

Riluzole: a glimmer of hope in the treatment of motor neurone disease

Early experience confirms that riluzole improves survival and is well tolerated

The recently established Australian Motor Neurone Disease Registry estimates that 1200 Australians are living with motor neurone disease (MND), and 370 new patients are diagnosed each year. Most patients die within 3 years of diagnosis. Aetiological mechanisms implicated in the development of MND have been linked to the glutamatergic neurotransmitter system, with excessive activation of glutamate receptors at the synaptic cleft now believed to trigger destruction of motor neurones.¹ This “excitotoxicity” theory of MND gave rise to the development of new therapeutic approaches and, ultimately, clinical trials involving riluzole. This drug was initially thought to act solely as an inhibitor of glutamate release, although subsequent postulated effects include indirect antagonism of glutamate receptors and inactivation of neuronal voltage-gated sodium ion channels.

Regardless of the precise mode of action, two large trials in the 1990s established the efficacy of riluzole in the treatment of MND.^{2,3} A double-blind, placebo-controlled study undertaken in 155 patients with MND showed a significant prolongation of survival and an improvement in functional outcome measures for those treated with 50 mg of oral riluzole twice daily.² A larger, dose-ranging study undertaken in 959 patients confirmed the beneficial effect of riluzole on survival, being in the order of 3–6 months.³ In the original study,² the therapeutic effect of riluzole was more prominent in patients with bulbar-onset MND, while the second study found no significant differences in the responses of bulbar- and limb-onset groups.³ Subsequent retrospective analyses suggest a survival benefit even longer than 6 months in both patient groups, but these data have been confounded by recent general improvements in the care of MND patients, particularly the use of percutaneous endoscopic gastrostomy for nutritional support and non-invasive ventilation for

respiratory insufficiency, in the setting of a multidisciplinary approach to care.⁴

Riluzole remains the only medication to slow the progression of a neurodegenerative disease, leading to an increased survival for patients with MND.⁵ In some countries including Australia, riluzole’s manufacturer had difficulty gaining a listing for the medication on pharmaceutical benefits schemes, in part due to issues related to “quality of life”, despite trial data documenting

Pharmaceutical Benefits Scheme (PBS) criteria for riluzole authority (June 2003)

Approved indication

Treatment of motor neurone disease

PBS indication for authority

Initial treatment of motor neurone disease, as diagnosed by a neurologist, in patients aged 75 years or less, with disease duration of 2 years or less and who have at least 60% of predicted forced vital capacity within 2 months prior to commencing riluzole therapy and who:

- 1) are ambulatory, and
 - a) have not undergone tracheostomy, and
 - b) have not experienced respiratory failure;

OR

- 2) are not ambulatory, and
 - a) have not undergone tracheostomy, and
 - b) have not experienced respiratory failure, and
 - c) are either able to use upper limbs or able to swallow.

The date of diagnosis and the results of spirometry (in terms of percentage of predicted forced vital capacity) must be supplied with the initial authority application.

improvement in patient longevity.^{2,3} Quality of life is a nebulous measure and the findings using quality-of-life scales in MND clinical trials have proved inconsistent to date.⁶ After dissecting arguments related to quality-of-life issues, and with intense lobbying by the MND community — patients, clinicians and care groups — riluzole was finally listed by the Australian Pharmaceutical Benefits Scheme (PBS) in June 2003 (see Box for criteria).

Linked to the original riluzole trials were studies conducted to establish the safety profile of riluzole in MND patients, including the Riluzole Early Access Program run here in Australia. The primary objective of these open-label, single-treatment studies was to enable patients with MND to receive riluzole therapy pending its commercial availability, health authority approval and, in the case of Australia, listing on the PBS. Through such a process, the safety profile of riluzole was expanded. These later studies established that riluzole was generally well tolerated by patients with MND. Adverse events were predominantly gastrointestinal, with nausea, weight loss and dysphagia being the most frequent,⁷ although it may be argued that the latter symptoms more likely reflect disease activity itself.

Measurement of full blood count before initiation of therapy is suggested, as, rarely, blood dyscrasias may develop with riluzole. As riluzole is metabolised hepatically and significant hepatotoxicity occurs in about 0.2% of patients,⁷ testing liver function monthly for the first 3 months and then at 3 monthly intervals remains important. However, patients with MND can have or develop abnormal liver function for many reasons other than taking riluzole, including the use of alternative therapies, emphasising the need for baseline measurements before initiating riluzole therapy and withholding the drug if liver function is grossly abnormal (eg, liver enzymes elevated above five times normal).

When should MND patients commence taking riluzole? Certainly, any patient with clinically probable or definite MND (based on a combination of upper and lower motor neurone abnormalities in two to three spinal regions) warrants consideration. It could be argued that, given suggestions that patients benefit most from therapeutic intervention in the early stages of MND, the earlier riluzole is started the better. It is inevitable that, by giving riluzole to patients in whom MND is suspected, a few patients in the “possible” and “probable” clinically diagnosed categories will receive this treatment for conditions other than MND, with the correct diagnosis only becoming apparent over time.⁸ However, given the putative neuroprotective properties of riluzole, this approach has no identifiable drawbacks. Giving riluzole to patients with advanced disease is problematic, and the current PBS guidelines for authority prescriptions of riluzole stipulate that the date of MND diagnosis (disease duration, \leq 2 years) and the results of respiratory testing (forced vital capacity, \geq 60%) must be supplied with the initial authority application. Obtaining adequate measures of vital capacity may be difficult in patients with bulbar onset, although the use of face masks in specialised respiratory units may circumvent this difficulty. Finally, patients must be aged \leq 75 years to qualify for PBS subsidisation, primarily because there is limited information regarding the benefits of riluzole in the older age group.⁹

Questions remain about the benefits of riluzole on survival in patients with advanced MND, and whether the effect of riluzole on motor neurones diminishes over time.¹⁰ Certainly, there is no

evidence to suggest that riluzole reverses motor neurone degeneration and, despite extensive counselling about what to expect, patients may have unrealistic expectations of riluzole therapy.

My own experience in the trial setting was that when their deficits did not diminish, some patients ceased taking riluzole, believing it not to be beneficial. This reinforces the need for a detailed discussion between the treating physician and the patient with MND at the time of commencing riluzole. Patients need to understand the role of riluzole therapy; specifically, that it is not a cure, but that it has been established to slow the rate of deterioration in muscle function and thereby increase longevity and quality of life. Clearly, good communication skills and empathy are needed when conveying this information to the patient and their family.

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