Riluzole, disease stage and survival in ALS

Lancet Neurol 2018
Published Online
March 7, 2018
http://dx.doi.org/10.1016/S1474-4422(18)30091-7
See Online/Articles
http://dx.doi.org/10.1016/S1474-4422(18)30054-1

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. Despite being associated with a short survival benefit of 2–3 months equating to a 9% increase in 1-year survival,[1,2] the subsequent adoption of riluzole as a treatment for ALS was perhaps reflective of a desperate need for therapeutic options in the face of this devastatingly progressive disease.[3] More than two decades after riluzole was first approved for ALS, a more efficacious treatment is yet to be discovered.

Despite increasing scientific rhetoric on the subject, the mechanism of therapeutic benefit afforded by riluzole remains undetermined. Several pathways have been postulated, ranging from central anti-glutaminergic modulation of excitotoxic pathways, mitochondrial function, and changes to fat metabolism, to peripheral axonal effects on persistent sodium channel function and potentiation of calcium-dependent potassium currents.[4] To clarify the mechanism of action of riluzole in patients with ALS, a post-hoc study by Ton Fang and colleagues published in *The Lancet Neurology*[5] selectively explored the potential for riluzole to exert differential effects across disease stages. Analysing data from the original dose-ranging trial comprising 959 patients randomly assigned to riluzole (50 mg/day, 100 mg/day, or 200 mg/day) or placebo,[6] Fang and colleagues showed that 100 mg/day of riluzole was associated with longer survival in the last clinical stage of ALS before death (stage 4) compared with placebo (hazard ratio 0·55, 95% CI 0·36–0·83; log-rank p=0·037). The time from stages 2 or 3 to subsequent stages or death did not differ between riluzole treatment groups and placebo. These findings suggest that the disease-modulatory effects and survival benefits of riluzole occur in an advanced stage of disease.

Although the earliest stage of ALS was not analysed in the current study by Fang and colleagues, findings from several open-label non-randomised trials have suggested that the greatest benefit occurs at earlier disease stages.[7–9] Early disease modulation was also suggested by findings from another study,[10] which showed that partial normalisation of central and peripheral dysfunction occurred in the first 8 weeks of riluzole use in patients with relatively early-stage ALS. The argument for earlier efficacy might seem more conceptually feasible than later effects, given the lower likelihood that any treatment could confer a significant neuroprotective effect within a severely depleted population of dead and dying motor neurons, such as might occur in the advanced disease stages of ALS. The contrasting notion proposed by Fang and colleagues,[5] suggesting benefit at the endpoint of the disease, warrants careful reconsideration of these hypotheses. Specifically, perhaps riluzole might affect or activate different therapeutic pathways dependent on disease stage. For example, modulation of excitotoxicity might be an early transient effect, with other molecular pathways becoming more involved later. Such a proposition would certainly be in keeping with the wide-ranging, multimodal effect of riluzole on neural activity.[4]

Fang and colleagues' study challenges the current clinical landscape in ALS, in which prolongation of life at a time of severe, progressive disability might be considered less desirable for patients, their carers, and indeed, the treating clinicians. When discussing treatment options, patients and clinicians must also take into account the established absence of motor functional improvement determined through previous riluzole trials,[6] an effect that might be justified by the proposed late-disease-modifying effect. Encouragingly, a meta-analysis of riluzole[1] has shown that small but significant functional improvements in bulbar and limb function independent of muscle strength occur with its use, with apparent subtype differences also emerging.[7] Overall, these observations suggest the need for clarification of the mechanisms of action of riluzole in large prospective trials, surveying all clinical stages of ALS.

Despite major clinical trial efforts and advancements towards understanding the genetic, epigenetic, and molecular pathways linked to ALS pathophysiology over the years, therapeutic translation has remained disappointingly slow. This is testament to the aetiological complexity and underlying heterogeneity of the disease.[11] The use of staging systems, as shown in Fang and colleagues' study, is a potential platform that should be considered further. Although no universal system is currently recognised, improved disease-staging criteria might provide more robust frameworks to account for the heterogeneity of ALS,[12] so that factors such as variable

rates of disease progression will not confound the benefits of a treatment effect or the timing for greatest efficacy. In the setting of the many forthcoming trials in ALS, such considerations will be important to achieve successful patient outcomes, and can only encourage the possibility of more targeted and effective treatment options in an era of precision medicine.

*Thanuja Dharmadasa, *Matthew C Kiernan*
Brain and Mind Centre, University of Sydney and Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Sydney, NSW 2040, Australia (TD, MCK)
matthew.kiernan@sydney.edu.au

We receive research funding from Forefront, a collaborative research group supported from the National Health and Medical Research Council of Australia program grant (#1037746).

1 Miller R, Mitchell J, Moore D. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* 2012; **3:** CD001447.
2 Kiernan M, Vucic S, Cheah B, et al. Amyotrophic lateral sclerosis. *Lancet* 2011; **277:** 942–55.
3 Dharmadasa T, Henderson R, Talman P, et al. Motor neurone disease: progress and challenges. *MJA* 2017; **206:** 357–62.
4 Cheah B, Vucic S, Krishnan A, Kiernan M. Riluzole, neuroprotection and amyotrophic lateral sclerosis. *Curr Med Chem* 2010; **17:** 1942–99.
5 Fang T, Al Khleifat A, Meurgey J, et al. Stage at which riluzole treatment prolongs survival inpatients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study. *Lancet Neurol* 2018; published online March 7. http://dx.doi.org/10.1016/S1474-4422(18)30054-1.
6 Lacomblez L, Bensimon G, Leigh P, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. *Lancet* 1996; **347:** 1425–31.
7 Traynor B, Alexander M, Corr B, Frost E, Hardiman O. An outcome study of riluzole in amyotrophic lateral sclerosis—a population-based study in Ireland. 1996–2000. *J Neurol* 2003; **250:** 473–79.
8 Zoing M, Burke D, Pamphlett R, Kiernan M. Riluzole therapy for motor neurone disease: An early Australian experience (1996–2002). *J Clin Neurosci* 2006; **13:** 78–83.
9 Riviere M, Menininger V, Zeisser P, Munsat T. An analysis of extended survival in patients with amyotrophic lateral sclerosis treated with riluzole. *Arch Neurol* 1998; **55:** 526–28.
10 Geevasinga N, Menon P, Ng K, et al. Riluzole exerts transient modulating effects onf cortical and axonal hyperexcitability in ALS. *Amyotroph Lateral Scler Frontotemporal Degen* 2016; **17:** 580–88.
11 Turner M, Hardiman O, Benatar M, et al. Controversies and priorities in amyotrophic lateral sclerosis. *Lancet Neurol* 2013; **12:** 310–22.
12 Al-Chalabi A, Hardiman O, Kiernan MC, Chiò A, Rix-Brooks B, van den Berg LH. Amyotrophic lateral sclerosis: moving towards a new classification system. *Lancet Neurol* 2016; **15:** 1182–94