RILUZOLE — WHAT IS ITS IMPACT IN OUR TREATMENT AND UNDERSTANDING OF AMYOTROPHIC LATERAL SCLEROSIS?

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ALTHOUGH CHARCOT FIRST DESCRIBED amyotrophic lateral sclerosis (ALS) in 1874, this disease has remained enigmatic. For many years ALS has been synonymous with "no cause and no cure." Only recently has the mystery of ALS begun to be slowly unveiled, and potential treatments have become a reality.

Abnormal glutamate metabolism is one of the most plausible explanations of the ALS disease process.[1] Patients with ALS are less able to metabolize oral monosodium glutamine and have increased concentrations of serum and cerebrospinal glutamate while its tissue concentration in the central nervous system is reduced. The fact that several exogenous excitotoxins that act as glutamate agonists cause motor neuron toxicity supports the idea that glutamate excitotoxicity may be a cause of ALS. The glutamate transporter removes excess glutamate from the extracellular space. Rothstein et al.[2,3] found that the glutamate transporter concentration in glial cells is significantly lower in the brain and spinal cord of patients with ALS. Glutamate attachment to its postsynaptic receptor allows sodium and calcium ions to enter motor neurons. When calcium enters motor neurons in excess, a series of calcium-dependent enzymes that are usually suppressed (e.g., lipid peroxidase, nitric oxide synthetase, xanthine oxidase) are activated, causing the production of free radicals and nitric oxide, which leads to neuron death.[4] Even if the cause of ALS is not yet known, the use of medications altering the cell death process may slow or retard the overall disease process. This concept is called neuroprotection.[4]

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In this issue, Wagner and Landis[5] review riluzole in the treatment of ALS. Riluzole was originally developed as an anticonvulsant, but its potent antiglutamate effects led investigators to test its efficacy in patients with ALS.[6] In 1995, on the basis of two independent clinical trials that showed riluzole modestly prolonged survival and the time to tracheostomy in patients with ALS, riluzole received approval from the Food and Drug Administration, becoming the first drug approved for treatment of ALS.[7,8]

The effectiveness of medications is determined only by well-designed controlled clinical trials. Clinical trials for ALS are difficult because the diagnosis of ALS is based solely on clinical features, and there are no surrogate markers for objective assessment of the effectiveness of the drug. The prospective, randomized, placebo-controlled, double-blind design, although only recently used in ALS studies, is the gold standard for definitive clinical trials. The World Federation of Neurology Subcommittee of Motor Neuron Disease issued the El Escorial diagnostic criteria (based on the distribution and presence of both upper and lower motor neuron signs along with the absence of other diseases that can explain the signs found in the patient).[9] Recently, it also published the Guidelines for Clinical Trials so that patients entering clinical trials are diagnosed in a uniform fashion, and clinical trials are performed in a manner that will meet rigorous clinical, analytical, and ethical standards.[10]

Clinical Significance of Riluzole

The riluzole trials[7,8] largely followed both of these criteria. The earlier study, which had a number of difficulties, as were summarized by Wagner and Landis, should be considered a Phase II and III study.[7] The number of patients was relatively small (155) but adequate for an exploratory study. Patients treated with riluzole 100 mg/d had a prolonged survival at 12 months of treatment. This study was promising enough to proceed to a large Phase III trial. The second clinical trial also has been criticized, but the problems differ from those of the earlier study.[8] The length

of the study period depended on the countries that participated in the trial. In this multicenter, multinational study, the French centers began the trial much earlier than the rest of the European countries, the US, and Canada. However, the entire study was completed on the basis of the original schedule in the French centers, causing some irregularity in the duration of treatment. Such irregularity may have affected the analysis. The second study also failed to reproduce some of the positive results of the earlier study. In particular, the better survival in patients with bulbar-onset ALS and the beneficial effects found during manual muscle testing could not be verified. On the other hand, troublesome imbalances between the study groups noted in the Phase II and III trials were avoided in the second study. These differences clearly were likely to be the result of the sample size in the first study, emphasizing the pivotal importance of large-scale Phase III trials. Most importantly, however, the improvements in the primary end points (survival time and time to tracheostomy), although modest, were statistically significant in both studies, favoring riluzole 100 mg/d over placebo.[7,8]

Death and time to tracheostomy as the primary end points in clinical trials for ALS deserve some discussion. Although death is an incontrovertible event in ALS, the clinical course leading to death can be strongly influenced by many factors other than the drug under study. Aggressive use of antibiotics for pneumonia, enteral tube feeding, noninvasive ventilator use, and even the abilities of the primary caregiver may alter the disease course and thus prolong survival. Because the timing of an elective tracheostomy varies substantially, the point at which it is done in the disease process may influence the outcome.[11] Furthermore, care of patients with ALS may differ considerably from country to country. If patient care and management varied among countries, this may have influenced the study results. Although controlling for variations such as these will not be easy, addressing such questions is crucial in future clinical trials.

