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THERAPEUTIC ADVANCES IN SPINAL MUSCULAR ATROPHY: A REVIEW OF DISEASE-MODIFYING AND GENE REPLACEMENT THERAPIES

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ABSTRACT

Spinal muscular atrophy (SMA) is a genetic disorder affecting the neuromuscular system, characterized by significant morbidity and mortality due to muscle weakness. The condition arises from the homozygous disruption of the survival motor neuron 1 (SMN1) gene, which results from homozygous mutation, conversion, or deletion. This disruption leads to insufficient production of the survival motor neuron (SMN) protein, essential for the maintenance and functioning of motor neurons. SMA's clinical features are categorized into four main phenotypes, determined by the age at which symptoms begin and the highest level of motor function achieved, though the disease's severity can vary widely. Although there is currently no cure for SMA, understanding its molecular genetics has facilitated the development of pre-clinical models and novel innovative treatment approaches. Patients often face progressive muscle weakness, respiratory issues, feeding challenges, and a diminished quality of life.

The number of Survival Motor Neuron 2 (SMN2) gene copies is an important disease modifier that influences clinical severity. Recent advances, including nusinersen, risdiplam, and onasemnogene abeparvovec, have significantly improved survival and motor outcomes. This review summarizes current disease-modifying therapies, emerging therapeutic strategies, and future directions in the management of spinal muscular atrophy. Although important challenges remain, early diagnosis and timely access to these therapies have transformed the outlook for patients with SMA.

KEYWORDS: Spinal muscular atrophy; Survival motor neuron protein; SMN1; SMN2; Nusinersen; Risdiplam; Onasemnogene abeparvovec; Gene therapy.

INTRODUCTION

Spinal muscular atrophy (SMA) is a severe neuromuscular disease characterized by degeneration of alpha motor neurons in the spinal cord, resulting in progressive proximal muscle weakness and paralysis.[1] It is brought on by homozygous disruption of the survival motor neuron 1 (SMN1) gene through mutation, conversion, or deletion. This results in inadequate synthesis of the survival motor neuron (SMN) protein, which is necessary for the upkeep and operation of motor neurons. Reduced SMN expression causes severe muscle weakness, loss of α-motor neurons, and frequently early death. [2] It is one of the most common genetic causes of infant mortality and affects individuals across a broad spectrum of disease severity.

Based on the age of onset and maximum motor function attained, the clinical characteristics of SMA can be divided into four primary phenotypes, although the severity of the condition varies greatly [3]. Although there is no known cure for SMA, knowledge of its molecular genetics has led to the creation of pre-clinical models and a variety of possible treatment strategies. [4] Since these therapeutic approaches have recently entered early phase clinical trials, there is a lot of excitement in the SMA field.

SMA is thought to affect 1 in 6,000 to 1 in 10,000 live births worldwide, with regional and population-specific variations. For impacted families and healthcare systems, this range poses a substantial burden. Based on clinical severity and age of onset, SMA is divided into various categories, which have implications for epidemiology. SMA type IV, which has milder symptoms and an adult onset, is less common than SMA type I, which has a severe phenotype and an early outbreak. The incidence and prevalence of SMA may differ between nations and geographical areas. [5]

Patients commonly experience progressive muscle weakness, respiratory complications, feeding difficulties, and reduced quality of life. The number of copies of the Survival Motor Neuron 2 (SMN2) gene acts as an important disease modifier and influences clinical severity.

The understanding of SMA pathogenesis has been greatly enhanced by recent developments in molecular genetics, leading to the creation of targeted treatments that alter the course of the illness. With the advent of disease-modifying medications like risdiplam, nusinersen, and gene replacement therapy, the therapeutic landscape has changed and affected people's survival and functional outcomes have improved. Opportunities for prompt intervention have

been further improved by early diagnosis made possible by genetic testing and newborn screening programs.

In addition to highlighting recent developments and potential future directions in SMA research and management, this review attempts to give a thorough overview of the epidemiology, genetic basis, pathophysiology, clinical manifestations, diagnostic techniques, and current therapeutic approaches for spinal muscular atrophy.

Epidemiology:

SMA has a carrier frequency of one in 40 to 67 persons and an incidence of one in 11,000 live births which make SMA one of the most common autosomal recessive diseases and the leading cause of morbidity and mortality in children below five years [9]. Epidemiologically, however, numerous research show that SMA III is less common than other forms SMA, although the epidemiologic burden may vary across subtypes. According to Griffiths et al [10], SMA types I, II, and III accounted for 60%, 27% and 12% of all SMA patients respectively.

