Treatment of Patients with ALS: Implications for the Managed Care Pharmacist

Anthony Barisano and Jeffrey A. Kramer

ABSTRACT: The objective of this study was to present a perspective for the management of patients in the managed care environment with amyotrophic lateral sclerosis (ALS) parallel to that for patients with neoplasms, highlighting the potential contributions of the pharmacist.

This article presents a brief overview of ALS and illustrates a therapeutic parallel to the management of patients with cancer. Physicians often are reluctant to prescribe riluzole because it is not a cure for ALS. Oncologists, however, commonly initiate antineoplastic regimens with limited efficacy in their patients because such action allows the patient hope for alleviation of symptoms and an extended life expectancy. A similar approach to treating patients with ALS presents professional opportunities for the managed care pharmacist.

Such management of patients with ALS, if approached like that of patients with cancer, would enhance their quality of life and life expectancy. Treatment should be initiated early in the course of ALS; perhaps even before the diagnosis is definitive. Prolonging survival during the early stages of the disease allows the patient to remain independent and productive, establishing riluzole as a cost-effective therapy for ALS. Pharmacists can positively impact the pharmacologic management of ALS. Early access to a multidisciplinary team to confirm the diagnosis, initiate treatment, and manage the symptoms of ALS can reduce both complications and costs.

KEY WORDS: Amyotrophic lateral sclerosis (ALS), Oncology, Managed care pharmacist, Disease management, Riluzole

J Managed Care Pharm 1998: 599-604

A myotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by muscle weakness, wasting, spasticity, and weight loss that results in death in 50% of patients within three years.1 The estimated incidence for ALS ranges from 0.4–1.8 per 100,000 people per year worldwide,2 and the prevalence ranges from 4–6 per 100,000.3 ALS is more common in men than in women until age 70, when the rate becomes the same for both sexes. Average age of onset is in the mid-50s, but ALS can occur at any time after the teen years.4

ALS occurs in two forms: classic, which comprises more than 90% of ALS cases, and familial, which comprises 5%–10% of cases.4 Patients initially present with symptoms in an arm (40%–60%), such as weakness or difficulty performing delicate tasks, or in a leg (20%), such as tripping or foot dragging.5 Approximately 20%–25% of ALS patients present with bulbar symptoms, such as dysarthria, dysphagia, and sialorrhea.6

The initial stimulus for the development of ALS and the duration of the preclinical stage are not known. Electrophysiologic studies have shown the presence of denervation and reinnervation at the time of first clinical presentation, which suggests an ongoing occult process. Long before overt clinical deficits are apparent, some patients experience subtle clinical features, including cramps, fasciculation, and exercise intolerance. Some patients with bulbar disease report intermittent hoarseness or other speech impediments. In many cases, however, patients report excellent motor function until the time of their first clinical deficit.7
PATHOGENESIS OF ALS

There are currently four major hypotheses on the patho-
genesis of ALS: glutamate-induced excitotoxicity, autoimmu-
nity, deficiency of neuronal growth factors, and oxidative stress
induced by free radicals.\(^6\) Glutamate is the principal excitatory
neurotransmitter in the brain, and the accumulation of glut-
state in a synapse is an important factor in the development of
neuronal damage in ALS.\(^6,10\) The autoimmune theory is based
on the identification of antibodies to calcium channels in a
large percentage of patients with ALS, as well as to the neu-
ronal ganglioside GM1 in others.\(^8,11\) An insufficiency of neu-
rotrophic growth factors, including ciliary (CNTF), brain-
derived (BDNF), and insulin-like (IGF-I) neurotrophic growth
factors, also has been implicated in motor neuron degenera-
tion.\(^8,12\) Recent studies have shown mutations in the gene for
superoxide dismutase in some cases of familial ALS,\(^14\) and
there also is growing evidence that oxidative stress is impor-
tant in the initiation of sporadic ALS.\(^15\)

Each of these hypotheses is the basis for active research on
new therapies to better manage, and ultimately control, the
symptoms of ALS.\(^16\) For example, riluzole, the only FDA-
approved medication for ALS, is an antiallglutamate agent that
protects against glutamate excitotoxicity.\(^17\) Gabapentin, another
antiallglutamate agent available for use as an anticonvulsant, has
been tested with disappointing results in ALS.\(^18\) Several neu-
rotrophic growth factors, including IGF-1 (mecasermin), have been
studied as therapies for ALS, alone and in combination with
each other and with riluzole.\(^19\) Unfortunately, neurotrophic
growth factor trials have not conclusively proven that any
member of this class of agents is beneficial when used alone.\(^8,20\)

