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Spinal Muscular Atrophy- An Overview

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ABSTRACT
Spinal muscular atrophy (SMA) is a neurodegenerative disease characterized by degeneration of anterior horn in the spinal cord and motor nuclei in the lower brain stem which result in progressive muscle weakness and atrophy predominating in proximal limb muscles. The prevalence of approximate 1 in 10,000 live births affected by SMA. SMA is caused by deficiency of SMN (Survival Motor Neuron), a motor neuron protein. SMA is classified into four grades of severity (SMA I, SMAII, SMAIII, SMA IV) based on age of onset and motor function achieved. Molecular testing for homozygous deletion or mutation of the SMN1 gene allows efficient and specific diagnosis. There's no cure, but treatments can improve some symptoms and, in some cases, help child live longer. The disease-modifying treatments, including the antisense oligonucleotide Nusinersen, the gene replacement therapy Onasemnogene Abeparvovec, and, more recently, the small molecule Risdiplam, is progressively changing the natural history of the disease. In this review article, we try to deal with the history, types, diagnosis and treatment approaches of SMA.

KEY WORDS: Survival Motor Neuron, Anti Sense Oligonucleotides, Gene replacement Therapy.

I. INTRODUCTION

Spinal muscular atrophy (SMA) refers to a group of genetic disorders characterized by degeneration of anterior horn calls in the spinal cord and motor nuclei in the lower brain stem which result in progressive muscle weakness and atrophy [1]. The disease is characterized as an autosomal recessive condition with prevalence of approximate 1 in 10,000 live births affected by SMA [2].SMA is caused by deficiency of a motor neuron protein called SMN (Survival Motor Neuron). This protein is essential for normal motor function and the lack of it is caused by genetic flaws on chromosome 5 in the gene SMN1. The neighbouring SMN2 gene can compensate some of the functions of SMN1 and this is where some of the pharmaceutical companies trying to develop a drug which can enhance the effect of SMN2 [3].

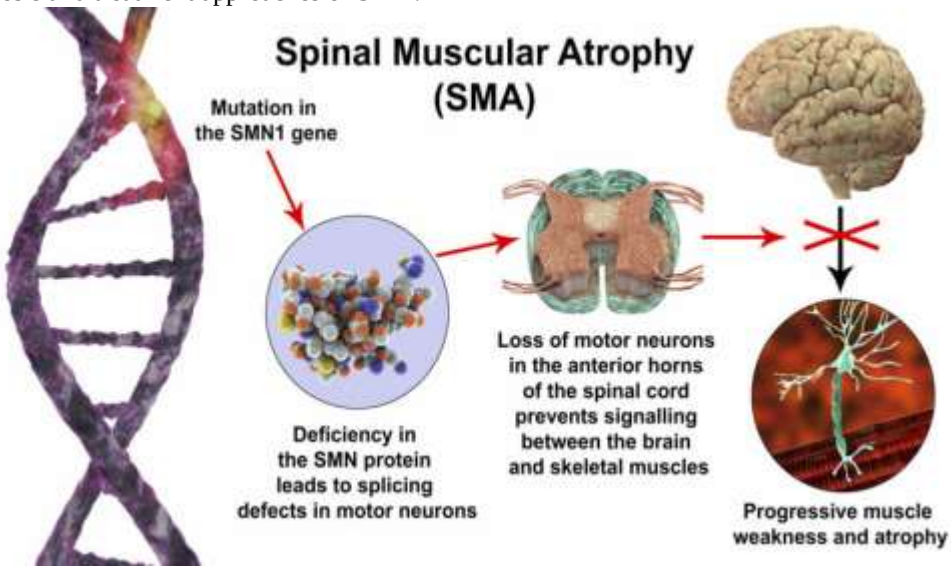

Figure 1: Illustration ofspinal muscular atrophy, SMA, a genetic neuromuscular disorder with progressive muscle wasting due to mutation in the SMN1 gene, deficiency in SMN protein, and loss of motor neurons.

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HISTORY

SMA was first discovered in infants in the early 1890's by physicians GuidoWerdnig and Johan Hoffman. Both men had noticed several cases of babies developing muscle weakness within the first few months of life. They also noticed that this condition seemed to run in families. Then by others who recognized variability of muscle weakness severity [4]. A century later, a consensus classification scheme outlining three SMA types was adopted, and in 2007 a Standard of Care document formalized the clinical treatment of patients with SMA. The SMN gene was identified as the causative gene in SMA in 1995, which has led to the development of SMA animal models and targeted therapeutic approaches to increase SMN protein levels. The increasingly successful preclinical testing of multiple therapeutic approaches during the last 10 years has led to great optimism that an era of successful clinical trials is fast approaching [3].

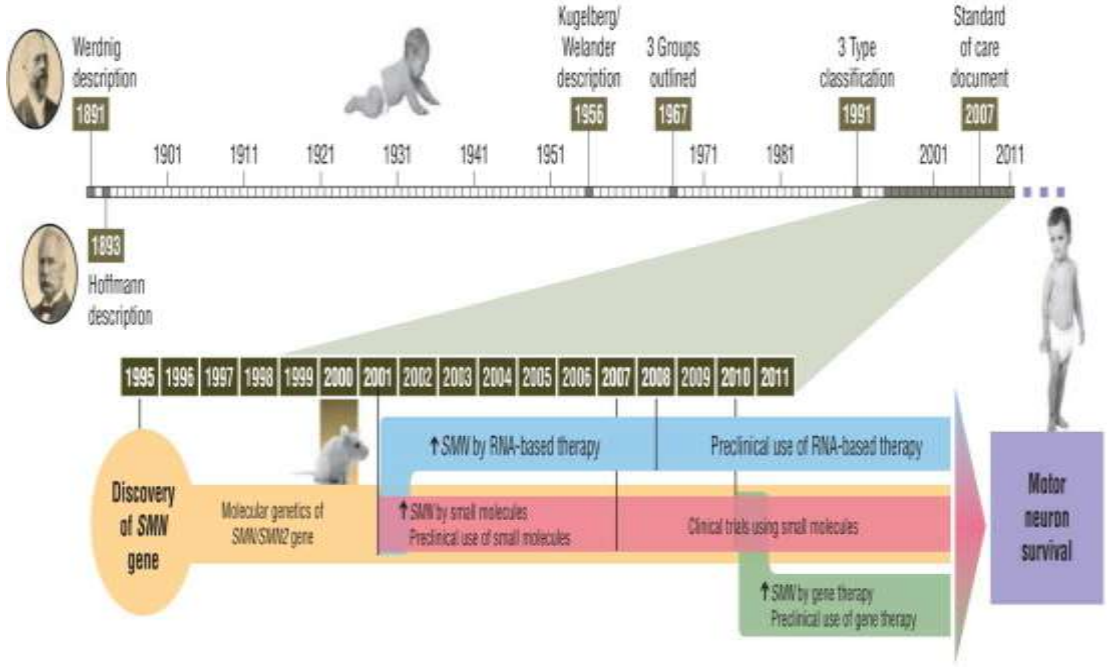

Figure 2:Spinal muscular atrophy (SMA) timeline.

