Case:

A 48 year old man presented reporting two years of increasing weakness that he first noticed in his left leg when he was bowling. With progression, he began to fall during his approach to the lane. Within a year, he found himself unable to walk quickly or run and could not stand from a squat. He then noted weakness in his left hand and then mild weakness in the right. He described leg cramping at night and hand cramping during use. He developed fasciculations in his legs, then in his arms. Over the prior year, his movements became slow and his limbs stiff. He had lost 20 pounds in the previous 2 years.

On examination, mental status was normal. Cranial nerve examination revealed slightly slowed speech, but normal tongue movements. Sparse fasciculations were observed in the tongue. There was a brisk jaw jerk. Motor exam revealed atrophy of the first dorsal interossei bilaterally and widespread fasciculations. There was increased tone in the legs more than in the arms. Toe tapping and fine finger movements were slow. Strength was reduced in the shoulder abductors, wrist extensors, finger extensors and abductors, and foot dorsiflexors on the left more than right.

Deep tendon reflexes were 3+ at the biceps, triceps, brachioradialis, quadriceps, and 2+ at the Achilles tendons. Hoffman was present briskly on the left. There was sustained clonus at the ankles and the toes were upgoing. The patient’s gait was stiff, and the stance phase on the left was particularly unsteady. There was poor foot elevation, but no clear foot drop. He could walk on heels and toes. Sensation and coordination were normal.

Vital capacity was 80% of expected. Testing revealed normal MRI of the cervical spine and brain. EMG met El Escorial Criteria for the support of a clinical diagnosis of ALS.

After discussing the risks and benefits of riluzole, he was provided with a prescription for riluzole 50mg tablets taken once per day in the morning for a week and then increased to twice daily. He was instructed to take the drug on an empty stomach, one hour before eating or two hours after eating. He was provided with a prescription for liver function tests monthly for three months and plans were made to monitor liver function tests every three months thereafter.

Rationale:

Riluzole is the only known disease-modifying therapy for ALS. Approved by the FDA in 1995, it has been in use for nearly two decades. Interestingly, riluzole was developed as a therapy for ALS before the creation of a genetic murine model of ALS. Riluzole blocks presynaptic release of glutamate, which is generally thought to be its mechanism of action in ALS. However, it also partially blocks post-synaptic NMDA receptors, and blocks sodium channels, thus the exact mechanism of action in ALS remains somewhat uncertain.

A pivotal trial for riluzole demonstrated an improved 12-month survival (riluzole 74%, placebo 58%) and a benefit on muscle strength. A dose-ranging studies investigated 50, 100, and 200mg
of riluzole per day noted tracheostomy-free survival of 50.4% (placebo), 55.3% (50 mg riluzole), 56.8% (100 mg riluzole), and 57.8% (200 mg riluzole) respectively\(^5\). After adjustment for baseline characteristics, 100mg daily dose was associated with a 35% decreased risk of death over the duration of the study relative to placebo \((p = 0.002)\). In this trial, the most common adverse events were nausea, asthenia, and increases in liver function tests, and the risk-benefit ratio appeared most favorable at the 100mg/d dosage level.

Pharmacodynamic studies support a wide inter-patient variability in riluzole blood levels\(^6\), and adverse events have been shown to correlate with riluzole blood concentration\(^7\), however survival benefit has not\(^8\). And, while pharmacogenetic studies demonstrate an effect of CYP1A1 and CYP1A2 polymorphisms on riluzole blood level, they do not support an effect on survival\(^9\).

A trial investigating the effect of riluzole therapy in elderly patients and those with advanced disease failed to demonstrate a treatment effect, but was under-enrolled and ultimately lacked sufficient statistical power to adequately address the question\(^10\).

A meta-analysis of four trials of riluzole demonstrated a 9% increased probability of surviving 12 months in ALS patients taking riluzole, but no difference at 18 months and no benefit in strength\(^11\). Observational studies have demonstrated effect sizes ranging from 4 to 12 months survival benefit, but are subject to greater bias\(^12-14\).

In randomized controlled trials, nausea and asthenia are approximately 1.5 times more common in patients on riluzole than placebo\(^5,15\). Some experts recommend a starting dose of 50mg daily to reduce the occurrence of nausea. Vomiting, diarrhea, anorexia, dizziness, and reduced hemoglobin trended toward being more common in patients treated with riluzole\(^15\). Increases in ALT to >3 times the upper limit of normal were more common in patients treated with riluzole\(^15\). For this reason, it is recommended that liver function tests be measured every month for the first three months of therapy, every three months for the first year, and periodically thereafter (http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=e49d207d-8e32-4183-94ba-cd264f124090).

Data supports the cost-effectiveness of riluzole as a therapy. One cost-effectiveness analysis of riluzole demonstrated a cost of £22,086 per quality-adjusted life year (QALY)\(^16\), another $12,013 per QALY\(^17\).

Riluzole utilization has increased since 1997, when 45% of ALS patients were taking riluzole\(^18\). Utilization is now 60% in the US and nearly 100% in France, Italy, and Germany\(^19\). Patients’ perception of a small therapeutic benefit is a common reason for patients declining riluzole therapy\(^20\), though cost remains another important factor. The most influential factor in patients’ decision to use riluzole remains the knowledge and enthusiasm of the treating physician\(^18\).
Evidence Base:

The following clinical recommendation statements are quoted verbatim from the referenced clinical guidelines and represent the evidence base for the measure:

- Riluzole should be offered to slow disease progression in patients with ALS (Level A).  

- Riluzole 50 mg twice a day is reasonably safe and probably prolongs median survival by about two to three months in patients with amyotrophic lateral sclerosis. (No level of evidence listed.) This is a Cochrane review.  

- ALS patients should be offered treatment with riluzole 50 mg twice daily (Class 1A, GPP)  

- Patients treated with riluzole should be monitored regularly for safety (Class 1A, GPP).  

- Treatment should be initiated as early as possible after the patient has been informed of the diagnosis taking into account expected therapeutic benefits and potential safety issues (class 1A). Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers. (GPP)  

- Treatment with riluzole should be considered in PMA and PLS patients who have a first degree relative with ALS. (GPP)  

References:


NeuroPI Case Study: Disease Modifying Pharmacotherapy