A recent estimate indicates that the incidence rates of SMA types I, II, and III are around 5.5, 1.9, and 1.7 per 100,000, respectively [11]. SMA arises from the absence of exon 7 in the SMN protein

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A recent estimate indicates that the incidence rates of SMA types I, II, and III are around 5.5, 1.9, and 1.7 per 100,000, respectively [11]. SMA arises from the absence of exon 7 in the SMN protein amounts of functional SMN proteins; the key contributors to the clinical heterogeneity in SMA are changes in the copy numbers of the SMN2 paralogous gene. Clinical traits and the amount of SMN2 copies are inversely correlated [12].

Moreover, the SMA severity is related to the time of disease onset during life, approximately 60% of people with SMA experience severe symptoms and pass away in their early years

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Epidemiology and Disease Burden

With a carrier frequency of one in 40 to 67 individuals and an incidence of one in 11,000 live births, SMA is one of the most prevalent autosomal recessive diseases and the primary cause of morbidity and mortality in children under five. Although the epidemiologic burden may differ among subtypes, multiple studies indicate that SMA III is less prevalent than other forms of SMA. According to a recent estimate, the incidence rates of SMA types I, II, and III are approximately 5.5, 1.9, and 1.7 per 100,000, respectively. There is an inverse relationship between clinical characteristics and the quantity of SMN2 copies. Additionally, the severity of SMA is correlated with when the disease first manifests in life; roughly 60% of SMA patients have severe Advances in genetic testing and the recent introduction of newborn screening programs have enhanced early diagnosis and enabled prompt therapeutic intervention. Disparities in healthcare access, treatment affordability, and awareness still present serious obstacles despite these advancements, especially in low- and middle-income nations. As a result, SMA continues to be a significant public health issue, highlighting the need for more research, better screening techniques, and fair access to new treatments. [6]

Molecular Genetics

SMA's severity was a mystery until the genetic etiology was identified: how could a single gene deficiency cause such a broad range of clinical severity? The Melki laboratory's 1995

finding that a homozygous deletion in the SMN1 gene on chromosome 5q13 causes 95% of instances of SMA, regardless of type, marked the beginning of the answer to this puzzle. Each allele of the SMN gene in humans has a centromeric form (SMN2) and a telomeric form (SMN1). The SMN protein is encoded by full-length mRNA transcripts produced by the transcription of the SMN1 gene. Except for a C to T alteration in an exonic splicing enhancer that causes exon 7 to be excluded during transcription, the SMN2 gene is identical to the SMN1 gene. The resulting shortened protein is quickly broken down and is not functional. Crucially, only a small portion of the total mRNA transcripts (~10–15%) resulting from the SMN2 gene do retain exon 7, which encodes the normal SMN protein, since exon 7 has not been completely excluded from SMN2 mRNAs.

Due to the lack of a functional SMN1 gene, all SMA patients rely on their ineffective SMN2 gene to create the SMN protein required for survival. Therefore, SMA is brought on by an SMN protein shortage that causes selective motor neuron degeneration for unclear reasons. The variation in SMN2 gene copy number observed in SMA patients answered the severity conundrum. A favourable connection between SMN2 copy quantity and milder phenotype was verified by many subsequent genotype/phenotype investigations. SMN2 copy number is undoubtedly not the sole phenotypic variable, even if it is currently recognized as the main factor influencing the severity of SMA.[17]

Three adult patients with mild 3b phenotypes and only two copies of SMN2 were reported by Prior and colleagues. This seemingly contradictory finding was explained by the fact that these patients had a c.859G>C exon 7 mutation, which produced an exon splice enhancing element that increased the production of full-length SMN protein and produced a milder phenotype. As knowledge of SMA molecular biology continues to grow, new genetic modifiers are likely to be discovered. Therefore, SMN2 copy number alone is insufficient to accurately predict disease severity or phenotype. These findings are valuable for genetic counselling and support the future inclusion of SMA in newborn screening programs. As a result, it is not always possible to infer the SMA phenotype from the SMN2 copy number determination alone, which is important to know when providing genetic counselling to patient families. The SMA gene test might eventually be added to newborn screening panels due to the availability of genetic testing that has been clinically validated.