CLINICAL DESCRIPTION AND CLASSIFICATION

SMA is clinical classified into four phenotypes on the basis of age of onset and motor function achieved [4].

Table 1: Classification of SMA

	Age of onset	Highest function achieved
Type I (Werdnig- Hoffmann disease)	0-6 months	Never sit
Type II (intermediate)	7-8 months	Sit never stand
Type III (mild, Kugelberg-Welander disease) in adulthood	> 18 months	months Stand and Walk during adulthood
Type IV (adult)	2°-3° decade	Walk unaided

SMA type 1 (Werdnig-Hoffmann disease) is the most severe and common type, which accounts for about 50% of patients diagnosed with SMA. Classically infants with SMA type I have onset of clinical signs before 6 months of age, never acquire the ability to sit unsupported and, if no intervention is provided, generally do not survive beyond the first 2 years [5]. These patients have profound hypotonia, symmetrical flaccid paralysis, and often no head control. Spontaneous motility is generally poor and antigravity movements of limbs are not typically observed. In the most severe forms decreased intrauterine movements suggest prenatal onset of the disease

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and present with severe weakness and joint contractures at birth and has been labeled SMN 0. Some of these children may show also congenital bone fractures and extremely thin ribs [6].

Within SMA type I at least 3 clinical subgroups can be defined according to the severity of clinical signs: a) severe weakness since birth/neonatal period, head control is never achieved; b) onset of weakness after the neonatal period but generally within 2 months, head control is never achieved; c) onset of weakness after the neonatal period but head control is achieved. Some of these children may be able to sit with support [7].

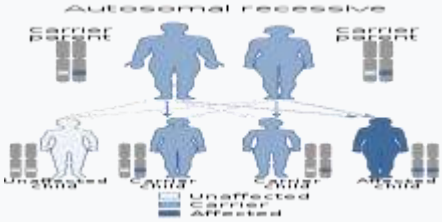
Clinically, all children with SMA type I show a combination of severe hypotonia and weakness, with sparing of the facial muscles, invariably associated with a typical respiratory pattern. The weakness is usually symmetrical and more proximal than distal, with lower limbs generally weaker than upper limbs. Deep tendon reflexes are absent or diminished but sensitivity is preserved. The spared diaphragm, combined with weakened intercostal muscles, results in paradoxical breathing. The involvement of bulbar motor neurons often gives tongue fasciculation, poor suck and swallow with increasing swallowing and feeding difficulty over time. Aspiration pneumonia is an important cause of morbidity and mortality. In the last few years there has been increasing evidence that some cases with severe SMA type I (generally carrying 1 copy of SMN2) may have heart defects [9], mostly atrial and ventricular septal defects and a possible involvement of the autonomic system that may be responsible for arrhythmia and sudden death.

SMA type II is characterized by onset between 7 and 18 months of age. Patients achieve the ability to sit unsupported and some of them are able to acquire standing position, but they do not acquire the ability to walk independently. Deep tendon reflexes are absent and fine tremors of upper extremities are common. Joint contractures and kyphoscoliosis are very common and can occur in the first years of life in the more severe type II patients [9]. Weak swallowing can be present but is not common while weakness of the masticatory muscles more often affects the ability to chew. There is a spectrum of severity ranging from weak children who are just able to sit unsupported and are more prone to respiratory signs and early scoliosis to relatively stronger children who have much stronger trunk, limb and respiratory muscles. Patients at the weak end of the spectrum may develop respiratory failure requiring mechanical ventilation [8].

SMA type III (Kugelberg-Welander disease) includes clinically heterogeneous patients. They typically reach all major motor milestones, as well as independent walking. However, during infancy they develop proximal muscular weakness. Some might need wheelchair assistance in childhood, whereas others might continue to walk and live productive adult lives with minor muscular weakness. Patients who lose ambulation often develop scoliosis and other medical problems related to poor mobility such obesity and osteoporosis. Concerning natural history data on 329 SMA type III patients, 2 subgroups of severity have been suggested on the probability of being able to walk by 10 years and on increased probability to lose walking by the age of 40 years. Significant differences losing ability to walk were observed in relation to those with an onset of weakness before (SMA III a) and after age 3 years of age (SMA III b)

SMA type IV has been added to this classification to describe those patients with adult onset (> 18 years) and mild course. This group includes patients who are able to walk in adulthood and without respiratory and nutritional problems. Since all SMA types belong to a single spectrum and share the same etiology, patient selection for clinical trials is actually independent of the historical classification,and is essentially determined by the intervention characteristics and the choice of endpoints.

CAUSES



Spinal muscular atrophy has an autosomal recessive pattern of inheritance.

Figure 3: Genetics of Spinal muscular atrophy

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Spinal muscular atrophy is caused by a genetic mutation in the SMN1 gene.[11]

Human chromosome 5 contains two nearly identical genes at location 5q13: a telomeric copy SMN1 and a centromeric copy SMN2. In healthy individuals, the SMN1 gene codes the survival of motor neuron protein (SMN) which, as its name says, plays a crucial role in survival of motor neurons. The SMN2 gene, on the other hand – due to a variation in a single nucleotide (840.C→T) – undergoes alternative splicing at the junction of intron 6 to exon 8, with only 10–20% of SMN2 transcripts coding a fully functional survival of motor neuron protein (SMN-fl) and 80–90% of transcripts resulting in a truncated protein compound (SMNΔ7) which is rapidly degraded in the cell.[10]

In individuals affected by SMA, the SMN1 gene is mutated in such a way that it is unable to correctly code the SMN protein – due to either a deletion occurring at exon 7 or to other point mutations (frequently resulting in the functional conversion of the SMN1 sequence into SMN2). Almost all people, however, have at least one functional copy of the SMN2 gene (with most having 2–4 of them) which still codes 10–20% of the usual level of the SMN protein, allowing some neurons to survive. In the long run, however, the reduced availability of the SMN protein results in gradual death of motor neuron cells in the anterior horn of spinal cord and the brain. Skeletal muscles, which all depend on these motor neurons for neural input, now have decreased innervation (also called denervation), and therefore have decreased input from the central nervous system (CNS). Decreased impulse transmission through the motor neurons leads to decreased contractileactivity of the denervated muscle. Consequently, denervated muscles undergo progressive atrophy (waste away).