In a controlled, randomized clinical trial, riluzole slowed
the progression of ALS and improved the survival of patients.\(^21\)
The survival benefit was confirmed in a second dose-ranging
study.\(^22\) Even with riluzole and nonpharmacologic therapies to
control the symptoms of ALS,\(^23\) however, the long-term prog-
nosis for ALS patients is poor. Use of a wheelchair or feeding
tube often is necessary, and ventilatory assistance usually is
required to sustain survival. As described above, approximate-
ately half of ALS patients die within three years of the onset of
the disease, mainly as a result of respiratory failure.\(^1\)

PARALLEL BETWEEN CANCER AND ALS

Several characteristics of ALS, from the grim prognosis to
the emphasis on extending survival time and improving quali-
y of life rather than curing the disease, are similar to those of
various cancers. This parallel suggests that patients with can-
cer and patients with ALS can be managed similarly and that
practitioners treating patients with ALS might benefit from the
experience of hematologists and oncologists.

Most of the drugs used to treat cancer are tested in clinical
trials that use survival as a primary endpoint, because surro-
gate markers for incurable chronic conditions are suboptimal
for monitoring purposes. A Kaplan-Meier curve, commonly
used to depict the survival benefit of antineoplastic drug regi-
mens, illustrates the survival benefit of riluzole compared with
placebo (see Figure 1).\(^21\) This type of analysis is useful because
data from all study patients are included regardless of survival
outcome; results are not skewed by the omission of data for
specific patients.

Despite the shortcomings of existing drug therapies for
some cancers, disease specialists commonly prescribe these
regimens for their patients because treatment provides the
patient with hope, not for a cure but for a longer life and relief
from symptoms of the disease. Many oncologists realize that
initiating a treatment plan inspires hope by giving the patient a
sense of control over the disease.\(^24\) A similar benefit is gained
when using riluzole in ALS.

For example, palliative care is used to treat multiple myelo-
ma. Like ALS, this form of cancer is relatively rare and usually
results in patient mortality.\(^25\) Treatment for multiple myeloma,
in the form of antineoplastic chemotherapy and radiation, is
not initiated to achieve a cure but to improve the patient’s
quality of life by controlling bone pain, fractures, hypercal-
cemia, and renal failure.\(^26\) Significantly, survival can be pro-
longed by two years in treated patients as compared to
untreated patients.\(^27\)

Until riluzole was shown to significantly increase survival

Figure 1. Kaplan-Meier Survival Curves for Riluzole
Compared with Placebo in Patients with ALS (n=478)\(^24\)
in ALS,12 the only pharmacological interventions available for patients with ALS were for symptom relief. Many neurologists, however, remain reluctant to prescribe this drug for their ALS patients. This reluctance may be attributed to a concern that the patient will develop unrealistic expectations. Experience with patients with cancer has shown, however, that providing a drug, even one with limited efficacy, usually does not engender false expectations but rather helps the patient cope with the reality of the disease.26 One study found that the psychological status of patients with ALS is strongly related to outcome;27 patients with a good psychological status had a lower risk of dying and a longer survival time than did those with psychological distress. Prescribing riluzole may, therefore, have an effect beyond its physiological one: the psychological status of the patient may be improved, having a further beneficial effect on the patient’s physical health.

**INITIATION OF PHARMACOLOGIC THERAPY**

Several other agents are currently under investigation for the treatment of ALS, but as noted above, riluzole is the only one that has been shown to extend survival of ALS patients.21,22 As more drugs are tested, they must be compared with each other and with riluzole.16 To ensure that clinical trials involving patients with ALS are rigorous and standardized, the World Federation of Neurology Subcommittee of Motor Neuron Disease issued the El Escorial diagnostic criteria (see Table 1).28 The El Escorial criteria also can be used by physicians to help with the diagnosis of ALS in difficult cases.29

