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Review Article

Unraveling innovative treatments for spinal muscular atrophy: a brief review

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ABSTRACT

In the past few years, there have been amazing breakthroughs in treating spinal muscular atrophy (SMA), which is a big deal considering it's been studied for over a hundred years. Now, there are three approved therapies that all work to increase SMN protein production. They do this by fixing the genetic problem either by replacing the faulty SMN1 gene or by helping the SMN2 gene produce more of the right kind of protein. One way they do this is by using a special virus called adeno- associated viral vectors (AAV9) to deliver the gene therapy because the SMN1 gene is small enough to fit inside. The paper discusses the evolution of SMA treatment, focusing on advancements like gene therapy and new drug treatments. It highlights challenges in interpreting efficacy, especially regarding disease classification. Despite successes, issues like limited trial populations and varying disease stages pose complexities in care. With expanding treatment options, including those in advanced development stages, the landscape of SMA management grows more intricate. However, the importance of timely diagnosis and interdisciplinary clinical management remains crucial, recognizing that despite drug treatments, many patients still face significant disease burdens. This article aims to give a quick rundown of spinal muscular atrophy, starting from when people first noticed the disease up until now, when there are some really cool new treatments that are changing how the disease affects people.

Keywords: Gene therapy**,** Spinal muscular atrophy, SMN1 gene, SMN2 gene, Efficacy, SMN protein

INTRODUCTION

Spinal muscular atrophy is a rare, worsening, genetic disease affecting nerves and muscles. It happens due to missing or faulty parts in a gene called SMN, leading to the loss of a crucial protein. This results in progressive muscle weakness and degeneration due to issues with nerve function.[1,2] When the SMN protein, made by this gene, goes missing, it causes motor neurons to die.[3] The disease happens when there's a complete deletion of the gene on both chromosomes, or when one chromosome has a deletion and the other has a point mutation. This leads to a lack of SMN proteins, resulting in the breakdown of lower motor neurons.[4] SMA is believed to be the leading genetic cause of infant mortality.[6] The main feature of the disease is the breakdown of specific cells in the spinal cord, called anterior horn cells. This causes a gradual weakening of muscles close to the center of the body, leading to different levels of muscle shrinkage. SMA is one of the more common single-gene neurodegenerative diseases, with an estimated occurrence of about 1 in every 6,000 to 10,000 newborns.[5]

About 95% of cases are caused by changes in the SMN1 gene found on chromosome 5q13.[3] The chance of SMA occurring is roughly 1 in every 10,000 to 20,000 births, and the number of people carrying the gene is about 1 in every 40 to 70 individuals in the general population.[6] In humans, there are two types of the SMN gene: telomeric SMN1 and centromeric SMN2. SMN1 makes complete messenger RNA (mRNA) that codes for the fully working

SMN protein. SMN2 is almost the same as SMN1, but a small change means that in 85% of cases, a part of the mRNA called exon 7 gets left out when it's being prepared. This makes the protein useless and it gets broken down quickly. About 15% of SMN2 mRNA still includes exon 7 and can make some working protein. People with SMA don't have any SMN1, so they rely on their SMN2 gene.[3] SMA is split into five types, numbered from 0 to 4, where lower numbers mean the condition is more severe.[6,2]

Type 0

The most serious type starts before birth, and babies have severe breathing problems soon after they are born.

Type I

Werdnig-Hoffmann disease is a severe type that begins before a baby is 6 months old, and they can't sit without help.

Type II

Dubowitz disease is a middle-ground type that starts before a child is 18 months old. They can sit by themselves but can't stand or walk without assistance.

Type III

Kugelberg-Welander disease is a milder type that begins after a child is 18 months old. They can stand and walk without needing help

Type IV

The mildest type starts after a person is 30 years old.[6]

In SMA Type 1, individuals can't sit without assistance and is the main genetic reason babies die in their first months, with a life expectancy of less than 2 years. In SMA Type 1, patients show symptoms before they're six months old, like being floppy and having less movement on their own. They might also breathe in a strange way. SMA Type 2 is less severe, and symptoms start when a child is between 6 and 18 months old. Patients can sit without help but can't walk on their own. They might need breathing support with a machine before they become adults and may have problems with their bones and joints, like a severe curve in the spine (scoliosis) and stiff joints.[4] In SMA type 3, symptoms start either when a person is a baby or during their teenage years. All forms of SMA get worse over time, but how quickly this happens varies. SMA Type 1 usually gets worse quickly, while Type 3 progresses more slowly. The differences in how SMA affects people are mostly because of how many copies of SMN2 they have. SMN2 is a gene similar to SMN1, but it makes a protein missing a part called exon 7 because of how it's put together. However, it still makes some useful SMN proteins, just not as much. About 95% of SMA cases happen because there are missing parts in both copies of the SMN1 gene (survival of motor neuron 1) on chromosome 5. Sometimes, changes in other genes can also cause SMA, but this is less common.[5]

Table 1: Different types of spinal muscular atrophy (SMA) based on age of onset, severity, and motor milestones associated with each type.