Muscles of lower extremities are usually affected first, followed by muscles of upper extremities, spine and neck and, in more severe cases, pulmonary and mastication muscles. Proximal muscles are always affected earlier and to a greater degree than distal muscles.

The severity of SMA symptoms is broadly related to how well the remaining SMN2 genes can make up for the loss of function of SMN1. This partly depends on the number of copies of the SMN2 gene present on the chromosome.Whilst healthy individuals usually carry two SMN2 gene copies, people with SMA can have anything between 1 and 5 (or more) of them; the greater the number of SMN2 copies, the milder the disease severity. Thus, most SMA type I babies have one or two SMN2 copies; people with SMA II and III usually have at least three SMN2 copies; and people with SMA IV normally have at least four of them. However, the correlation between symptom severity and SMN2 copy number is not absolute and there seem to exist other factors affecting the disease phenotype.

Spinal muscular atrophy is inherited in an autosomal recessive pattern, which means that the defective gene is located on an autosome. Two copies of the defective gene – one from each parent – are required to inherit the disorder: the parents may be carriers and not personally affected. SMA seems to appear de novo (i.e., without any hereditary causes) in around 2–4% of cases.

Spinal muscular atrophy affects individuals of all ethnic groups, unlike other well-known autosomal recessive disorders, such as sickle cell disease and cystic fibrosis, which have significant differences in occurrence rate among ethnic groups. The overall prevalence of SMA, of all types and across all ethnic groups, is in the range of 1 per 10,000 individuals; the gene frequency is around 1:100, therefore, approximately one in 50 persons are carriers. There are no known health consequences of being a carrier. A person may learn carrier status only if one's child is affected by SMA or by having the SMN1 gene sequenced.

Affected siblings usually have a very similar form of SMA. However, occurrences of different SMA types among siblings do exist – while rare, these cases might be due to additional de novo deletions of the SMN gene, not involving the NAIP gene, or the differences in SMN2 copy numbers.

DIAGNOSIS

A blood test is available to look for deletions or mutations of the SMN1 gene. This test identifies at least 95 percent of SMA Types I, II, and III and may also reveal if a person is a carrier of a defective gene that could be passed on to children. If the SMN1 gene is not found to be abnormal or the individual's history and examination are not typical of SMA, other diagnostic tests may include electromyography (which records the electrical activity of the muscles during contraction and at rest), nerve conduction velocity studies (which measure the nerve's ability to send an electrical signal), muscle biopsy (used to

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diagnose many neuromuscular disorders), and other blood tests. [11]

Symptomatically, SMA can be diagnosed with a degree of certainty only in children with the acute form who manifest a progressive illness with paradoxical breathing, bilateral low muscle tone and absent tendon reflexes.

EARLY DIAGNOSIS

Early diagnosis of SMA, at the asymptomatic stage of the disease, allows for

Preimplantation testing

Preimplantation genetic diagnosis can be used to screen for SMA-affected embryos during in-vitro fertilization.

Prenatal testing

Prenatal testing for SMA is possible through chorionic villus sampling, cell-free foetal DNA analysis and other methods.

New-born screening

Routine new born screening for SMA is becoming increasingly commonplace in developed countries, given the availability of causative treatments that are most effective at the asymptomatic stage of the disease. [16]

Carrier testing

Those at risk of being carriers of SMN1 deletion, and thus at risk of having offspring affected by SMA, can undergo carrier analysis using a blood or saliva sample. The American College of Obstetricians and Gynaecologists recommends all people thinking of becoming pregnant be tested to see if they are a carrier. The carrier frequency of SMA is comparable to other disorders like thalassemia and in a north Indian cohort has been found to be 1 in 38. However, genetic testing will not be able to identify all individuals at risk since about 2% of cases are caused by de novo mutations and 5% of the normal population have two copies of SMN1 on the same chromosome, which makes it possible to be a carrier by having one chromosome with two copies and a second chromosome with zero copies. This situation will lead to a false negative result, as the carrier status will not be correctly detected by a traditional genetic test.

MULTIDISCIPLINARY CARE IN SMA

While being a monogenetic neuromuscular disease, the resulting phenotypic spectrum is complex and SMA is generally perceived as a systemic disease. Accordingly, care for patients with SMA requires the interdisciplinary management of respiratory, nutritional and gastroenterological, orthopaedic, and psychosocial issues. [12] A 2007 consensus statement, issued by the International Standard of Care Committee for SMA, to address the 5 priority care areas for SMA, found that, high priority components of meaningful change relate to immediate concerns with breathing, feeding, swallowing, and the ability to communicatefor those affected by type 1 SMA. For patients with types 2 and 3 SMA, priorities include disease stabilization, independence and the ability to perform basic personal tasks, and reducing muscle fatigue. In most cases, patients and caregivers perceive benefit in maintenance of current abilities and avoiding decline in function. They indicate that even small improvements in functional abilities would be meaningful, especially if these contribute to the increase in ability to independently perform activities of daily living. [13]

Nevertheless, the implementation of standards of care is highly variable and is influenced by cultural perspectives, socioeconomic factors, and the availability of regional resources. Due to advances and improvements in care over the last decade, an updated version of recommendations on diagnosing SMA and patient care was published only recently.[12]

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Figure 4: Paradigm of multidisciplinary care of SMA,incorporating disease-modifying therapies with supportive care. Novel disease-modifying medications and evolving multidisciplinary supportive management need to occur concomitantly to achieve the best possible outcome for SMA patients. The multidisciplinary team should and may include a varietyof medical specialties that ideally follow up both the as-yet untreated patients as part of providing aStandard of Care and patients that undergo specific therapies

Nutritional aspects play a significant role in the multidisciplinary management of children with SMA1 and SMA2, particularly in the treatment of nutritional derangements including swallowing and gastrointestinal problems. The increase in the knowledge on nutritional aspects of patients with SMA is crucial for the appropriate management of patients. However, the lack of specific, standardized and coordinated nutritional assessment for SMA patients is common and the use of reference data developed for healthy children increases the risk of inadequate nutritional support because of the peculiar nature of SMA. [14]

CLINICAL MANAGEMENT

Over the past decade, there has been a marked improvement in the ability of clinicians to manage the multiple respiratory, nutritional, orthopaedic, rehabilitative, emotional and social problems that develop in the majority of these patients. A notable achievement in this regard was the development of a comprehensive standard of care document by Wang and a collaborating panel of experts that was published in 2007and is currently being updated. This document established guidelines for managing the multiple expected clinical problems that develop in patients with SMA as they age. [15]