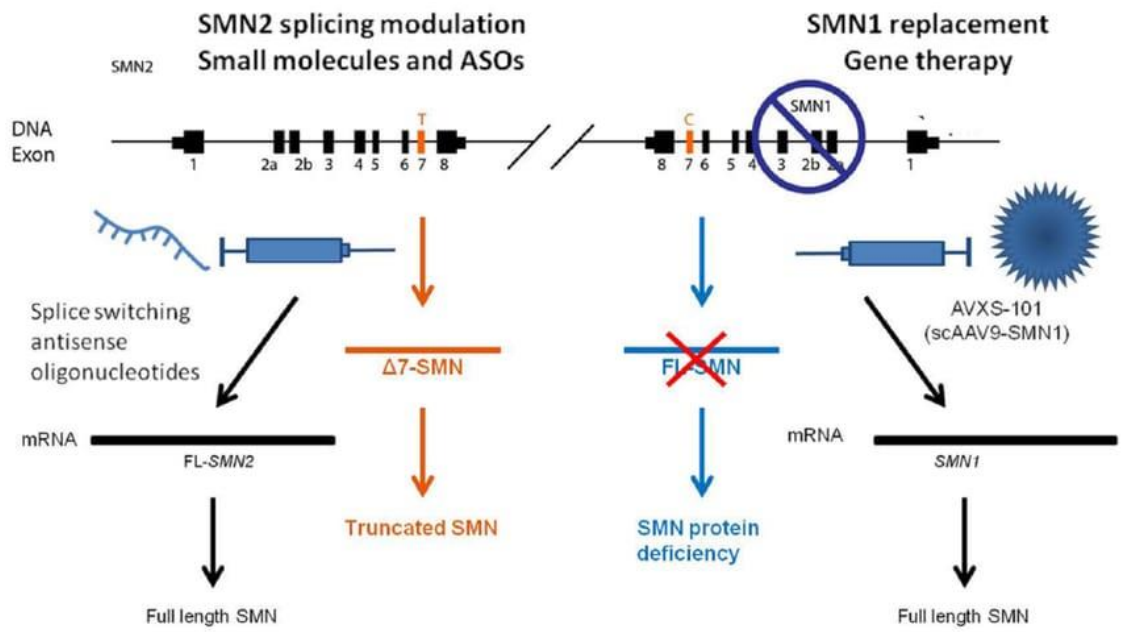

Figure 1. Molecular genetic basis of SMA and therapeutic approaches targeting SMN protein restoration through SMN2 splicing modulation and SMN1 gene replacement therapy. Adapted from [23]

MOLECULAR PATHOLOGY

While a thorough examination of the pathophysiology of SMA is outside the purview of this paper, certain remarks are necessary. SMN is present in the cytoplasm and nucleus, where it is a component of the SMN complex, a multi-protein complex that is crucial for pre-mRNA splicing and spliceosomal small nuclear ribonuclear protein (snRNP) formation [31]. The cells of SMA mice exhibit abnormal snRNP biogenesis. The axons of motor neurons have also been shown to contain the SMN protein. These findings have raised an important question: does the SMN protein have a distinct role in motor neurons, even if it affects RNA processing processes in all cells? One economical explanation might be that motor neuron growth, survival, or both are negatively impacted by the downstream effects of aberrant RNA processing brought on by inadequate SMN expression. In this way, a worldwide change in splicing, for instance, may have a distinct impact on the transcriptome of motor neurons due to the transcriptome's uniqueness. Research on the important function or functions of the SMN protein in SMA is ongoing and has the potential to further our knowledge of fundamental motor neuron biology, which may be pertinent to other illnesses affecting the lower motor neuron.[18]

Classification of SMA

About 50% of people with SMA are diagnosed with type 1 (Werdnig-Hoffmann disease), which is the most severe and prevalent kind. Infants with SMA type I typically do not live past the first two years of life if no intervention is given, exhibit clinical symptoms before the age of six months, and never learn to sit unassisted. These individuals frequently have no head control, symmetrical flaccid paralysis, and severe hypotonia. Antigravity limb motions are seldom seen, and spontaneous motility is usually low. The most severe variants, known as SMN 0, appear with significant weakness and joint contractures at birth and indicate prenatal start of the illness due to diminished intrauterine movements.[14]

Based on the severity of clinical signs, at least three clinical subgroups can be identified within SMA type I: a) extreme weakness from birth, unable to control one's head; b) weakness that develops after the newborn period, usually within two months; head control is never attained c) weakness that develops after the newborn period yet head control is attained. With assistance, some of these kids might be able to sit. Clinically, every kid with SMA type I have a mix of extreme hypotonia and weakness with facial muscle sparing, which is always accompanied by a normal breathing pattern. Lower limbs are often weaker than upper limbs, and the weakness is typically symmetrical and more proximal than distal. There are either no deep tendon responses or very few.[15]

Paradoxical breathing is caused by a weaker intercostal muscle and a sparing diaphragm. Bulbar motor neuron involvement frequently results in tongue fasciculation, poor sucking and swallowing, and progressively worsening swallowing and feeding difficulties. One significant contributor to morbidity and death is aspiration pneumonia. Over the past few years, there has been growing evidence that some individuals with severe SMA type I (typically carrying one copy of SMN2) may have heart defects primarily atrial and ventricular septal defects, as well as potential autonomic system involvement that could cause arrhythmia and sudden death.[16]

SMA type II typically presents between 7 and 18 months of age. Patients are able to sit without assistance, and some are able to stand, but they are unable to walk on their own. Fine tremors of the upper extremities are frequent, and deep tendon reflexes are absent. The more severe type II individuals may develop joint contractures and kyphoscoliosis in their early years of life. While weakening of the masticatory muscles more frequently affects the ability to chew, impaired swallowing is rare. There is a range of severity, from comparatively stronger children with significantly stronger trunk, limb, and respiratory muscles to weak

youngsters who can only sit unassisted and are more susceptible to respiratory symptoms and early scoliosis. Respiratory failure that necessitates mechanical ventilation can occur in patients at the weak end of the spectrum [16].

