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 20,000 Americans, with a little over 5,000 new cases diagnosed each year in the U.S.[1,] Men are slightly more likely than women to develop ALS, however, with increasing age, the prevalence becomes more equal between men and women. Most people who develop ALS are between 40-75, but can affect people of any age.[2] 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. When symptoms begin in the arms or legs, it is referred to as "limb onset" ALS. When speech or swallowing problems are noticed first, it's referred to as "bulbar onset" ALS.[2] 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.[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.[3]

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

Radicava® is an intravenous medication. In clinical trials, Radicava® was shown to slow decline in the loss of physical function in people with ALS.[4]

ABOUT *RELDESEMTIV*

In collaboration with Astellas, Cytokinetics is developing *reldesemtiv*, a next-generation fast skeletal muscle troponin activator (FSTA), as a potential treatment for people living with ALS and spinal muscular atrophy (SMA).

Skeletal muscle contractility is driven by the sarcomere, the fundamental unit of skeletal muscle contraction composed of several key proteins. Skeletal muscle myosin is the motor protein that converts chemical energy into mechanical force through its interaction with actin. A set of regulatory proteins, which includes tropomyosin and several types of troponin, make the actin-myosin interaction dependent on changes in intracellular calcium levels.

Reldesemtiv slows the rate of calcium release from the regulatory troponin complex of fast skeletal muscle fibers, which sensitizes the sarcomere to calcium, leading to an increase in skeletal muscle contractility.

Reldesemtiv was the subject of a Phase 2, hypothesis-generating clinical study in SMA which showed increases in the distance patients could walk in six minutes, a validated measure of endurance consistent with the mechanism of action in patients treated with *reldesemtiv*. *Reldesemtiv* was also the subject of FORTITUDE-ALS, a Phase 2 clinical trial in ALS. The trial did not achieve statistical significance for its primary endpoint of change from baseline in slow vital capacity after 12 weeks of dosing, but all patients on all doses of *reldesemtiv* declined less than patients on placebo for SVC and ALSFRS-R with clinically meaningful differences emerging over time.

Cytokinetics

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

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