A Controlled Trial of Riluzole in Amyotrophic Lateral Sclerosis

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At the time of this study, ALS was known to be a progressive and fatal neurodegenerative condition, though no medications had been shown to slow disease progression. Several lines of research had, however, suggested the involvement of the glutamatergic system (via toxic glutamate accumulation in neuronal synapses) in the pathogenesis of ALS. For this reason, medications that modulated the glutamatergic system were considered as potential treatment options for ALS, and preclinical studies had supported a role for Riluzole in glutamatergic neurotransmission. As such, the goal of this trial was to study the efficacy of RIluzole in ALS, in terms of survival and long-term functional status.

Experimental design and statistics: This study was a randomized, double-blind, placebo-controlled trial conducted in outpatient clinics in France. Inclusion criteria included an age of 20-75yrs and a clinical status indicative of probable or definite ALS. Exclusion criteria are noted below.[1] Eligible patients were randomized (stratified by limb vs. bulbar-onset disease) to receive either 100mg Riluzole daily (50mg BID) or placebo. Follow up evaluations occurred every 2 months. Primary and secondary efficacy outcomes were assessed at 12 months or at 12 + 24 months post-randomization. Patients receiving placebo were ultimately switched to Riluzole after the efficacy analysis following final enrollment. Primary efficacy outcomes included 1) the 12-month survival rate (with principal events including death or tracheostomy placement), and 2) changes in functional status (limb and bulbar function, subjective symptoms, results of clinical exam) at 12 months. Secondary efficacy outcomes included muscle strength (MRC grading), respiratory function (FVC values), the Global Clinical Impression of Change scale, and subjective reports of symptoms (cramps, fasciculations, etc). Standard labs (LFTs, CK, CBC/CMP) and serum Riluzole concentrations were evaluated routinely. Patients were withdrawn from the study in the event of a serious adverse event, a significant LFT elevation, or if requested by the patient.[2] Statistical analyses included log-rank statistics for survival rates and least-squares methods for the slopes related to the decline in scores of functional status.

Results: A total of 155 patients (32 with bulbar-onset, 123 with limb-onset) were enrolled (N=77 to Riluzole, N=78 to placebo). Of note, 24 of these patients met inclusion criteria but did not fully meet exclusion criteria, though they were still enrolled, and their data were included in the final intention-to-treat analysis. Baseline patient characteristics were otherwise similar among the two groups (**Table 1**). Regarding the primary outcomes, 1yr survival was significantly higher in the Riluzole (74%) vs. placebo group (58%, $p = 0.01$, **Fig. 1**)[3], with a 38.6% mortality reduction with Riluzole at 1yr; survival data showed a similar pattern at 21 months ($p = 0.046$)[4]. Notably, survival curves seemed to differ based on bulbar vs. limb-onset sub-group: differences in 1yr survival were significant and marked in the bulbar-onset group (73% Riluzole, 35% placebo) but non-significant and modest in the limb-onset group (74% Riluzole, 64% placebo, **Fig.1**). In terms of functional status, the rate of decline for each score of functional status was slower in the Riluzole vs. placebo group, but with significant group differences only in the rate of muscle strength decline (**Fig 2**). Finally, 27 patients in the Riluzole vs. 17 patients within

[1] Exclusion Criteria: >5yrs of symptoms, FVC <60%, presence of other life-threatening disease, hepatic or renal dysfunction, pregnancy, EMG/NCS evidence for conduction blocks, paraproteinemia, CNS lesions accounting for symptoms, dementia

[2] Withdrawal did not mean study termination, as all such patients were still followed q2 month via intention-to-treat protocol

[3] Removing the 24 patients that did not meet exclusion criteria from the model yielded similar though non-significant results at 1yr (71% survival with Riluzole, 60% with placebo)

[4] Cox proportional hazard models identified several prognostic variables, present at study entry, that affected survival (**Table 2**). Statistical correction for these variables led to group differences only in 12 and not 21-month survival rates

the placebo group discontinued treatment, mostly related to worsening asthenia or elevated AST/ALT levels (**Table 3**). However, many patients in the Riluzole group tolerated LFT elevations well and did not withdraw from treatment.

Conclusions: Overall, this study was among the first to show a significant survival benefit of Riluzole in patients with ALS, with the additional benefit of a slower rate of muscle strength decline over time. In general, Riluzole also appeared to be well-tolerated. Despite an unknown mechanism of action of Riluzole, this positive effect on muscle strength at least suggested that it may interfere with motor neuron degeneration. Notably, the survival benefit to Riluzole was more robust in patients with bulbar-onset disease, though the study authors suggest that this may have been purely related to chance in their population, and the similar trends and group differences in survival rates in both the limb and bulbar-onset subgroups suggested that Riluzole was likely beneficial for both. Ultimately, the positive results from this study led to further clinical trials aimed at securing Riluzole treatment for ALS.

Additional reading, if interested:

1) Lacomblez, L. et. al., Dose-ranging study of Riluzole in amyotrophic lateral sclerosis. Lancet (1996). 347 (9013): 1425-31.

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