Riluzole is most effective in the early stages of ALS8 and should be offered to all patients as early as possible in the disease process to prolong the early, less severe stage of the disease in which the patient has greater capacity to maintain the activities of daily living. Some ALS experts recommend introducing riluzole even before a definitive diagnosis has been made; this strategy diminishes the risk of missing the opportunity for the most effective treatment.31 If pharmacologic treatment has not begun before a diagnosis of ALS is made, it should be initiated quickly thereafter to maximize survival benefits. The physician should discuss with the patient the results of the clinical trials, expected side effects, and cost before prescribing riluzole.31

**ADVERSE EVENTS**

Some neurologists are comfortable prescribing riluzole before the diagnosis is confirmed because of its favorable adverse event profile.34 A total of 794 patients received riluzole (50, 100, or 200 mg/day) in phase II/III studies. The most commonly reported adverse events were asthena (18% vs. 12% for patients receiving placebo), nausea (16% vs. 11%), lung function decrease (13% vs. 10%), and dizziness (7% vs. 3%).32 The occurrence rates of asthena, somnolence, vertigo, nausea, vomiting, and perioral paresthesia were found to be dose related.

Laboratory tests in which changes were most commonly reported included certain liver function tests. Serum alanine aminotransferase (ALT) levels greater than three times the upper limit of normal were reported in 6.5% of patients treated with 100 mg/day of riluzole (the recommended dose) as compared with 1.7% of placebo-treated patients.31,32 Aspartate aminotransferase (AST) levels were elevated in 14.3% of patients receiving 100 mg/day of riluzole and 3.8% of placebo-treated patients.31 Spontaneous reversal of aminotransferase levels despite continued therapy was reported,31 and in most other cases a decrease to twice the upper limit of normal or to baseline occurred within two months after riluzole was withdrawn.31,32

Because riluzole is extensively metabolized and subsequently excreted in the urine,33 functional hepatic or renal impairment will reduce the clearance of riluzole and may make side effects more pronounced or more likely to occur.

**RILUZOLE INTERACTIONS**

There are several key variables that pharmacists should monitor in patients receiving riluzole. Riluzole is metabolized through cytochrome p450-dependent glucuronidation and hydroxylation, primarily via isoenzyme CYP 1A2.34 Lower activity of this isoenzyme in women may lead to higher serum levels of riluzole. Pharmacists also should consider the drugs administered concomitantly with riluzole. Combination therapy with compounds that inhibit CYP 1A2 (e.g., caffeine, theophylline,

**Table 1. El Escorial Criteria for the Diagnosis of ALS: Lower Motor Neuron and Upper Motor Neuron Signs in Four Regions**

<table>
<thead>
<tr>
<th>Region</th>
<th>Lower Motor Neuron (LMN)*</th>
<th>Upper Motor Neuron (UMN)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulbar</td>
<td>jaw, face, palate, tongue, larynx</td>
<td>clonic jaw, gag reflex, forced yawning, pathologic deep tendon reflexes, spastic tone</td>
</tr>
<tr>
<td>Cervical</td>
<td>neck, hand, arm, diaphragm</td>
<td>clonic deep tendon reflexes, pathologic deep tendon reflexes, spastic tone</td>
</tr>
<tr>
<td>Thoracic</td>
<td>back, abdomen</td>
<td>loss of superficial abdominal reflexes, pathologic deep tendon reflexes, spastic tone</td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>back, abdomen, leg, foot</td>
<td>clonic deep tendon reflexes, extensor plantar response, pathologic deep tendon reflexes, spastic tone</td>
</tr>
</tbody>
</table>

*LMN signs—Weakness, atrophy, fasciculations
*UMN signs—Pathologic spread of reflexes, clonus
Adapted with permission.
quionolones, and amitriptyline) or induce the activity of the cytochrome system (e.g., rifampin and barbiturates) may result in significant changes in riluzole serum levels.\textsuperscript{31}

Administration of riluzole with a high-fat meal decreases absorption of the medication, reducing peak blood levels by approximately 45% and the area under the time-concentration curve by 20%.\textsuperscript{32} Pharmacists can be instrumental in ensuring that monitoring is appropriate and can help in the management of any difficulties that patients encounter with riluzole therapy.