Patients with SMA type III (Kugelberg-Welander disease) exhibit a wide range of clinical characteristics. They usually achieve independent walking and all of the main motor milestones. However, they experience proximal muscle weakness in infancy. While some people may continue to walk and lead fulfilling adult lives with mild muscle impairment, others may require wheelchair assistance as children. Scoliosis and other mobility-related conditions such obesity and osteoporosis are common in patients who lose their ability to walk [16–18]. Two subgroups of severity regarding the likelihood of being able to walk by the age of ten and the greater likelihood of losing walking by the age of forty have been proposed based on natural history data on 329 SMA type III patients.

This classification now includes SMA type IV, which describes people with moderate course and adult onset (> 18 years). Patients without respiratory or dietary issues who are able to walk as adults are included in this category. Patient selection for clinical trials is really independent of the historical categorization and is mostly influenced by the features of the intervention and the choice of outcomes because all SMA types are part of a single spectrum and share the same etiology.

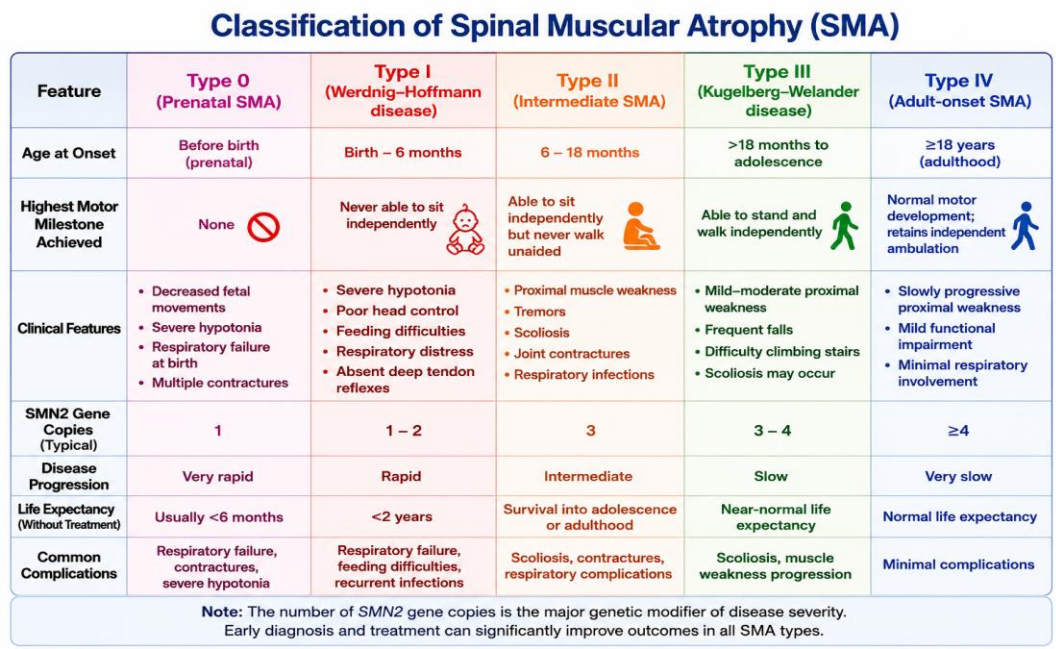

Figure 2. Classification of spinal muscular atrophy (SMA) based on age of onset, motor milestones, clinical features, SMN2 copy number, disease progression, life expectancy, and common complications.

Clinical features

Muscle atrophy and weakness are the main clinical manifestations of SMA. As in NP7, weakness is typically symmetrical, with proximal muscles being more affected than distal groups (see "Patterns of Weakness, Classification of Motor Neuron Disease & Clinical Diagnosis of Sporadic ALS" in this issue). The seminal pathology known as anterior horn cell degeneration, as well as the relevant clinical features of symmetrical, proximal predominant extremity weakness that also affects axial, intercostal, and bulbar musculature, have been identified and emphasized in reports over the past 125 years that describe the clinical manifestations and wide range of clinical severity [7]. In 1991, the Muscular Dystrophy Association (MDA)-sponsored International Consortium on Spinal Muscular Atrophy formalized the various phenotypes that had been described into a classification system. Based on the age of onset and the highest level of motor function (e.g., sitting or standing), this classification identified three SMA types. Later changes included a type 0 for patients with prenatal onset and death within weeks, a type 4 for adult-onset cases, and a division of the type 3 category based on age of onset [8]. This system is still applicable in the genetic era and offers helpful clinical and prognostic data, despite the fact that there are variations in severity even within a single type and that up to 25% of patients are difficult to accurately classify.

