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Spinal Muscular Atrophy: A Multidisciplinary Approach to Diagnosis, Emerging Therapies Recent and Advance Gene Therapy, and Rehabilitation

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ABSTRACT

Spinal muscular atrophy (SMA) is a serious neuromuscular condition marked by the gradual loss of α-motor neurons, resulting from inadequate production of survival motor neuron (SMN) protein. Progress in molecular genetics has enabled the creation of specialized treatments, revolutionizing SMA treatment and patient outcomes. This review explores the molecular mechanisms underlying SMA, current diagnostic techniques, and recent therapeutic approaches, including disease-modifying gene therapies such as **antisense oligonucleotides (Nusinersen), small molecules (Risdiplam), and AAV9 gene delivery (Onasemnogene abeparvovec).** Additionally, the review discusses the emerging potential of **CRISPR/Cas9-based gene editing** and the role of **comprehensive care strategies**, including rehabilitation and multidisciplinary management, in improving quality of life. A comparative analysis of FDA-approved treatments highlights their clinical efficacy, safety, and long-term implications. Furthermore, the review underscores the importance of combining gene therapies with supportive care techniques to optimize SMA management. As research advances, an integrated approach incorporating novel gene-editing tools and personalized treatment strategies may further enhance therapeutic outcomes, providing hope for a more effective and long-term solution for SMA patients.

Keywords: : *Survival Motor Neuron, Nusinersen, Onasemnogene, Abeparvovec, CRISPR*

1. INTRODUCTION

Spinal muscular atrophy (SMA) is a genetic condition that impacts the nervous system, leading to the progressive degeneration of α-motor neurons in the spinal cord. This leads to reduction in muscular power and symmetrical muscle wasting. The condition is caused by mutations in the survival motor neuron 1 (SMN1) gene, which produces the SMN protein. This protein is essential for various cellular functions, including mRNA splicing, the assembly of ribonucleoproteins, mRNA transport in neurons, and protein production (baranello.et.al 2021)(1,2). Although the SMN2 gene is present in most individuals with SMA, it cannot fully compensate for the loss of SMN1 because about 85% of its transcripts skip exon 7 due to a splice site mutation, resulting in a non-functional version of the SMN protein..(3,4) A significant phenotypic moderator of illness severity, SMN2 gene copies vary throughout the population, with higher copies being linked to less severe symptoms, despite the fact that SMN2 only expresses a tiny amount of functional SMN protein (~15%). SMA is still the most common hereditary cause of infant mortality, affecting about 1 in 11,000 babies (5,6,7) Based on clinical severity and age of onset, SMA is divided into various categories, which also affect epidemiology. SMA type IV, which has milder symptoms and an adult start, is less prevalent than SMA type I, which frequently has an early outbreak and a severe phenotype (8,9). The frequency and prevalence of SMA may differ among nations and geographical areas.

Type 0 SMA

with beginning during pregnancy or the first few days of infancy, this is the most severe and uncommon type of SMA. A newborn with SMA type 0 may not live for more than a few months and frequently shows signs of significant muscle weakness (10). **Werdnig-Hoffmann illness), or SMA type I** The most prevalent kind of spinal muscular atropy, with symptoms usually emerging half a year prior of age. Infants with this condition may never develop the capacity to stand and sit on their own.

Breathing problems, extreme reduction in muscular power, and a reduced duration of life without treatment are key characteristics of SMA type I. (11).

Type II SMA

This kind of SMA typically appears between 6 months and 18 months of age. While affected individuals can usually sit, they may face difficulties either while remaining upright or when moving by foot .The medical condition progresses at varying rates for each person(12). **(Kugelberg–Welander disease)**

SMA type III

This type of condition typically appears after the age of 18 months. Although individuals displaying this particular form may eventually gain the the proficiency in independent walking, reduction in muscular power and progression of atrophy over time. Individuals those who have affected may have a relatively normal duration of life. (13).