**IMPLICATIONS FOR MANAGED CARE**

Several factors in the care of patients with ALS have particular relevance for managed care. Use of El Escorial criteria will assist in accurate and efficient early diagnosis, minimizing unnecessary and costly testing. Expenditures of $10,000–$20,000 have been documented during the initial phase of diagnosis as a result of the physician's desire to identify a disease other than ALS, which would eliminate the need for discussing the dire prognosis.\textsuperscript{33} Unpublished data show, not unexpectedly, that the cost of ALS is related to the severity of the disease, with the terminal state of illness resulting in an annualized expenditure of nearly $80,000 in direct costs and lost income.\textsuperscript{34} Educational efforts to accelerate the diagnosis of ALS for the dual purposes of relieving uncertainty and initiating early treatment should encompass both primary care and specialty staff, in view of evidence that a diagnosis of ALS continues to be one of exclusion, even for many neurologists.\textsuperscript{35}

As discussed above, riluzole is most effective when therapy is started during the early stages of the disease,\textsuperscript{36} and it may even be prudent to begin therapy before a definitive diagnosis has been made.\textsuperscript{37} Riluzole is not inexpensive, and physicians may hesitate to prescribe a costly agent before a patient is experiencing severe symptoms. An oncologist would not hesitate to prescribe an expensive drug, however, as soon as a tumor was detected, knowing that earlier intervention results in improved long-term outcome for patients. Riluzole should be viewed similarly, because early treatment supports a higher level of independent function by the patient before the loss of motor neurons is widespread.\textsuperscript{38} Use of recently published guidelines for the use of riluzole will help determine which patients are likely to benefit from therapy with this medicine.\textsuperscript{39}

Results of a recent pharmacoeconomic study showed that riluzole use is cost effective: hospitalization was delayed in riluzole-treated patients, though the savings were offset by additional services required during the extended survival period. The authors concluded that increases in both longevity and productivity resulting from riluzole therapy provide societal benefits that outweigh the increase in expenditures.\textsuperscript{40}

Two important aids in making treatment decisions are the ALS Standard of Care Consensus on Diagnosis and Management of ALS\textsuperscript{37} and the riluzole usage guidelines mentioned previously.\textsuperscript{38} These documents were created to assist ALS health care providers with recommendations for diagnostic criteria, symptoms management, and pharmacologic treatment. In addition, a database of ALS outcomes, called the ALS CARE (clinical assessment, research, and education) Project, was developed with the goals of identifying opportunities to improve the quality of care for ALS patients; describing diagnostic and treatment strategies and patient outcomes; providing ALS centers with data to evaluate and improve their practices; publishing objective data on temporal trends and regional differences in the care of patients with ALS; and developing hypotheses for future clinical trials.\textsuperscript{39}

Another important factor in the management of patients with ALS is that, for patients with cancer, care is optimized through a multidisciplinary approach.\textsuperscript{40} A patient with ALS may need the services of a nutritionist, speech therapist, and respiratory therapist.\textsuperscript{41,42,43} Many patients will initially deny that they have a terminal disease; once they have accepted this fact, they may become depressed. Depression often can be treated with psychological support from the physician but may require referral to a psychiatrist and treatment with antidepressants.\textsuperscript{44} Patients who have remained at home should be visited periodically by home care personnel to review family and psychosocial problems, imminent crisis situations, and the need for equipment or community services. Each of these health care professionals is an important member of a team providing a continuum of compassionate care to the patient with ALS. Early access to these specialists who help manage the symptoms of ALS can reduce complications and therefore reduce overall health care costs.\textsuperscript{45}

A variety of pharmacologic agents may be used in the course of an ALS case (see Table 2);\textsuperscript{46} the pharmacist can contribute significantly to the multidisciplinary team's care of the patient by monitoring response to and tolerance of each prescribed medicine and making suggestions for appropriate modifications. As ALS progresses and muscle wasting becomes more serious, muscle mass and total body weight are reduced,\textsuperscript{47} so a reduction in the dosage of many drugs may be required to avoid drug toxicity. For instance, insulin requirements change as muscle mass and physical activity diminish. Diabetic patients with ALS often have a declining energy need but continue the same energy intake, thereby increasing insulin requirements. When meal schedules and the composition of meals alter as ALS progresses, other changes in insulin dosage may be required. Most diabetic patients have been taught to take early morning and late afternoon insulin injections, planned to coincide with peaks in glucose production. If patients with ALS are being tube-fed by continuous infusion, insulin should be administered at regularly spaced intervals.