PULMONARY

The ultimate cause of death in infants and children with type 1 and 2 SMA is usually respiratory failure.Atherapeutic relationship with an experienced pulmonary specialist familiar with paediatric neuromuscular disorders need to be established at the time of initial diagnosis. There is early involvement of the expiratory muscles of ventilation with relative sparing of the diaphragm. In infants with type 1 SMA, the early implementation of non-invasive ventilatory support has been shown to improve survival and quality of life. Bi-level positive airway pressure, when applied with appropriate pressure settings and mask placement, is well tolerated, does not affect hemodynamic balance and may increase chemosensitivity and improve daytime hypercapnic ventilatory drive. Patients with this degree of respiratory weakness also have a weak cough that puts them at increased risk of aspiration and hypoxemia secondary to mucus plugging as well as increased risk of recurrent pulmonary infections. Infants at risk for mucus plugging should be monitored with overnight oximetry during acute illnesses and assisted airway clearance methods, such as manual suctioning, is recommended. Generally, the use of antibiotics should be applied to these infants during any acute illness because of the risk of pneumonia and associated pulmonary complication [15]

The goal of pulmonary intervention in type 1 infants is to improve quality of life and not necessarily to prolong life. For example, non-invasive ventilation can prevent and may reverse changes in chest wall compliance and lung development. Ultimately, however, a decision must be made about what to do once non-invasive ventilatory support is not sufficient. The use of a tracheostomy and permanent ventilatory support can be successfully implemented in individuals with SMA. However, a commitment to lifelong, full-time ventilatory support is an individual choice for the child'sfamily which must be discussed in a multi-disciplinary setting, ideally involving a palliative care team [15].

The management of respiratory function in type 2 or non-ambulant SMA children (i.e. type 3 children who with progression of illness eventually lose ambulation) is similar to that of type 1 infants, however the complications are less severe. Physical examination and assessment of cough effectiveness and respiratory muscle function should be routinely monitored. For children who are greater than 5 years of age, forced vital capacity can be routinely monitored and non-invasive ventilatory support can be managed long-term. Nocturnal hypoventilation should also be treated with non-invasive ventilation [15].

GASTROINTESTINAL AND NUTRITIONAL

Gastrointestinal complications are common in individuals with SMA, and it is not clear if this is due to defect in gastrointestinal mobility or nutritional deficiencies. Infants with type 1 SMA often have prolonged feeding times and tire quickly. This reduction in feeding can be the firstsign of progressive weakness and can lead

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to failureto thrive and aspiration. Gastrointestinal dysfunction includes difficulty feeding and swallowing due to bulbar dysfunction and manifests as tongue weakness, difficulty opening the mouth and poor head control. Other associated problems include gastrointestinal reflux, delayed gastric emptying and constipation. These complications are also seen in individuals who, for other reasons, cannot sit or stand, and are less commonly seen in ambulant individuals with SMA. [15]

The management of aspiration associated with feeding and dysphagia includes changing food consistency to include semi-solid and thickened liquids. However, in infants with type 1 SMA, early gastrostomy and laparoscopic Nissen fundoplication (if gastrointestinal reflux is present) is recommended because of the importance of maintaining proper nutrition and to reduce the risk of infection secondary to aspiration. The surgery can be performed soon after diagnosiswhen the infant is healthy so that the infant will not become hungry as oral feeding decreases. [15]

Malnutrition, secondary to decreased oral intake can also be an insidious problem for some type 2 SMA children and adolescents. Malnutrition and periods of fasting should be avoided, since these behaviours may contribute to reduction of muscle mass and subsequent impaired function. In clinical practice, height and weight plots in individuals with SMA can be deceiving due to reduced lean body mass. In fact, high functioning, non-ambulatory individuals with SMA are prone to adiposity, despite their low resting energy expenditure and are at risk of becoming overweight. To manage these complications, each child should be evaluated individually during routine visits by a dietitian with the goal of maintain the growth curve and to avoid inadequate or excessive intake. Because of the tendency for decreased bone mineral density with increasing age, adequate intake of vitamin D and calcium should be provided [15].

ORTHOPAEDIC AND MUSCULOSKELETAL COMPLICATIONS

Weakness and impaired mobility predispose to numerous musculoskeletal issues. Early recognition and appropriate management are helpful in maintaining function, preventing deterioration in vital capacity and improving quality of life. In non-ambulatory individuals with SMA, contractures are common and regular stretching and bracing programs to preserve flexibility and prevent contractures are the main goals of therapy. Manual and motorized wheelchairs may be initiated as early as 18–24 months of age. Children who are able to bear some weight and have some trunk control may utilize a standing frame or mobile-stander with ankle-foot orthoses. Physical therapy can help to maximize endurance, fitness and safety by incorporating activities such as swimming, aquatic therapy and adaptive sports. Neuromuscular fatigue appears to contribute to functional limitations in individuals with SMA. Wheelchairs and modifications in the environment and at home should be considered to allow for safe accessibility and to optimize independence. Scoliosis occurs in almost all non-ambulant individuals with SMA. When untreated, scoliosis causes chest-cage deformities with subsequent respiratory restriction. Spinal fusion and bracing are the treatments of choice for scoliosis, however there is no clear consensus for their efficacy [15].

RECENT ADVANCES IN INNOVATIVE THERAPEUTIC APPROACHES FOR SMA

The therapeutic approaches for SMA are generally categorized into SMN dependent and SMN independent therapies, which can further divide into four branches of development respectively. The yellow circle in Figure 5 indicating SMN1 gene replacement therapy of the SMN-dependent pathway highlights its difference from the other three therapies in the SMN-dependent category, which mainly target SMN2. The dashed lines of the outer rims connecting the SMN-dependent and SMN-independent approaches imply the potential for combinatory effect as a "cocktail therapy" [16]

Among different approaches, strategies with the most promising clinical data for SMA have been achieved through upregulating FL SMN2 production by modulating splicing or replacing functional exogenous SMN1 gene via a viral vector. In parallel with the treatment pipeline of SMN-dependent approaches, neuroprotective agents, myostatin inhibitors, skeletal muscle troponin activators, and stem cell therapy are examples of adjunctive SMN-independent therapies. [16]