Diagnostic approaches of spinal muscular atrophy

Clinical manifestations of SMA vary, from severe early-onset variants to milder adult-onset ones. Atrophy, hypotonia, and muscular weakness are the main clinical signs. SMA patients may also have scoliosis, musculoskeletal contractures, and breathing issues; therefore, it is recommended to recognize these clinical signs early, as timely intervention can significantly impact the prognosis and quality of life for affected individuals.

1.Clinical evaluation

The first step in diagnosing SMA is a comprehensive clinical evaluation. The medical professional does a physical examination, gathers a thorough medical history, and evaluates motor function. To find any known cases of SMA or associated neuromuscular disorders, the clinical evaluation includes a study of family history. It is crucial to keep in mind that in cases with mild or unusual symptoms, SMA could not be the initial suspect.[9]

2.Electromyography

Electromyography (EMG) serves as a diagnostic method to evaluate the electrical activity within muscles and nerves. In the context of SMA, EMG might indicate neurogenic

alterations, suggesting motor neuron issues. This technique aids in differentiating SMA from other neuromuscular conditions and offers insights into the degree of motor neuron involvement[5].

3. Nerve conduction studies

Nerve conduction studies (NCS) assess the functionality of peripheral nerves. In cases of SMA, NCS results can either be normal or exhibit slight irregularities. These assessments assist in excluding other neurological disorders and provide further evidence to support an SMA diagnosis [10].

4.Muscle biopsy

Although muscle biopsy is not the primary diagnostic approach for SMA, it can confirm the absence of muscle pathology, thereby excluding conditions such as muscular dystrophy. Typically, muscle biopsies in SMA reveal atrophy and denervation, reinforcing the diagnosis [11].

5. Serum creatine kinase levels

Evaluating serum creatine kinase (CK) levels can be beneficial in distinguishing SMA from muscular dystrophies. As in SMA, CK levels seem to be normal to mildly elevated or within range, whereas in muscular dystrophies, CK levels are elevated significantly [5]

6. Newborn screening

A crucial and quickly developing component of pediatric healthcare is newborn screening for spinal muscular atrophy (SMA), which aims to identify and treat this debilitating genetic condition early. Early detection of infants with SMA is one of the main advantages of newborn screening. Newborn screening enables early intervention and therapy, in contrast to the past when diagnosis frequently happened after symptoms appeared [5].

7.Genetic testing

Genetic testing is considered the most reliable method for diagnosing SMA, offering a conclusive diagnosis by pinpointing the exact genetic mutation and assessing the condition's severity. The typical procedures for genetic testing include: (a) The main genetic test for SMA focuses on examining the SMN1 gene. The majority of SMA cases are due to deletions or mutations in this gene, which result in decreased levels of SMN protein. This test is both highly specific and sensitive, allowing for a very accurate diagnosis of SMA [12]. (b) Besides analyzing SMN1, determining the number of SMN2 gene copies can provide insights into the severity of the disease. Patients with more SMN2 copies seem to have milder forms of disease, while patients who have fewer copies typically have more severe forms of disease

8. Next-generation sequencing

Next-generation sequencing (NGS) is an effective method for detecting rare or unusual mutations in the SMN1 gene. It is particularly beneficial when standard genetic tests fail to provide a diagnosis. Additionally, NGS can identify other uncommon genetic disorders that may resemble SMA [5].

9. Prenatal testing

To detect SMA in the fetus, genetic testing can be done during pregnancy. Amniocentesis or chorionic villus sample can be used for this. If the fetus is impacted, early intervention and informed reproductive choices are made possible by early detection.A number of ethical concerns are brought up by prenatal testing for spinal muscular atrophy (SMA), including those pertaining to informed consent, autonomy, disability rights, and the possibility of prejudice. The goal, advantages, restrictions, and possible repercussions of SMA prenatal testing must be clearly understood by prospective parents. They ought to have access to thorough information regarding SMA, including the prognosis, possible treatments, and the psychological effects of a favorable outcome. [13]

Management and Supportive Care

Despite the availability of disease-modifying treatments, supportive care is still a key component of the therapy of spinal muscular atrophy (SMA). Patients with SMA need lifelong multidisciplinary treatment from neurologists, pulmonologists, physiotherapists, orthopedic surgeons, dietitians, speech and language therapists, psychologists, and genetic counselors since the disease causes progressive muscular weakening that affects various organ systems. Maintaining respiratory function, optimizing nutrition, preserving mobility, avoiding problems, increasing independence, and improving general quality of life are the key goals of supportive care. Individualized treatment regimens should take into account the patient's age, functional level, disease subtype, and degree of illness.