Type IV SMA

With symptoms that start in adulthood, this is the mildest type of SMA. Exercise intolerance, twitching, and muscle weakness are possible symptoms for those who are affected. Life aging is normal, and the condition progresses slowly (14). A cohort of 227 patients with spinal muscular atrophy from Brazil included 20 incidences of SMA type 4. The largest cohort of spinal muscular atrophy type 4 patients is included in this study, which also offers neurophysiological, genetic, radiological, and practical features that could be used as biological markers for upcoming SMA-specific genetic treatments. (15)

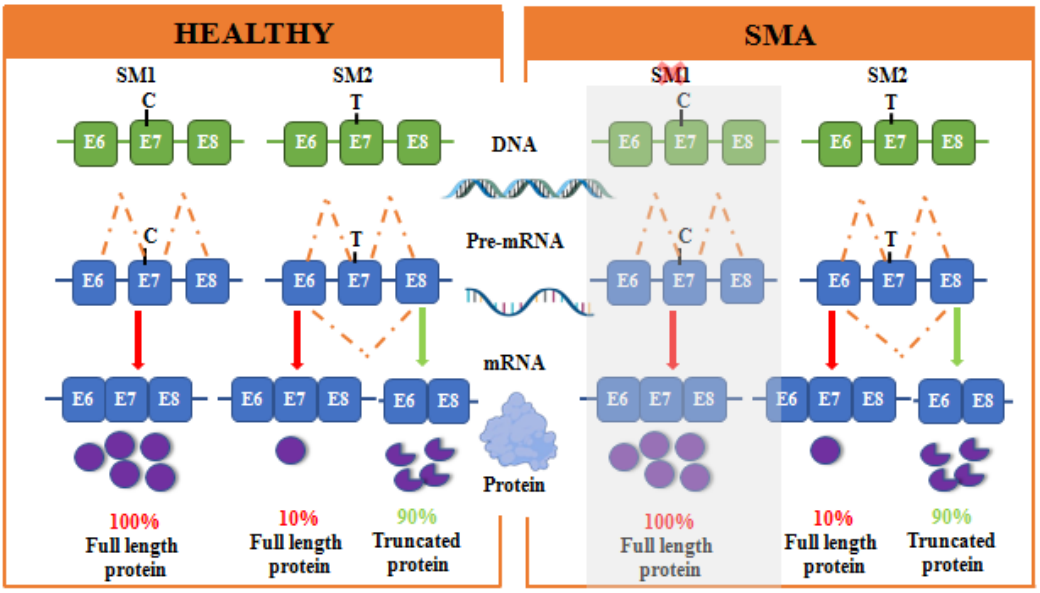

Figure 1. Genetic Mechanism and Molecular Basis of Spinal Muscular Atrophy

Spinal muscular atropy molecular mechanisms

The fundamental molecular processes associated with spinal muscular atrophy (SMA) are centered on the deficiency of functional SMN protein and its detrimental effects on motor muscle cells and neurons. Degeneration occurs when motor neurons' levels of functional SMN protein decline.(16) These neurons are crucial for conveying signals from the spinal cord to the muscles, and the absence of adequately functioning SMN protein renders them susceptible leading to harm and ultimately cell demise. This degeneration manifests as reduction in muscular power and atrophy.(17) The SMN protein is vital for the assembly of small nuclear ribo nucleoproteins (snRNPs), which are necessary for mRNA splicing.(18) A deficiency in SMN disrupts snRNP assembly, resulting in widespread splicing abnormalities across various genes, which further aggravates the dysfunction of motor neurons.(19) Although SMA primarily affects motor neurons, the consequent reduction in muscular power and atrophy are significant clinical manifestations. The absence of neural signals from the compromised motor neurons leads to muscle disuse, which contributes to muscle wasting.(20)Additionally, the (NMJ) neuromuscular junction, the site of communication between motor neurons and muscle cells, is also impaired in SMA.(21) Muscle weakness and contractures are caused by the disruption of this vital communication channel results the loss of functioning motor neurons. (22)

Techniques utilized for diagnosis of SMA.

Spinal Muscular Atrophy manifests through a range of clinical characteristics, which can vary from profound, early-occurring

types to more moderate, delayed-onset variants. The primary clinical symptoms encompass reduction in muscular power, hypotonia , and atrophy. Additionally, individuals with SMA may experience challenges in respiration, scoliosis and joint contractures.(23) Early identification of these clinical indicators is crucial, as prompt intervention can greatly influence the prognosis and enhance the quality of life for those affected.