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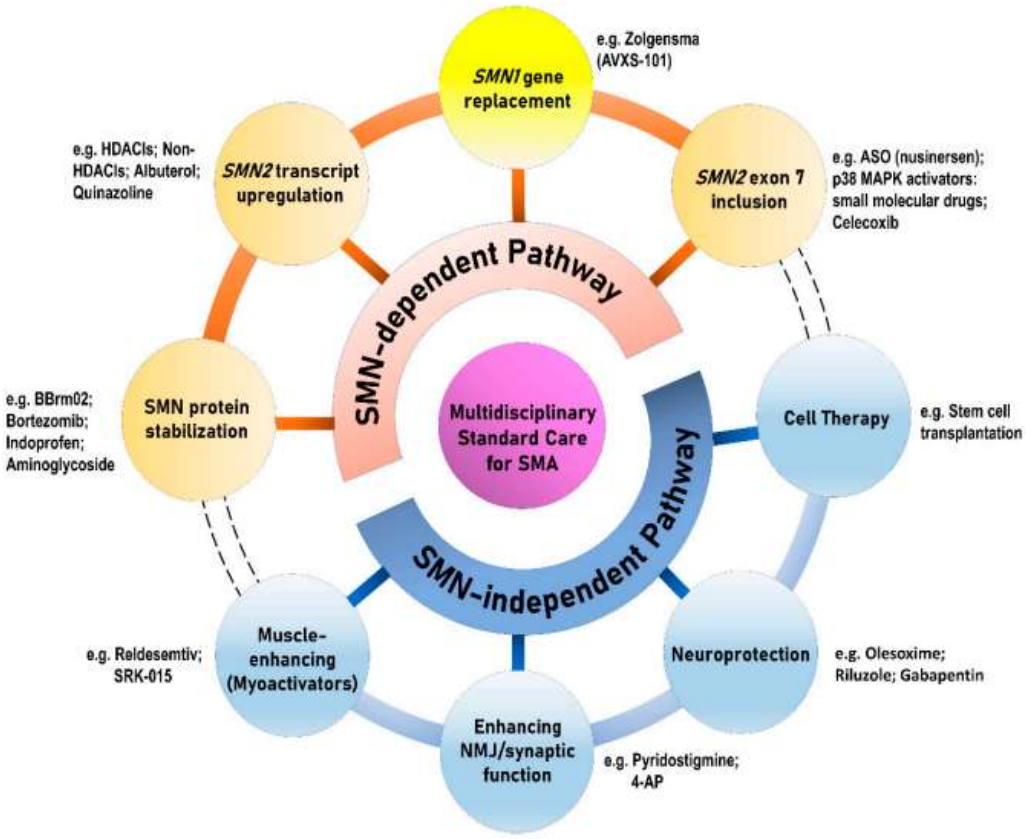

Figure 5. Therapeutic approaches for SMA. ASO: antisense oligonucleotide; HDACI: histone deacetylase inhibitor; NMJ: neuromuscular junction.

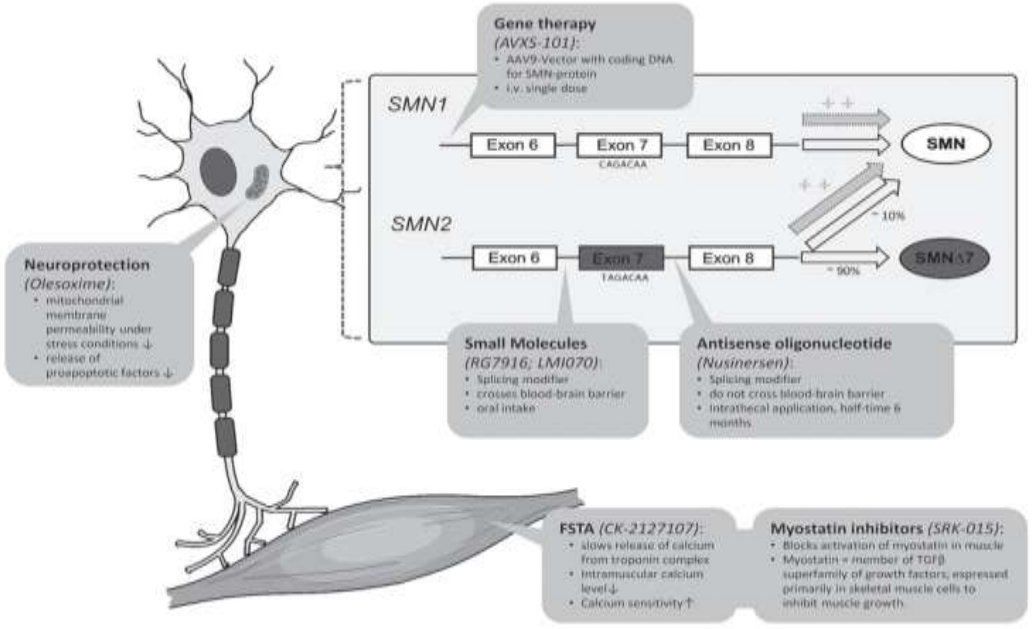

Figure 6. Illustration of therapeutic approaches in SMA involving molecular mechanisms of action, FSTA = Fast Troponin Activator.

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Therapeutic Pathways	Pathologic Points	Therapeutic Targets	Therapeutic Agents	Trial Status (Completed or Ongoing)/Results
SMN-dependent	*SMN1* mutation	*SMN1* replacement	Zolgensma (AVXS-101)	FDA-Approved
	Alternative splicing of *SMN2* mRNA	Promote exon 7 inclusion	• Nusinersen (Spinraza) • Risdiplam (RG7916) • Branaplam (LMI070)	• Nusinersen: FDA-approved • Risdiplam: ongoing phase 2/3 placebo-controlled; approaching FDA-approved • Branaplam: ongoing phase 1/2 open-label
	Decreased full length SMN mRNA	Upregulation of *SMN2* transcript	• HDACIs, e.g., PBA, VPA, • Non-HDACIs: Hydroxyurea • Celecoxib • Quinazoline (RG3039) • Albuterol • Prolactin	• PBA: completed placebo-controlled; negative • VPA: completed placebo-controlled; negative • Hydroxyurea: completed placebo-controlled; negative • Celecoxib: ongoing phase 2 open-label • Quinazoline: suspended • Albuterol: completed open-label; positive but lacking large controlled trials data • Prolactin: preclinical
	SMN protein degradation	Stabilizing SMN protein	• Aminoglycoside • Bortezomib • BBrm02 • Indoprofen • polyphenols	All are preclinical
SMN-independent	Anabolic abnormalities	Muscle-enhancing agent (Myoactivators)	• SRK-015 • Reldesemtiv (CK-2127107) • BIIB110 (ALG 801) • Follistatin	• SRK-015: ongoing phase 2 open-label • Reldesemtiv: completed phase 2 placebo-controlled; pending • BIIB110: ongoing phase 1a • Follistatin: preclinical
	Neuromuscular junction defect	Enhancing neurotransmitters	• Pyridostigmine (Mestinon) • 4-aminopyridine (4-AP)	• Pyridostigmine: completed placebo-controlled trial; pending • 4-aminopyridine: completed placebo-controlled trial; pending
	Motor neuron loss	Neuroprotection	• Riluzole • Gabapentin • Olesoxime (TRO19622)	• Riluzole: completed open-label; negative • Gabapentin: placebo-controlled trial; negative • Olesoxime: suspended
		Cell therapy for neurotrophic support	Stem cells	Preclinical

