between patients.
5. Patients taking riluzole are unlikely to be subjectively aware of any change in their disease progression.
6. Riluzole is well tolerated by most people, though a small number find there is a significant increase in their levels of fatigue, sometimes muscle twitching, or gastrointestinal effects, e.g. nausea. In our experience significant side-effects enough to stop the drug are rare.
7. Riluzole may cause a rise in the blood levels of liver enzymes. This requires regular monitoring for all patients taking the drug during the first year of therapy, then annual blood tests afterwards. In our experience significant rises in liver enzymes are extremely rare, they often respond to reduced dosage (50 mg daily), and always to stopping the drug altogether.
8. Most family doctors are willing to share responsibility for the monitoring of riluzole, and we will provide them with information on the drug if they are not familiar with its use.
9. Riluzole has been approved for NHS prescription and should be available to you if you decide you want to take it.



Riluzole remains the one agent that has been shown in reasonably well-designed randomized trials to have some impact on survival

We cannot predict whether riluzole will retain a place in the treatment of MND in the future (as combination therapy, for example). The step-wise development of the now highly successful chemotherapy regimens for childhood leukaemias and against the human immunodeficiency virus, are useful models from which to draw inspiration for the future of MND therapy. Riluzole is simply the first small but positive step toward effective treatment.

### BIAS?

Can the reader (can we ourselves?) believe a word of what we have written? We have been intimately involved in the development of riluzole and inevitably are emotionally (as well as intellectually) engaged with its use in MND. We believe that this engagement is a far more potent bias than possible financial 'conflicts of interest' (which are stated at the end). We do not have any on-going financial interest in this product, or in the company that makes it. Perhaps this dilemma can only be resolved by a 'pro' and 'contra' debate. We leave the Editor (and the reader) to decide whether a 'contra' argument is needed to redress the balance of this article.

### NOTE ADDED IN PROOF

In their database analysis of riluzole use, Traynor and colleagues concluded that the early

beneficial effect of riluzole was not sustained (Traynor et al. 2003)

### ACKNOWLEDGEMENTS

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### COMPETING INTERESTS

MRT, CES and PNL have received modest honoraria for speaking to Aventis Pharmaceuticals staff (previously Rhone Poulenc Rorer). PNL has been funded to do a clinical trial, and has received consultancy fees from Aventis. A health economics study within the department was funded by Aventis. The Charcot Young Investigator Prize awarded to AAC by the Motor Neurone Disease Association was funded in part by Rhone-Poulenc-Rorer (which later became Aventis).

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