Another critical question that Wagner and Landis raise is whether statistical significance in prolonging life really has any clinical significance in the treatment of ALS. Neither study included quality-of-life or pharmacoeconomic assessments.[7,8] ALS inevitably results in death, and thus, as seen in the 1960s at the beginning of the clinical trials for cancer, any evidence of prolonging of life may be seen as sufficient to conclude that a treatment has a "significant" impact. However, physicians and patients want to know whether the drug can improve disease-related quality of life. These assessments are included in ongoing ALS trials. Neurologic and pharmaceutical investigators need to ask these specific questions, as part of a Phase IV study.

Considering all these issues, what is the impact of riluzole? Riluzole is the first drug ever approved for the treatment of ALS. For neurologists, the disclosure and discussion of the diagnosis is probably the most stressful and difficult task in their practice. In the past, they had little hope to offer their patients. Riluzole has changed this situation. Although it does not improve the symptoms and its effects may be modest, I believe that having hope is extremely important for these patients. Based on our experience with many patients, we sense that hope is one of the most important factors in improving the quality of life for patients with ALS. In terms of future research into treatment, we must begin somewhere. Having one drug treatment may help us uncover new insights into the disease process and examine the glutamate toxicity hypothesis further. In addition, riluzole may be able to be used with other drugs currently being investigated, such as insulin-like growth factor-I (IGF-I).

When to Prescribe Riluzole

What should we recommend to our patients? In my practice, I recommend riluzole to patients as soon as the diagnosis of ALS is established. The results of the two studies suggest that riluzole works better during the first 12–16 months of treatment than later. This finding may indicate that riluzole is more effective in the early stages of ALS. This possibility also poses the issue of whether the drug should be prescribed when the patients may be in the earliest stages of the disease, when the diagnosis of ALS is only suspected. It is generally agreed that when a diagnosis can be made of "definite" ALS (at least 3 body regions of bulbar, cervical, thoracic, or lumbosacral regions manifesting both upper and lower motor neuron signs) based on El Escorial diagnostic criteria or "probable" ALS (at least 2 regions showing both upper and lower neuron signs, but the region with upper motor neuron signs being above the region of lower motor neuron signs), the disease is already well advanced. Starting the drug only when the diagnosis is clear would miss an opportunity for more effective treatment.

This question remains unanswered at this point, but I would not hesitate to recommend treatment if the diagnosis of ALS is "suspected." Another dilemma is economic. Physicians must be cost-conscious when they prescribe drugs. The reality is that Medicare, the major national insurance program in the US for the elderly or disabled, does not cover any prescription drugs. Some commercial insurers and managed care organizations have limited coverage for costly drugs. Such policies place undue financial strain on patients and their families who want to try riluzole. I believe that I am obligated to tell all patients that the drug has modest effects by discussing the study results as summarized by Wagner and Landis.[5] I remind them that if they take no riluzole, the disease process will not differ markedly. We must carefully discuss the impact of riluzole, because patients must feel that there is hope if they cannot afford the drug. I also recommend aggressive general care, including physical rehabilitation for patients with ALS. Because of the availability of specific drugs for ALS, including riluzole and IGF-I (potentially as the second approved medication) and newer investigational drugs, rehabilitation in ALS may become a reality in the near future.[12]

Summary

Riluzole marks the beginning of pharmacotherapy for patients with ALS. Our task is to fully identify the impact of riluzole in ALS treatment. The ALS Clinical Assessment Research and Education (ALS CARE) is an ambi-

tious database in North America created to establish the benchmarks for patient care and management.[13] Such a program may allow us to analyze the use and impact of riluzole in the treatment of ALS. In the spring of 1997, just 1 year since the approval of riluzole, several more potential drugs for ALS are on the horizon. If a single medication is not sufficient to alter the disease course significantly, we must investigate drug combinations to determine potential additive or synergistic benefits.[14] Although far from ideal, riluzole is allowing clinicians and researchers to lift a corner of the veil surrounding ALS to glimpse the possibility of effective treatment. ≏

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