Genetic test

Genetic testing is considered the benchmark of excellence for identifying spinal muscular atrophy (SMA). This approach helps determine the precise genetic mutation, offers a definitive diagnosis, and aids in assessing the condition's severity paraphare. Typically, genetic testing encompasses the following techniques) The SMN1 gene analysis is the main genetic evaluation for SMA. The majority of SMA instances result from mutations or deletions in this gene, which lower the levels of the SMN protein. This test is characterized by its high specificity and sensitivity, enabling a precise diagnosis of SMA.(24) (b) Additionally, assessing the number of SMN2 gene copies can offer valuable information regarding the seriousness of the disease. Patients with a greater number of survival motor neuron 2 copies generally exhibit moderate forms of SMA, while those with fewer copies tend to experience more severe manifestations.(25)

Clinical evaluation

To diagnose SMA, a comprehensive clinical evaluation is the first step. The medical professional does a physical examination, gathers a thorough medical history, and evaluates motor function (26). A review of family history is another component of the clinical evaluation to identify any established cases of SMA or similar neuromuscular diseases. It is crucial to keep in mind that in cases with moderate or unusual symptoms, SMA could not be the initial suspect (27).

Next-generation sequencing

One effective method for locating common or uncommon mutations in the SMN1 gene is next-generation sequencing (NGS). In situations where a diagnosis cannot be made using conventional genetic testing, it can be extremely helpful. Other uncommon genetic disorders that could resemble SMA can also be found with NGS (28).

Electromyography

Assessment of the electrical activity of muscles and nerves is done by the diagnostic procedure known as electromyography (EMG) (29). EMG has the potential to. show neurogenic alterations in SMA, indicating malfunctioning of the motor neurons. EMG can reveal the degree of motor neuron involvement and assist in differentiating SMA from other neuromuscular illnesses.(30)

Newborn screening

Early recognition and prompt management of spinal muscular atrophy (SMA), a debilitating genetic condition, are the goals of newborn screening, a vital and quickly developing area of pediatric healthcare. Finding afflicted infants early on is one of the main advantages of neonatal screening for spinal muscular atrophy. In contrast to earlier times when diagnosis frequently happened after symptoms appeared, newborn screening enables early intervention and therapy.(31)

Prenatal testing

To detect SMA in the fetus, genetic testing can be done during pregnancy. Amniocentesis or chorionic villus sampling are two methods for doing this. If the fetus is impacted, early diagnosis enables informed reproductive choices and prompt intervention (32). Ethical concerns surrounding test for spinal muscular atrophy during pregnancy (SMA) include matters of informed consent, individual autonomy, disability rights, and the risk of bias. Expectant parents should be well-informed about the objectives, benefits, limitations, and potential results of prenatal testing for SMA. They should also have access to detailed information about the condition, including its prognosis, available treatments, and the emotional impact of a positive diagnosis.(33)

Muscle biopsy

Muscle biopsies can be performed to rule out diseases like muscular dystrophy and confirm the absence of muscle pathology, although they are not the main diagnostic method for SMA. The diagnosis of SMA is supported by muscle biopsies, which usually reveal atrophy and denervation (34).

Serum creatine kinase levels

Serum creatine kinase (CK) levels serve as a useful marker in differentiating SMA from muscular dystrophies. In individuals with SMA, CK levels typically remain within the normal range or show only a slight increase. In contrast, muscular dystrophies are characterized by significantly elevated CK levels(35).

Recent Approaches of Spinal Muscular Atropy

Antisense Oligonucleotide (ASO:Nusinersen) (Spinraza®)

The US FDA approved Nusinersen as the first SMA drug in December 2016, and the European Medicines Agency did the

same in May 2017. The synthesis of SMN protein from SMN2 messenger RNA is enhanced by the antisense oligonucleotide nusinersen. It attaches itself to the SMN2 pre-mRNA's intron 7's restrictive splicing sequence, resulting in the incorporation of exon 7 into the mature mRNA enables the production of full-length SMN protein. (36). Because of its enormous size and low (BBB) permeability, nusinersen is delivered through several intrathecal injections. This restricts its use beyond the intravascular space. Nusinersen levels in the CSF attain a steady therapeutic state about 28-64 days of the first dose [37-38]. Patients are treated every four months for the rest of their lives and get four loading doses (days 0, 14, 28, and 63).

The most common side effects of LP-related are vomiting, headache, and back discomfort [39].