Table 2: Novel therapeutic approaches in spinal muscular atrophy: current clinical and preclinical trials [16]

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Drug (manufacturer)	Nusinersen (Biogen/Ionis)	scAAV9-SMN (Avexis/Novartis)	Risdiplam (Roche/PTC/SMA Foundation)	Branaplam (Novartis)
Category	ASO	Gene therapy	Small molecule	Small molecule
Mechanism	SMN2 splice switching	Viral-mediated SMN replacement	SMN2 splice switching	SMN2 splice switching
Delivery route	Intrathecal	Intravenous	Oral	Oral
Dosage frequency	Four loading doses over 2 months, followed by single dose every 4 months	Once	Daily	Once weekly
Tissue distribution				
-Cell targets	CNS	Systemic (lost from mitotically active cells)	Systemic	Systemic
-Topographical distribution	Possibility of high drug levels in caudal and low levels in rostral regions of the spinal cord (humans) (86). CSF flow dynamics could potentially affect drug distribution.	IV and CSF delivery shows transduction of motor neurons in the spinal cord (pre-clinical work in mice and non-human primates) (31,87).	Distributes to a similar extent in the brain, plasma and muscles (pre-clinical study in mice, rats and monkeys) (89)	Not reported
-Neuronal tropism	ASOs are taken up well by neurons compared to other cell types.	Efficient transduction of motor neurons (88)	Likely shows similar uptake levels in all tissue types	Likely shows similar uptake levels in all tissue types
Pharmacokinetics	Median time to max (T_m) in plasma, 1.7–6 h; Mean terminal elimination half-life in CSF, 135–177 days and in plasma, 63–87 days (61)	Not reported	Not reported	Not reported
Pharmacodynamics	Exon 7 inclusion increased by 20–40% across the spinal cord. SMN levels increased in motor neurons (86); SMN induction is likely limited by amount of SMN2 pre-mRNA; Speed of SMN induction and thresholds needed for efficacy are unknown.	Possibly results in a relatively rapid induction of SMN compared to other approaches. How long increased SMN levels are sustained over the long-term is not known.	Likely causes a dose-dependent induction of SMN in CNS and other tissues; SMN induction is likely limited by amount of SMN2 pre-mRNA.	Likely causes a dose-dependent induction of SMN in CNS and other tissues; SMN induction is likely limited by amount of SMN2 pre-mRNA.
Long-term durability	Requires monthly dosing (following the initial four loading doses) to sustain SMN levels	Possible stable long-term expression in terminally differentiated cells with single administration	Requires daily dosing to sustain SMN levels	Requires daily dosing to sustain SMN levels
Potential toxicities	• Mild renal toxicity • mild thrombocytopenia • complications arising from repeated lumbar punctures	• Potential inflammatory reaction during administration • exclusion of subjects with antibodies for AAV9 in serum • insertional genotoxicity leading to oncogenesis	• Potential off-target effects • possible build-up of toxic byproducts after prolonged daily dosage	• Potential off-target effects • possible toxic byproduct build-up after prolonged daily dosage

Table 3: Illustrates the current status of development of specific drugs.

SMN-DEPENDENT THERAPIES FOR SMA

The most tempting treatment approach in SMA is to upregulate SMN2, retaining in all patients, to function as the missing SMN1, either by activatingthe SMN2 gene or by modulation of SMN2 splicing. Theupregulation of SMN2 transcription is done by activating promoter, enhancing exon 7 inclusion, introducing SMN1 gene via a viral vector, modulating SMN protein

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translation, and preventing SMN protein degradation. [16]

PREVIOUS SMN-DEPENDENT TRIALS WITH INDEFINABLE OUTCOMES

Histone deacetylase inhibitors (HDACIs) are demonstrated for their ability to increase SMN2 transcription through the modification of chromatin structure in vitro and in vivo SMA models. Potential HDACIs proposed to benefit SMA, includes valproic acid, phenylbutyrate, and trichostatin A. These drugs activate the SMN2 promotor, driving increased FL SMN. However, regardless of any putative effect observed in vitro, no beneficial effect of HDACIs has carried over to clinical trials. Several other molecular mechanisms (e.g., histone phosphorylation, ubiquitination, and DNA methylation) are known to affect SMN2 expression. Hydroxyurea, an FDA-approved non-HDACI agent, was found to increase the amount of FL SMN transcript and protein in vitro. However, a small pilot trial on types 2 and 3 SMA showed no statistically significant benefit, followed by negative results of a further placebo-controlled trial. Albuterol is a β-adrenergic agonist which has been shown to increase FL SMN transcript levels in vivo. Two open-label trials of albuterol showed increased FL-SMN transcripts and improvements of motor function in types 2 and 3 SMA patients. However, no data of further placebo-controlled trials are available in order to validate the benefit of albuterol in clinical practice for SMA. Despite promising pre-clinical data, there are negative results following clinical trials of valproic acid combined with acetyl-L-carnitine, phenylbutyrate, hydroxyurea, and somatotropin. Their further development was discontinued, yet albuterol is still broadly prescribed off-label. [16]

NUSINERSEN: THE FIRST APPROVED SPLICING-MODIFY THERAPY FOR SMA

Antisense oligonucleotides (ASOs) are short, synthetic single-stranded nucleic acids that bind complementary sense sequences in targeted RNAs in order to either promote RNase-mediated degradation or modify splicing by acting as a steric hindrance to the binding of RNA splicing factors. Development of splice-switching oligonucleotide platforms to target SMN2 pre-mRNAs has resulted in the first FDA-approved treatment for SMA—Nusinersen/Spinraza. This ASO with a modified nucleotide backbone hybridizes with the intronic splice silencer N1 in SMN2 pre-mRNAs to promote exon 7 inclusion, leading to an increase in full-length SMN protein (Figure. 7). Nusinersen is administered by intrathecal injections as it is unable to cross the blood brain barrier. It has been shown to increase SMN protein levels both in vitro and in pre-clinical models of SMA. [17]