Respiratory management

Since respiratory muscle weakness is the primary cause of morbidity and death in SMA, respiratory treatment is one of the most important components of supportive care. It is crucial to regularly evaluate oxygen saturation, pulmonary function, and breathing issues associated to sleep. Chest physical therapy, mechanical insufflation-exsufflation (cough-assist devices), suctioning, and breathing exercises are examples of airway clearing procedures that help eliminate respiratory secretions and lower the risk of infections. While invasive mechanical

ventilation may be necessary in extreme circumstances, non-invasive ventilation (BiPAP) is frequently used to support breathing during sleep or respiratory failure. To reduce pulmonary problems, annual influenza vaccination, pneumococcal immunization, and timely treatment of respiratory infections are advised.[19]

Nutritional management

Due to bulbar muscular weakness and decreased physical activity, many people with SMA have dysphagia, poor weight growth, malnutrition, gastroesophageal reflux, and constipation, making nutritional care equally crucial. Frequent evaluation by a speech-language pathologist and dietician aids in the early detection of eating issues. Plans for nutrition should minimize obesity and malnutrition while providing enough calories, protein, vitamins, and minerals. To guarantee safe and sufficient nutritional intake, patients with severe dysphagia or recurrent aspiration may need enteral feeding via a nasogastric or gastrostomy tube.

Physiotherapy and rehabilitation

Rehabilitation and physical therapy are crucial for preserving functional independence and averting further issues. Low-impact physical activities, stretching regimens, strengthening exercises where necessary, and daily range-of-motion exercises all assist maintain muscle flexibility and lessen joint stiffness. Additionally, the goal of physiotherapy is to preserve mobility and posture while postponing the onset of contractures. Occupational therapy helps patients using wheelchairs, orthotic supports, adaptive equipment, environmental changes, and techniques to carry out everyday tasks more independently. Improving long-term functional results is greatly aided by early rehabilitation.[20]

Orthopedic management

Musculoskeletal issues including scoliosis, hip dislocation, joint contractures, and chest wall abnormalities are often caused by gradual muscle weakening, orthopedic care is essential. Frequent orthopedic assessments aid in the early detection of these issues. Ankle-foot orthoses, standing frames, spine braces, and sitting adjustments are examples of conservative therapy; nonetheless, surgical correction may be necessary for severe scoliosis or incapacitating abnormalities. Posture, seated balance, breathing, and general comfort are all enhanced by appropriate orthopedic therapies.[21]

Speech and swallowing therapy

Speech and swallowing treatment is advised for individuals who have bulbar muscle involvement that affects their ability to speak, chew, and swallow. Speech-language pathologists evaluate swallowing safety and communication skills, suggest suitable food textures, instruct swallowing strategies, and offer substitute communication devices when speech becomes significantly damaged. These treatments promote efficient communication while lowering the risk of aspiration pneumonia.

Psychological support and genetic counselling

Social services, educational support, peer support groups, and psychological therapy all aid families in overcoming these obstacles and enhancing their mental health. Affected families should also get genetic counseling to cover carrier testing, recurrence concerns, prenatal diagnosis, reproductive possibilities, and the autosomal recessive inheritance pattern of SMA.

Long-term follow-up

Regular evaluations of motor function, respiratory state, nutritional status, orthopedic problems, and therapeutic response should be part of long-term follow-up. Coordinated multidisciplinary care is still necessary to optimize therapeutic benefits, avoid problems, and improve the quality of life for people with SMA while novel disease-modifying treatments continue to improve survival and motor function.[22]

Disease-Modifying Therapies

The introduction of disease-modifying therapies (DMTs) has revolutionized the management of spinal muscular atrophy (SMA). Unlike supportive care, which mainly focuses on symptom management, these therapies target the underlying genetic defect by increasing the production of functional survival motor neuron (SMN) protein or replacing the defective SMN1 gene. Early treatment has been shown to improve motor function, survival, and overall quality of life, especially when initiated before significant motor neuron loss. Currently, the approved disease-modifying therapies for SMA include nusinersen, risdiplam, and onasemnogene abeparvovec, each offering a unique approach to modifying disease progression.

Nusinersen

Mechanism of action: Nusinersen functions by altering gene products. The SMN2 gene also produces SMN protein, but it has 11 nucleotide differences from SMN1, causing exon 7 to be skipped in 80–90% of mature RNA transcripts, which leads to the creation of a truncated, non-functional protein known as SMNΔ7. Nusinersen specifically targets a splicing silencer dependent on heterogeneous nuclear ribonucleoprotein A1 within the SMN2 pre-messenger RNA, located downstream of exon 7. This action modifies the splicing process, resulting in an increased production of transcripts that include exon 7.[25]

Dosage and Administration: Nusinersen is classified as an antisense oligonucleotide (ASO) and is part of the phosphorothioate (PS) oligodeoxynucleotides group. Typically, ASOs are unable to penetrate the blood-brain barrier, which requires them to be delivered intrathecally (IT) to be effective within the central nervous system (CNS). Nusinersen is characterized by a prolonged half-life of around five months. Initially, it is given as four loading doses over two months, and then maintenance doses are administered every four months. The dosage remains consistent across all age categories.[24]