Small Molecule (Risdiplam)

Risdiplam is a small molecule that alters the splicing of SMN2 pre-mRNA, encouraging the inclusion of exon 7 in the final mRNA and facilitating the production of full-length SMN protein.The FDA approved the drug in August 2020, followed by EMA approval in March 2021. It is taken orally once daily and spreads throughout the body, including the central nervous system, and achieves a plasma steady state within 7 to 14 days after the first dose. [41, 42]. The dose varies based on age and weight: 0.15 mg/kg once a day for infants under 2 months, 0.2 mg/kg once a day for those between 2 months and 2 years, and 0.25 mg/kg for those over 2 years and up to 19 kg. For individuals over 2 years old and weighing more than 20 kg, recommended dose is 5 mg once day.

Common side effects consist of skin rash, loose stools, mouth ulcers, and feelings of nausea. [43]

AAV9 gene delivery approach (Onasemnogene abeparvovec)

The US FDA authorized Onasemnogene abeparvovec, a recombinant AAV9-based gene therapy that is self-complementary and non-replicating. May 2019, followed by the European Medicines Agency in May 2020" A CMV enhancer and a chicken-β-actin hybrid promoter govern the vector's fully functional copy of the survival motor neuron gene [44]. It is given as a systemic, one-time IV infusion. Each kilogram has 1.1 × 1014 vector genomes. AAV9 viral titers of less than 1:50 are required for patients to be eligible for the injection.

Common side effects include nausea, vomiting ,pyrexia, and liver damage (45-47).

Table1 Comparison of FDA-Approved Treatments for Spinal Muscular Atrophy (SMA)(48)(49)

S.No	**ttribute**	**Nusinersen (Spinraza)**	**Risdiplam (Evrysdi)**	**Onasemnogen abeparvovec (Zolgensma)**	**CRISPR/Cas9**
1	**Class**	ASO	Small molecule	AAV-based gene therapy	CRISPR/Cas9 Gene Editing Splicing Regulatory Elements (SREs) Disruption
2	**Mechanism**	Improves SMN2 splicing to produce full-length survival motor neuron protein	Improves SMN2 splicing to produce a full-length survival motor neuron protein	Provides a functioning survival motor neuron trans gene	Direct **gene repair** of **SMN1** via Homology-Directed Repair (HDR) Cas9-mediated **disruption of ISS-N1 & ISS+100** to enhance **SMN2 exon 7 inclusion** → Increased **full-length** survival motor neuron **expression**

3.	**Route of Administration**	Intrathecal injection	Oral	Intravenous injection	Under Research (AAV, LNP, Exosomes)
4	**FDA-Approved Age**	All ages	More than two months	Greater than 2 years	Not approved
5	**Dosing Frequency**	4 loading doses in the first 2 months, then every 4 months	Daily	Single-dose treatment	Single-dose (Potential)
6	**Potential Challenges**	Lumbar puncture difficulties	Drug interactions	Presence of adeno-associated virus 9 antibodies at baseline	**Off-target effects,** immune response, ethical concerns **Long-term safety**, variable efficacy, delivery challenges
7	**FDA Approval Date**	December 2016	August 2020	May 2019	Not Approved
8	**Cost Estimate**	~$125,000 per dose	~$100,000–$340,000 per year	~$2.125 million (one-time treatment)	Not Determined
9	**Adverse Effects**	Lumbar puncture issues, proteinuria, thrombocytopenia	Diarrhea, rash, fever	Transaminitis, thrombocytopenia, troponemia, acute liver damage	Potential **genotoxicity,** immune response, neuronal toxicity

CRISPR/Cas9-Based Gene Editing

Genome-editing techniques offer a potential approach to correcting the SMA phenotype. One such method, ISS-N1, utilizes the CRISPR/Cas9 system to target and eliminate splicing regulatory elements (SREs) within intron 7 of SMN2. Similarly, ISS+100 functions in the same manner. Research has shown that disrupting these two SREs—ISS-N1 and ISS+100—through CRISPR/Cas9 significantly promotes exon 7 inclusion in SMN2, increases full-length survival motor neuron protein production in spinal muscular atropy patient-derived iPSCs and motor neurons, and extends the lifespan of germ line-corrected SMA mice to over 400 days. Although challenges remain in relation to the viability of applying this method in human beings, CRISPR/Cas9-mediated SRE disruption presents a promising avenue for the development of more effective SMA treatments.

