Cytokinetics

ABOUT

ALS

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that can attack both upper and lower motor neurons and causes degeneration throughout the brain and spinal cord. In patients with ALS, this progressive degeneration eventually leads to the death of the motor neurons. As these motor neurons die, the brain loses the ability to initiate and control muscle movement. With voluntary muscle action progressively affected, patients in the later stages of the disease may become totally paralyzed.[1]

PREVALENCE OF ALS

ALS affects as many as 30,000 Americans, with an estimated 5,600 new cases diagnosed each year in the U.S.[1,2] ALS is 20% more common in men than women, however, with increasing age, the prevalence becomes more equal between men and women. The life expectancy of an ALS patient is 3-5 years from the time of diagnosis with 90-95% of those diagnosed with ALS having the sporadic form (SALS). Of the remaining ALS patient population, 5-10% have a family history of the disease (familial ALS, FALS). In cases of familial ALS, there is a 50% chance each offspring will develop the disease.[1]

SYMPTOMS OF ALS

The onset of ALS may be so subtle that the symptoms are often overlooked. The earliest symptoms may include twitching, cramping or stiffness of muscles; muscle weakness affecting an arm or a leg; slurred and nasal speech; or difficulty chewing or swallowing. These general complaints can then develop into more obvious weaknesses or atrophies that may cause a physician to suspect ALS.[2]

The parts of the body affected by the early symptoms of ALS depend on which motor neurons are damaged or lost first. In some cases, symptoms initially affect one of the legs and the patients may experience awkwardness when walking or running. Some patients first experience the effects of the disease in a hand or arm as simple tasks requiring manual dexterity such as buttoning a shirt, writing, or turning a key in a lock become difficult. Other patients notice speech problems.[2]

Regardless of the part of the body first affected by the disease, muscle weakness and atrophy spread to other parts of the body as the disease progresses. Patients have increasing problems with moving, swallowing, speaking or forming words. Symptoms of upper motor neuron involvement include tight and stiff muscles and exaggerated reflexes including an overactive gag reflex. Symptoms of lower motor neuron degeneration include muscle weakness and atrophy, muscle cramps, and fleeting twitches of muscles that can be seen under the skin.[2]

DIAGNOSING ALS

No one test can provide a definitive diagnosis of ALS, although the presence of upper and lower motor neuron signs in a single limb is strongly suggestive.[2] ALS is a rule-out diagnosis based on a series of clinical examinations and diagnostics. Clinical diagnosis depends upon history, physical examination, and laboratory and radiographic evaluations that are consistent with ALS while excluding other diseases that may mimic ALS.[1] Patients with ALS often demonstrate signs and symptoms of both upper and lower motor neuron damage that cannot be attributed to other causes.[2] The time to diagnosis is highly variable and depends on the severity of the initial symptoms and how aggressive the patient is in seeking a definitive diagnosis.

Because the onset of ALS may be subtle, it can take up to one year for a patient to see a generalist or primary care physician. Depending on the symptoms, the patient may see other specialists before seeing a neuromuscular specialist or neurologist. The average neurologist may only see one ALS patient per year and may therefore be uncomfortable making the definitive diagnosis, even if he or she suspects ALS. For that reason, patients are often referred to an ALS Center of Excellence (CoE) to see an ALS specialist for diagnosis and subsequent patient management. As the disease progresses, patients who are unable to travel to a CoE may be cared for by a local neurologist who coordinates with an ALS specialist.

PROGRESSION OF ALS

ALS begins in one region of the nervous system and causes the upper and lower motor neurons to die in that area; then the muscles they control become weaker and smaller. The strength of any voluntary muscle group can be affected in ALS, including those muscles that control facial expressions, chewing, swallowing, speaking, breathing, and areas such as the neck, arms, trunk and legs. ALS can start in any muscle group and then move to any other; however, there is no predictable direction of where the weakness may spread next. The only exception is that when one arm or leg is involved first, then the opposite arm or leg is likely to weaken next.[3] Because of difficulty swallowing and chewing, maintaining weight can become a problem. In later stages of the disease, patients generally have difficulty breathing as the muscles of the respiratory system weaken. Patients eventually lose the ability to breathe on their own and must depend on support of a ventilator for survival. Patients also face an increased risk of pneumonia during later stages of ALS.[2]

TREATING ALS

Currently there is no cure for ALS, so effective symptom management and quality of life improvements are two of the primary goals in ALS patient care.[2]

Approximately 50% of patients are treated at a CoE and, in the United States, there are 67 well-established CoEs for ALS care.[1] At these CoEs, patients are seen as often as necessary (typically every 3-6 months) by a multidisciplinary treatment team and have access to a full range of specialists. This team consists of neuromuscular specialists, nurses, physical therapists/orthotists, occupational therapists, speech therapists, nutritionists, pulmonologists, gastroenterologists and psychologists/social workers/psychiatrists.

There are currently two drugs approved by the Food and Drug Administration (FDA) for the treatment of the disease – Rilutek® (riluzole) and Radicava™ (edaravone). Rilutek® is believed to reduce damage to motor neurons by decreasing the release of glutamate. Clinical trials with ALS patients demonstrated that Rilutek® provided an early increase in survival among the patients in whom treatment failed during the study (tracheostomy or death) by 60-90 days. The drug may also extend the time until which a patient needs ventilatory support. Rilutek® does not reverse the damage already evident in motor neurons, and patients taking the drug must be monitored for liver damage and other possible side effects. Radicava™ is an intravenous medication. In clinical trials, Radicava™ was shown to slow decline in the loss of physical function in people with ALS.[5]

RATE OF PROGRESSION	PROPORTION OF PATIENTS	LIFE EXPECTANCY
Rapid	10%	Less than 1 year
Average	80%	3-5 years
Slow	10%	Up to 10+ years

ABOUT *TIRASEMTIV*

Cytokinetics is developing *tirasemtiv,* a fast skeletal muscle troponin activator (FSTA), as a potential treatment for people living with ALS and certain other debilitating diseases and conditions associated with muscle weakness and fatigue or neuromuscular dysfunction. *Tirasemtiv* selectively activates the fast skeletal muscle troponin complex and increases its sensitivity to calcium, resulting in increased skeletal muscle force while delaying the time to muscle fatigue. *Tirasemtiv* has been granted orphan drug designation and fast track status by the U.S. FDA and orphan medicinal product designation by the European Medicines Agency for the potential treatment of ALS.

Tirasemtiv has been studied in clinical trials that have enrolled over 1000 people internationally. In preclinical studies and early clinical trials, *tirasemtiv* demonstrated increases in skeletal muscle force in response to neuronal input and delays in the onset and reductions in the degree of muscle fatigue. In a completed Phase 2b clinical trial, *tirasemtiv* reduced the decline of slow vital capacity (SVC), a key measure of respiratory function in patients with ALS, but the study did not meet its primary endpoint of change in the ALS Functional Rating Scale – Revised (ALSFRS-R) score. The most common adverse events observed during treatment with *tirasemtiv* were dizziness, fatigue, and nausea. It is currently the subject of VITALITY-ALS, a Phase 3 clinical trial designed to assess the effects of *tirasemtiv* versus placebo on SVC and other measures of skeletal muscle strength in patients with ALS. It is also being studied in an open-label extension clinical trial called VIGOR-ALS for patients who have completed their participation in VITALITY-ALS.

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Cytokinetics, Inc.
280 East Grand Avenue
South San Francisco, CA 94080
650 624 3000
cytokinetics.com

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