SMA	Description	Onset	Motor milestones
Type 0	The most severe form with onset in the prenatal period	Prenatal	Severe respiratory problems after birth
Type 1	Werdnig Hoffmann disease; severe form	Before six months	Inability to sit unsupported
Type 2	Dubowitz disease; intermediate form	Before 18 months	Can sit unaided, but not stand or walk
Type 3	Kugelberg-Welander disease; mild form	After 18 months	Can stand and walk unaided
Type 4	The mildest form	After 30 years	Generally mild symptoms

DISCUSSION

Spinal muscular atrophy (SMA) is a devastating genetic disorder that affects the motor neurons, leading to muscle weakness and atrophy.[9] Until recently, there were limited treatment options available for SMA patients. However, with the advent of gene therapy, the treatment landscape has changed dramatically.

Gene therapy

Onasemnogene abeparvovec (Zolgensma) is a gene therapy that has revolutionized the treatment of SMA. It is the first approved gene therapy for SMA and has shown remarkable efficacy in clinical trials.

Zolgensma works by delivering a functional copy of the SMN1 gene to motor neurons, thereby increasing the production of the survival motor neuron (SMN) protein (8). This leads to improved motor function and survival in SMA patients.

Pharmacological profile

The pharmacological profile of Onasemnogene abeparvovec has been extensively studied. It has been

shown to have a favorable safety profile, with most adverse events being mild and transient. The clinical profile of Zolgensma has also been well-characterized, with significant improvements in motor function and quality of life reported in clinical trials.[11]

Therapeutic bridge

In some cases, Nusinersen may be used as a therapeutic bridge to Onasemnogene abeparvovec in premature neonates with Type 1 SMA. This approach has been shown to be effective in improving motor function and survival in these patients.

The use of Nusinersen as a therapeutic bridge is based on the understanding that premature neonates with Type 1 SMA may not be eligible for Onasemnogene abeparvovec due to their young age or medical instability. In these cases, Nusinersen can provide a temporary solution to improve motor function and survival until the patient is eligible for gene therapy.

Efficacy

Studies have demonstrated that Nusinersen can improve motor function and survival in premature neonates with Type 1 SMA. In one study, patients who received Nusinersen as a therapeutic bridge showed significant improvements in motor function, with some patients achieving milestones such as sitting and standing.

Additionally, Nusinersen has been shown to increase survival rates in these patients, with some studies reporting a significant reduction in mortality.

Mechanism of action

Nusinersen works by modifying the splicing of the SMN2 gene, leading to an increase in the production of the survival motor neuron (SMN) protein. This increase in SMN protein helps to improve motor function and survival in patients with SMA.

Benefits

The use of Nusinersen as a therapeuitic bridge offers several benefits including.

Improved motor function

Neusinersen has been shown to improve motor function in premature neonates with Type 1 SMA, allowing them to achieve milestones such as sitting and standing.

Increased survival

Nusinersen has been shown to increase survival rates in premature neonates with type 1 SMA, reducing the risk of mortality.

Bridge to gene therapy

Nusinersen can provide a temporary solution until the patient is provide a temporary solution until the patient is eligible for gene therapy, such as Onasemnogene abeparvovec.

Limitations were that while Nusinersen has been shown to be effective as a therapeutic bridge, there are some limitations to its use. These include, the effects of Nusinersen may wear off over time, requiring repeated dosing. Nusinersen may not be available in all regions or countries, limiting access to this treatment option.[7]

Table 2: Overview of gene therapy approaches for spinal muscular atrophy: each approach has a different vector, gene, dose, and route of administration, highlighting the various strategies being explored for gene therapy in SMA.

Gene therapy approach	Vector	Gene	Dose	Route of administration
AAV-mediated gene therapy	AAV9	SMN1	2×10^11 vg/kg	Intravenous
Lentiviral vector-mediated gene therapy	Lentiviral vector	SMN1	1×10^10 TU/kg	Intramuscular
mRNA-based gene therapy	mRNA	SMN1	1×10^9 mRNA/kg	Intramuscular

Risdiplam

Risdiplam is taken orally every day and works by modifying splicing with small molecules. It is a liquid medicine taken by mouth that spreads throughout the body. It's a small molecule that adjusts SMN2 pre-messenger RNA (pre-mRNA) splicing.

The FDA has given approval for Risdiplam to treat individuals with spinal muscular atrophy who are at least 2 months old. Research on a similar compound, SMN-C5, in fibroblasts from type 1 spinal muscular atrophy patients suggests that Risdiplam might attach specifically to two spots in SMN2 pre-mRNA: the exonic splicing enhancer 2 in exon 7 and the 5′ splice site in intron 7.

Risdiplam helps include exon 7, boosting the production of complete SMN2 mRNA and functional SMN protein. In studies using mouse models of spinal muscular atrophy, Risdiplam caused a rise in functional SMN protein levels in both the central nervous system and non-neuronal tissues.[13]

CONCLUSION

In our article, we have extensively analyzed, the field of SMA has witnessed significant progress in the past five years, with the introduction of three disease-modifying treatments focusing on SMN2 splicing modulation or gene replacement therapy. These therapies, currently in advanced clinical development stages, offer a broader spectrum of drug treatment options for SMA. Timely diagnosis and treatment initiation are crucial for maximizing treatment effectiveness, with oral risdiplam demonstrating increased expression of functional SMN protein in the blood. Each therapeutic strategy has its own set of strengths and weaknesses, and clinicians must be well-informed to optimize patient care. Ultimately, the choice of SMA treatment depends on factors such as the patient's clinical profile, compliance, and the practicality of drug administration.

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