Regimens used to control cardiovascular problems such as hypertension and heart disease also may have to be altered in patients with ALS. Clinicians may note a decline in blood pressure in hypertensive patients as they approach the terminal stage of the disease. There are several possible explanations for this phenomenon, including decreased salt intake and improved medication compliance. Doses of antihypertensive medicines may need to be reduced.
Table 2. Pharmacologic Interventions for Symptomatic ALS\textsuperscript{37}

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Assessment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramping</td>
<td>Sleep disturbances</td>
<td>Quinine, phenytoin, diazepam</td>
</tr>
<tr>
<td>Spasticity</td>
<td>Unusual as a major problem</td>
<td>Baclofen</td>
</tr>
<tr>
<td>Pain</td>
<td>Sleep disturbances</td>
<td>Analgesics (including opiates)</td>
</tr>
<tr>
<td>Salivation</td>
<td>Laryngospasm, coughing</td>
<td>Atropine, amitriptyline</td>
</tr>
<tr>
<td>Depression/insomnia</td>
<td>Sleep disturbances</td>
<td>Antidepressants, anxiolytics</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Leg movements, myoclonus, apnea</td>
<td>Clonazepam, Sinemet CR</td>
</tr>
<tr>
<td>Infections</td>
<td>Results of decreased bronchial secretions</td>
<td>Antimicrobials, vaccines (e.g., pharylactic influenza, pneumococcal)</td>
</tr>
</tbody>
</table>

Adapted with permission.

Intolerance to new medications also may be a problem in patients with ALS. Tolerance is an important aspect of riluzole therapy because the initial gastrointestinal side effects may discourage patient compliance.\textsuperscript{37} These problems are managed by some ALS specialists by initially titrating riluzole, starting once daily with food, increasing to twice daily with food, and finally administering without food as recommended.\textsuperscript{37} Although the preceding procedure is not published, the pharmacist can recommend it as a practical method to improve tolerance during the initial stage of riluzole therapy.

The prescription of riluzole fosters optimism in patients with ALS. This hope for both alleviation of symptoms and extension of life has been shown to improve the patient’s quality of life, not only in oncology, but also in ALS.\textsuperscript{27} Rationing of health care resources should not be a factor in the physician’s prescribing decisions. As in oncology practice, such choices should not be made on an individual basis but should instead be made at the level of organizational guidelines.\textsuperscript{41}

As the physical condition of the patient deteriorates, critical decisions about life support systems must be made. These decisions should not be made at the last minute. The team is obligated to discuss life support issues with the patient and to fully inform the patient and the family of the consequences of choosing a life support system. This discussion should include the financial considerations, such as what will be provided by the patient’s health care coverage.\textsuperscript{37}

CONCLUSION

A multidisciplinary team, whether treating patients with ALS or neoplasm, often will be confronted with difficult ethical dilemmas and may be helped by discussing these issues with an ethics committee or consultant. The provision of riluzole, palliative medications, and supportive care, combined with the ethical issues of mechanical ventilation and end-of-life planning, are aspects of ALS treatment to which the pharmacist and the other members of the team apply their knowledge and experience to improve patient outcomes and quality of life.

Although chronic conditions such as ALS, infection with human immunodeficiency virus, and certain neoplasms are incurable today, they are nonetheless treatable. Providing comprehensive care to patients with such diseases is vital to the growth of the profession of pharmacy. Presently, most pharmacists are unfamiliar with ALS; yet if patients with the disease are not well managed, health care costs will increase without providing the patient an improved quality of life. Recent publications have documented the financial value of pharmacist involvement;\textsuperscript{14,23} reimbursement for cognitive health care professional services in global disease management inevitably will be justified by intermediate and long-term savings. Participation in the optimal management of patients with ALS by encouraging early riluzole therapy and applying other pharmacotherapeutic principles is an example of how pharmacists can be proactive, aggressive, and clinically adept in meeting these challenges.

\textbf{References}

Treatments of Patients with ALS: Implications for the Managed Care Pharmacist


20. Myocophenol T-IND expanded to a total of 450 patients; advisory committee does not find arguments for fundamental effect on ALS progression compelling. FDC Reports, The Pink Sheet, May 12, 1997: 59-78.


