Cytokinetics

ABOUT

SMA

SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is a genetic neuromuscular disease that affects the part of the nervous system that controls voluntary muscle movement. It is caused by a mutation of the survival motor neuron 1 (SMN1). In a healthy person, this gene produces a protein that is essential to the function of the nerves that control muscles. Without it, those nerve cells cannot function properly and eventually die, leading to debilitating muscle function and often fatal muscle weakness.

There are four primary types of SMA based on age of onset and the manifestation of the disease:[1,2]

- **Type I**, also known as Werdnig-Hoffmann disease, is the most common and most severe form of SMA, and the leading genetic cause of death for infants.
- **Type II** is diagnosed in children between the ages of 6 months and 2 years. The symptoms are less severe than Type I but become more noticeable in older children.
- **Type III**, also known as Kugelberg-Welander disease or juvenile SMA, is the mildest form of childhood SMA and typically does not shorten life expectancy.
- **Type IV** is very rare, usually appearing after age 35 with mild to moderate symptoms.

PREVALENCE OF SMA

SMA affects between 10,000 and 25,000 adults and children in the U.S. and accounts for 1 in 6,000 to 1 in 10,000 live births per year. Around eighty percent of the prevalent population is Type I or Type II. SMA can affect any race or gender.[1,3]

SYMPTOMS AND PROGNOSIS OF SMA

Symptoms and life expectancy vary from mild to severe, depending on the type of SMA. The most severe symptom of SMA is the weakening of the muscles necessary for breathing. In general, patients with SMA experience deterioration in their condition over time, but the prognosis varies depending on the type of SMA and the degree of respiratory impairment.[3]

DIAGNOSING SMA

Children with SMA generally appear normal at birth, but symptoms can develop in the first few months of life. For 95% of SMA Types I, II and III, a diagnosis of SMA can be confirmed by a blood test designed to identify genetic defects in the SMN1 gene.[4] In rare cases, doctors may order a muscle biopsy or tests to measure nerve conduction velocity and electrical activity in muscle.

TREATING SMA

Currently there is one FDA-approved treatment for SMA, Spinraza, an antisense oligonucleotide that targets SMN2, often referred to as the SMA "backup gene," causing it to make more complete SMN protein. In addition, treatment consists of managing symptoms and preventing complications, which may include physical therapy, muscle relaxants, heat application to relieve muscle pain and assistive devices such as supports, braces, orthotics or wheelchairs. Some individuals require additional therapy for speech, chewing and swallowing, and may require a feeding tube or assisted ventilation. Proper nutrition is also essential to maintaining weight and strength.[4]

SMA TYPE	SEVERITY	PERCENT OF PREVALENT POPULATION	AGE OF ONSET	SYMPTOMS	HIGHEST FUNCTION	LIFE EXPECTANCY
Type I (Infantile)	Severe	~10%	0-6 months	Very weak; difficulty breathing, sucking and swallowing	Unable to sit	<2 years
Type II (Intermediate)	Intermediate	~34%	6-18 months	Respiratory complications are common	Sits but unable to stand or walk independently	>2 years
Type III (Juvenile)	Mild	~45%	>18 months	Stands and walks	Can stand and walk, but with mobility issues later in life	Near normal
Type IV (Adult)	Mildest	~11%	Adult onset	Mild motor impairment	Able to walk, with gradual weakness and mobility issues later in life	Normal

ABOUT CK-2127107

In collaboration with Astellas, Cytokinetics is developing CK-2127107, a next-generation fast skeletal muscle troponin activator (FSTA) as a potential treatment for people living with SMA, chronic obstructive pulmonary disease (COPD), amyotrophic lateral sclerosis (ALS) and frailty. CK-2127107 is an investigational drug candidate intended to slow the rate of calcium release from the regulatory troponin complex of fast skeletal muscle fibers, which may improve muscle function and physical performance in people with SMA. It has been granted orphan drug designation by the U.S. Food and Drug Administration (FDA) for the potential treatment of SMA.

CK-2127107 has been the subject of five Phase 1 clinical trials in healthy volunteers, which evaluated safety, tolerability, bioavailability, pharmacokinetics, and pharmacodynamics. It is currently the subject of three ongoing Phase 2 clinical trials, enrolling patients with SMA, COPD, and ALS, and one Phase 1b clinical trial in elderly adults with limited mobility.

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