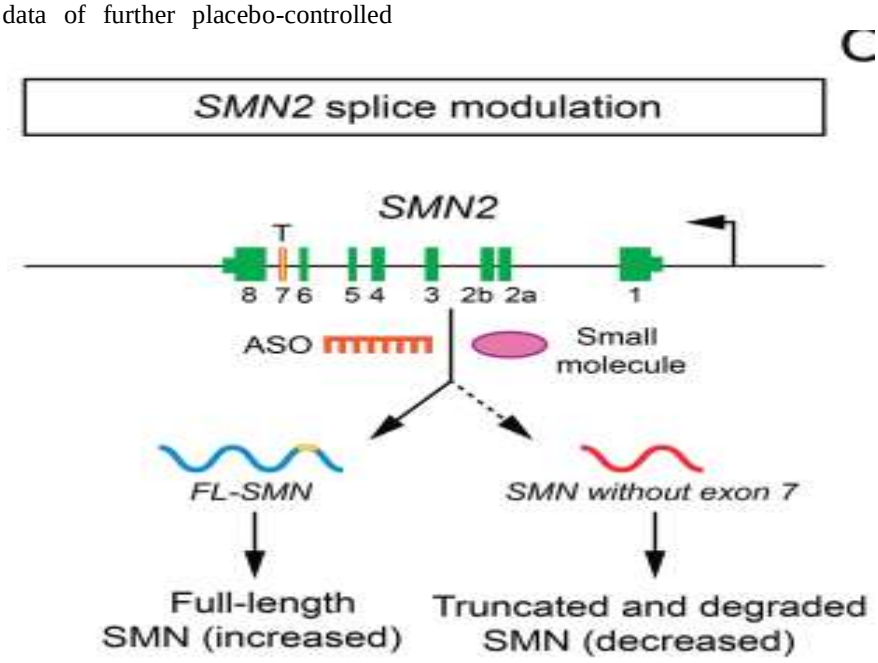

Figure7: SMN2 splice modulation.

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In 2011, a phase 1 trial of Nusinersen, demonstrated safety and effectiveness in SMA patients through delivery into the cerebrospinal fluid (CSF) space. The subsequent phase 3 placebo-controlled trial (ENDEAR) showed a significant improvement in motor function and survival in treated infants with type 1 SMA. The drug was approved by the Food and Drug Administration (FDA) in late December 2016. [16]

Nusinersenis a disease-modifying treatment approved for all patients with SMA. Nusinersen is a survival motor neuron-2 (SMN2) directed antisense oligonucleotide that enhances production of full-length survival motor neuron (SMN) protein and slows the progression of the disease. It is administered via intrathecal (IT) injection every 4 months after a series of loading doses. While repeated intrathecal injections are the standard approach to achieve adequate intrathecal distribution and targeting of the central nervous system (CNS), alternatives such as intrathecal catheter systems are being explored.[13]

However, besides a high price tag of $750,000 for the first year of treatment, questions about its long-term efficacy abound, and there are some restrictions to the use of Nusinersen. First, preclinical studies suggest a discrete time-window in neuromuscular development when increasing SMN levels are most effective. The data from human trials also support the importance of a therapeutic window for a SMN-augmented treatment. Unfortunately, SMA new born screening programs have not yet been extensively performed worldwide or even nationwide. On the other hand, patients with later-onset type 2 SMA showed significant motor improvement after treatment; however, whether the long-term effect will be seen when treatment is initiated in the later SMA phase with slow decline is still unclear. Second, because Nusinersen cannot penetrate the blood–brain barrier (BBB), beyond which the targeted rescuing MNs lie, there is unfortunately no practical alternative to periodic intrathecal administration. The risks of performing lumbar puncture in SMA patients include exacerbating respiratory compromise related to knee-to-chest flexion posture during the procedure, headache, and CSF leakage. Without modern imaging assistance, repeated intrathecal injections can present challenges in some chronic SMA patients with significant scoliosis. Third, the direct delivery of Nusinersen into the spine restricts SMN upregulation only at the CNS; however, there is emerging evidence that SMN also plays a vital role in peripheral tissues. Previous studies also demonstrated that peripheral SMN restoration compensates for its deficiency in the CNS and preserves MNs. However, because there is still no patient natural history available to validate the correlation between low SMN and the vulnerability of other organs beyond MNs, the systemic ASO delivery in a human trial is still under evaluation. [16]

GENE THERAPY FOR SMA: SMN1 GENE REPLACEMENT

Another approach that has shown success in treating SMA is gene replacement therapy. In this case, a wild-type copy of the SMN cDNA packaged in adeno-associated virus 9 vector (AAV9) is delivered intravenously (Fig. 8). AAVs are non-pathogenic, capable of crossing the blood brain barrier, and can efficiently transduce neurons. Following viral transduction, the SMN cDNA is maintained as a constitutively expressed episome, which offers long-term durable expression in terminally differentiated cells such as neurons after a single dose, but is diluted in mitotically active cells that might limit beneficial effects in non-neuronal tissues. The low rate of integration into the host genome reduces risk of oncogenesis. Avexis-101(scAAV9-SMN) (Avexis, Chicago, IL) uses double-stranded, self-complementary recombinant AAV vector (scAAV9) to deliver SMN cDNA leading to a rapid induction of SMN protein. This drug has shown marked improvements of survival and motor function in SMA mice in preclinical studies and efficacy in infantile SMA patients. The FDA recently granted the approval of Zolgensma (onasemnogene abeparvovec-xioi) to Avexis, Inc (Avexis, Inc, Chicago, IL) for the treatment of SMA patients less than two years of age. [17]

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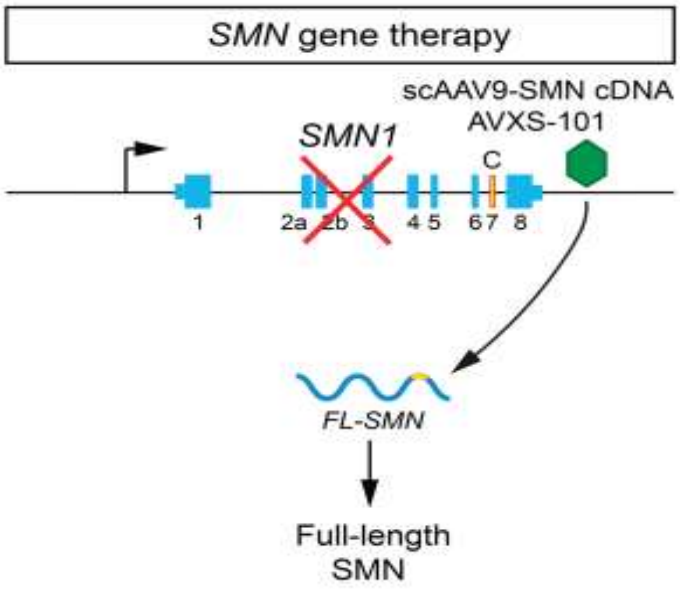

figure8: SMN gene therapy.