Clinical Efficacy: In the phase 3 ENDEAR trial, 51% of infants receiving treatment reached motor milestone responses, in contrast to 0% in the control group, and there was a 47% reduction in the risk of death or need for permanent ventilation (HR 0.53, P = 0.005). Approved in 2016 for all types of SMA, nusinersen has demonstrated ongoing motor improvements and survival advantages in long-term extension studies.[26]

Adverse Effects: Nusinersen is generally well tolerated. The most commonly reported adverse effects include headache, back pain, vomiting, constipation, and fever. Because it is administered intrathecally, post-lumbar puncture complications such as headache and back discomfort may occur. Regular monitoring of platelet count, coagulation parameters, and renal function is recommended during treatment.

Risdiplam

Mechanism of Action: Risdiplam, a pyridazine derivative that alters the splicing of pre-mRNA from the SMN2 gene to promote inclusion of exon 7, is the first oral medication created to treat SMA. It belongs to a class of small-molecule therapies approved for the treatment of SMA. Risdiplam enhances exon 7 inclusion in SMN2 mRNA, resulting in greater synthesis of functional SMN protein.

Dosage and Administration: Risdiplam is taken orally once a day; the dosage is based on the patient's age and weight, with a maximum of 5 mg for patients who are at least 2 years

old and weigh more than 20 kg.[25] Preclinical studies have shown that risdiplam reaches steady-state concentrations within 7–14 days and is distributed throughout both the central nervous system and peripheral tissues.

Clinical Efficacy: Risdiplam significantly improved motor function and survival in the FIREFISH (Type 1) and SUNFISH (Type 2/3) trials compared with untreated natural-history cohorts. Risdiplam, which was approved in 2020 for both adult and pediatric patients, has the benefit of oral administration, which makes it a favored choice for many families because of its noninvasive delivery.[26]

Adverse Effects: Risdiplam is generally well tolerated. The most commonly reported adverse effects include fever, diarrhea, rash, mouth ulcers, constipation, and upper respiratory tract infections. Regular clinical monitoring is recommended throughout treatment, although serious adverse events are uncommon.

Gene Replacement Thearpy

Onasemnogene abeparvovec

Mechanism of Action: Onasemnogene abeparvovec is a somatic gene therapy for SMA that is given intravenously. It is based on a self-complementary adeno-associated virus serotype 9 (AAV9) vector that carries a human SMN1 gene and is controlled by a constitutive hybrid CMV enhancer/chicken-b-actin promoter that should result in continuous SMN1 production.

Administration and Indications: AAV9 targets CNS neurons after passing through the blood-brain barrier. Human illness is not known to be caused by it. Before beginning treatment, patients must be tested for anti-AAV9 antibodies because elevated titers disqualify the patient. The therapy is approved for eligible patients with biallelic mutations in the SMN1 gene, in accordance with the regulatory guidelines of individual countries.

Clinical Efficacy: In STR1VE-US and STR1VE-EU investigations, 44%-59% of treated infants reached independent sitting by 18 months versus 0% historically, and 91%-97% survived free of permanent ventilation at 14 months. In 2019, onasemnogene abeparvovec received FDA approval for the treatment of children younger than two years of age with biallelic mutations in the SMN1 gene. Depending on the patient's clinical response and disease progression, some individuals may subsequently receive additional therapy with nusinersen or risdiplam to further improve long-term outcomes.[27]

Adverse Effects: Onasemnogene abeparvovec is generally well tolerated; however, elevated liver enzymes, vomiting, thrombocytopenia, and transient increases in cardiac troponin levels

have been reported. Liver function should be monitored before and after treatment, and corticosteroid prophylaxis is recommended to reduce the risk of hepatotoxicity.

Table 1. Comparison of currently approved disease-modifying therapies for spinal muscular atrophy (SMA).

Therapy	Mechanism	Route	Main Advantage	Limitation
Nusinersen	SMN2 splicing modifier	Intrathecal	Proven efficacy	Repeated lumbar punctures
Risdiplam	SMN2 splicing modifier	Oral	Easy administration	Long-term daily treatment
Onasemnogene abeparvovec	SMN1 gene replacement	Intravenous	One-time treatment	High cost and liver monitoring

Emerging Therapeutic Strategies

Significant progress has been made in the development of therapies for SMA, with treatment options advancing swiftly and early clinical trial outcomes offering renewed optimism for patients. Concurrently, there has been notable advancement in comprehending the clinical progression and natural history of the disease, which aids in expediting clinical trial implementation. However, new challenges are emerging with the advent of new therapies, such as issues related to treatment access due to the complexities, costs, and expertise needed for intrathecal administration. Continued efforts to determine the best methods for drug delivery and distribution, as well as defining the therapeutic window, will be crucial. As the field anticipates a new era of treatment, it is crucial to prioritize timely access to innovative, disease-modifying therapies and strive to develop treatments for SMA patients of all ages and severities.[30]