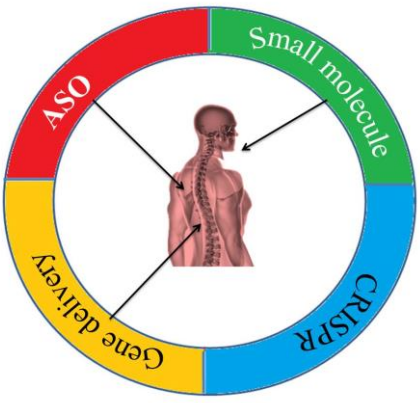

Figure 2. Gene therapies in SMA

Comprehensive Care and Rehabilitation Strategies for SMA

The multidisciplinary strategy that is frequently used in SMA management, which focuses on treating the disease's symptoms and consequences in addition to disease-modifying therapies. Supportive care techniques include the following and are intended to help people with SMA live better lives.

Table2 Multidisciplinary strategy, SMA management, Disease-modifying therapies and Supportive care techniques

S.No	Category	Approaches
1.	Physical Therapy	Exercises to maintain muscle strength and flexibility, prevent contractures, improve mobility
2.	Respiratory Care	Non-invasive ventilation (BiPAP, CPAP), suction devices, cough assist machines, tracheostomy if necessary
3.	Nutritional Support	High-calorie diet, swallowing assessments, feeding tubes (NG tube, G-tube) for severe cases
4.	Orthopedic Management	Bracing for scoliosis, spinal fusion surgery, orthopedic devices for posture support
5.	Speech & Swallow Therapy	Helps with swallowing difficulties and communication in severe cases
6.	Assistive Devices	Wheelchairs, standing frames, walkers, communication aids
7.	Medications & Treatments	Disease-modifying therapies (Nusinersen, Zolgensma, Risdiplam), symptom management drugs
8.	Psychosocial Support	Counseling, mental health support, family education, social integration programs
9	Ergotherapy	The goal is to support individuals with SMA in carrying out everyday duties and preserving their independence. Ergotherapists assist patients in developing their self-care abilities using a range of approaches and strategies,move more effectively and adjust to the modifications brought about by SMA.

Figure3.Multidisciplinary strategy, SMA management, Disease-modifying therapies and Supportive care techniques

Approaches to Combined Gene Therapy

Combining Zolgensma and Spinraza is one example of a comprehensive gene therapy approach for SMA that shows promise for increasing therapeutic efficacy and long-term results. Zolgensma can boost the total amount of SMN protein action in motor neurons and deliver the SMN1 gene instantly. By stimulating the SMN2 gene, spinraza can thus improve the

distribution of SMN proteins across cells and increase their production. Potential advantages of the combination strategy could include increased treatment efficacy, motor neuron coverage, and therapy duration. Patients with SMA may benefit from better improvements enhances neuronal survival and motor function, and an enhanced quality of life as a result.(51)

2. CONCLUSION

The landscape of spinal muscular atrophy (SMA) treatment has transformed significantly with the advent of gene-based disease-modifying therapies. **Nusinersen, Risdiplam, and Onasemnogene abeparvovec** have demonstrated substantial efficacy in improving motor function and prolonging survival, particularly when administered early. The comparative analysis of these FDA-approved therapies highlights their distinct mechanisms of action, administration methods, and therapeutic outcomes. Additionally, the emerging potential of **CRISPR/Cas9-based gene editing** offers a promising avenue for permanent genetic correction, though challenges such as safety, efficiency, and ethical considerations remain.

Beyond pharmacological interventions, **comprehensive care and rehabilitation strategies** play a crucial role in SMA management. A **multidisciplinary approach**, incorporating **physical therapy, respiratory support, and nutritional interventions**, is essential for optimizing patient outcomes. The integration of **supportive care techniques** with disease-modifying therapies ensures a holistic treatment approach, enhancing mobility, function, and the daily life and well-being of individuals living with spinal muscular atropy.

Looking ahead, **combining gene therapies with supportive care and novel genetic editing techniques** may lead to more effective, personalized treatment strategies. Continued research and clinical advancements will be instrumental in refining these therapies, ultimately working toward a potential cure for SMA. As new technologies emerge, an **interdisciplinary, patient-centered approach** will be key to addressing the complexities of SMA and improving long-term prognoses

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