Combination therapy

Boosting the levels of SMN protein in the body is not the sole method for addressing SMA. The deficiency of SMN protein affects various systems, pathways, and processes, and alternative spinal muscular atrophy (SMA) treatments focus on these areas. These methods are frequently referred to as "non-SMN" strategies. A significant number of these non-SMN strategies are aimed at the muscles or nerves. Numerous researchers are of the opinion that a combination of SMN-based and non-SMN therapies will offer the greatest advantage to individuals with SMA. This might involve patients with SMA using two medications simultaneously. Alternatively, they might receive one form of treatment during a particular

phase of the disease and switch to another treatment at a different phase. There is less agreement on whether using two similar treatments—such as two SMN-enhancing methods or two non-SMN methods targeting the same system—will yield any extra benefit. Although early results are encouraging, more clinical trials are needed to determine the optimal timing, safety, and long-term benefits of combination therapy in patients [29]

Gene-Targeting SMN Replacement Therapies

One of the most promising developments in spinal muscular atrophy treatment is gene-targeting SMN replacement therapy. This approach seeks to rectify the genetic defect at its source by reinstating functional levels of the SMN protein. This can be accomplished by either introducing a functional version of the SMN1 gene or enhancing the production of functional SMN protein from the SMN2 gene. By tackling the disease's root cause, these therapies contribute to maintaining motor neuron function, enhancing motor outcomes, and decelerating disease progression, especially when started soon after diagnosis. [28]

Stem cell therapies

Therapies utilizing stem cells could offer significant therapeutic advantages, including safeguarding the function of unaffected motor neurons, altering environmental toxicity, and replenishing both neuronal and non-neuronal cell groups. Stem cell therapy might complement SMN-targeted treatments by enhancing motor neuron survival, minimizing neuronal harm, and aiding in tissue regeneration. Nonetheless, additional preclinical and clinical research is necessary to confirm its long-term safety and effectiveness. [31]

Gene Editing (CRISPR/Cas9)

Gene-editing tools like CRISPR/Cas9 are under investigation as a possible future treatment for SMA. In contrast to existing therapies, gene editing seeks to permanently rectify mutations in the SMN1 gene. Although still in the preclinical phase, this approach has demonstrated encouraging outcomes in experimental models and could potentially offer a lasting therapeutic solution in the future.

Challenges and Future Perspectives

In the near future, the dominant strategy for handling SMA is expected to involve swift detection through newborn screening, along with early treatment using new drugs. Although there have been significant strides in therapies that modify the disease, numerous obstacles persist, such as inconsistent treatment responses, high costs, limited access, and the necessity for long-term safety data. Present difficulties also include establishing accurate and realistic

treatment expectations for families. Future studies should aim to discover dependable biomarkers for predicting treatment outcomes, enhance personalized therapy, and improve long-term monitoring. [28]

Broadening newborn screening initiatives and ensuring prompt treatment access will be crucial for achieving improved clinical results globally. Comprehending the biology of SMN restoration and developing a set of biomarkers (clinical, neurophysiological, functional, and molecular) that can indicate when further improvements are possible remains vital to standardizing therapeutic management worldwide.

The introduction of newborn screening (NBS) and the expanding treatment options across different age groups have created new challenges in clinical decision-making. Children with two SMN2 copies are thought to be at high risk of developing clinically evident illness, which is characterized by a sudden loss of motor units, and the best therapeutic medication is often the one that can be supplied quickly. Informing new parents of a positive screen for an irreversible motor neuron disease, taking steps to confirm diagnosis, and navigating sometimes complex therapeutic pathways, all within a narrow therapeutic window, require a health system that values collaboration and cooperation. Specialists, scientists, diagnostic laboratories, and community practitioners must collaborate to support families' therapeutic decision-making and simplify processes for approving and administering therapy. The high cost of gene replacement therapy, together with its limited availability in many low- and middle-income countries, continues to be a major barrier to equitable access to treatment worldwide.[32]

CONCLUSION

Spinal muscular atrophy has shifted from a condition managed mainly through supportive care to one that benefits from effective treatments, including disease-modifying and gene replacement therapies. The introduction of medications such as nusinersen, risdiplam, and onasemnogene abeparvovec has led to notable improvements in survival rates, motor skills, and overall quality of life, especially when treatment begins early. New methods, like combination therapies, gene editing, and stem cell treatments, show potential for further enhancing patient outcomes. Despite these advancements, challenges such as high costs, limited access, and the need for long-term safety data persist. To optimize the management of SMA and improve patient outcomes globally, ongoing research, expanded newborn screening, and equitable access to innovative therapies are crucial.

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