Zolgensma (onasemnogene abeparvovec-xioi) is a gene replacement therapy that uses a viral vector to deliver a functional copy of the SMN1 gene into neural cells. [13]. The self-complementary adeno-associated virus 9 (AAV9) was found to be the most promising gene-delivery vectors, because it is able to cross the BBB, and infected approximately 60% of MNs]. [16]Onasemnogene abeparvovec-xioi is administered as a one-time intravenous (IV) infusion and is only approved for the treatment of children less than 2 years of age because of current limitations of dosing (i.e. viral titres and increased likelihood of immune response) and the fact that this drug has only been tested for this age group.[13]

There are several advantages of scAAV9-based gene therapy that make it potentially superior to ASO SMN-augmentation therapy. First, scAAV9 gene therapy may require only a single intravenous infusion with a sustainable effect, whereas Nusinersen probably requires lifelong repetitive intrathecal treatment. Second, given that SMN protein is ubiquitously expressed, systemic intravenous delivery of the AAV-vector gene has the advantage of increasing SMN expression in other organs in the body. One of the notable concerns of AAV9-based gene therapy is the ubiquitous expression of SMN, leading to the nonspecific sequestration of essential RNAs and proteins through RNA–protein and protein–protein interactions, respectively. Furthermore, poor body-wide delivery of viral particles and likely immune response remains a concern for approaches based on gene replacement therapy[16]

The clinical trials have shown improvements in survival and respiratory and bulbar function and attainment of motor milestones, especially in children treated presymptomatically. Gene therapy vector dose is weight-dependent; the safety and efficacy of onasemnogene abeparvovec in a more heterogeneous population of older, heavier and/or symptomatic children receiving combination or sequential therapies is less well-defined and requires interrogation. [14]

Parental preference for a single IV injection and hopes for additional clinical benefits such as gains in function, reduction in fatigue and improved endurance were the major reasons for accessing onasemnogene abeparvovec.

The most common treatment-related adverse events were vomiting and elevated aminotransferase concentrations. Transient decreases in platelet counts were observed in all infants at approximately 7 days post onasemnogene abeparvovec with no active bleeding. Thrombotic microangiopathy (TMA) occurred in two infants formerly treated with Nusinersen.Both infants presented 1 week after onasemnogene abeparvovec infusionwith vomiting, transaminitis, thrombocytopaenia, haemolytic anaemia, and acute kidney injury. [14]

Standard guidelines for considering weaning and cessation of steroids is 4 weeks post–

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onasemnogene abeparvovec administration.However, based on our findings, suggest extending dosing, individualising the time and dose of therapy thereafter, dependent on laboratory parameters. [14]

BeforeAAV9 administration, children should be evaluated for underlying medical conditions, including severe or symptomatic liver disease, thrombocytopenia, or any other serious underlying medical conditions, that may heighten the risk of AAV9 therapy. Active infection may be a risk factor for developing thrombotic microangiopathy (TMA).In the STR1VE-EU study, respiratory infection was observed in a patient who died after treatment with onasemnogene abeparvovec. This patient's death indicates that viral illness can cause severe illness, even in individuals with treated SMA. This may be exacerbated for those who haverecently received gene therapy, because of corticosteroid treatment and potential adrenal insufficiency. Risk-benefit has to be carefully assessed before treatment. Counselling on possible adverse events is also required before dosing, and close clinical and laboratory monitoring is required in the weeks to months after treatment. Although gene therapy only requires a single administration, close follow-up and safety monitoring are essential [18]

Current prescribing information recommends liver function should be monitored for at least 3 months after onasemnogene abeparvovec infusion (weekly for the first month, and then at a minimum every other week for the second and third months, until results have normalized) [18]

ROLE OF PROPHYLACTIC PREDNISOLONE

SMA patients are treated with prophylactic prednisolone with the goal of attenuating serum aminotransferase elevations.Starting 1 day before onasemnogene abeparvovec infusion, systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight/day should be administered for a total of 30 days.For patients with unremarkable findings (normal clinical examination, total bilirubin, and prothrombin time, and ALT and AST concentrations belowtwo-times ULN), the corticosteroid dose should be tapered over the next 28 days (e.g., 2 weeks at 0.5 mg/kg/day and then 2 weeks at 0.25 mg/ kg/day). Steroid taper should not proceed faster than this recommended approach and may need to be longer and slower if more persistent abnormalities occur [18]

Another approach to target the SMN2 gene is by using small molecules. Bioavailable small molecules that also function to promote exon 7 inclusion in SMN2 mRNA have the advantage that they can be orally administered and have widespread tissue bioavailability. Two SMN-inducing small molecule therapies, Risdiplam (developed by Roche, Basel, Switzerland) and Branaplam (developed by Novartis, Basel, Switzerland), have proven to be as effective as ASOs and gene replacement in SMA mouse models and are being tested in ongoing clinical trials. [17]

RISDIPLAM

The most recent treatment approved by the FDA is Risdiplam, an orally administered, SMN2 splicing modifier for patients 2 months of age and older with SMA. The drug increases exon 7 inclusion and thus full-length SMN protein production from the SMN2 gene. [13]

The potential of distribution in both central and peripheral tissues makes Risdiplam a potent therapeutic agent for addressing SMA as a whole-body disease. Both trials in type 1 SMA patients (FIREFISH) and in types 2 and 3 patients (SUNFISH) demonstrated not only a significant increment of SMN protein in the blood but also an improvement of motor function with event-free survival. [16]

BRANAPLAM

Branaplam (LMI070) can interact with U1 snRNP to facilitate exon 7 inclusion of SMN2 transcript, and thereby increases SMN protein levels and improves phenotypes. An active phase 1/2 clinical trial of Branaplam is an open-label, first-in-human study with oral administration to evaluate the safety and efficacy in patients with type 1 SMA. The preliminary results showedsignificant improvement in the motor functions after 86 days of treatment. Five patients continued to improve after 127 days of treatment. [16]

CELECOXIB

Treatment with celecoxib, a cyclooxygenase 2 inhibitor, was shown to increase SMN in SMA cell and animal models. Celecoxib has several advantages in treating SMA, including the ability to cross the BBB and favourable safety profiles in humans. Celecoxib may serve as adjunctive therapy for SMA, particularly given the low safe doses required for SMN induction. [16]

QUINAZOLINE

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Blocking of decapping scavenger enzyme (DcpS) has been shown to increase FL-SMN2 transcript through upregulating SMN2 promoter activity. Quinazoline (Repligen or RG3039), a DcpS inhibitor, was demonstrated to increase SMN protein and survival in SMA mice. However, a phase 1b trial showed that even though RG3039 successfully blocked DcpS in patients' blood, the SMN protein level did not change significantly. Therefore, the pharmaceutic company concluded that RG3039 would be ineffective in SMA patients, and the further trial was halted. [16]

SMN PROTEIN STABILIZERS

Aminoglycoside antibiotics (from a class of FDA-approved drugs including tobramycin, geneticin, and amikacin) can mask premature stop codon mutations and promote read-through of exon 8, and thereby stabilize or increase the SMN level in patient fibroblasts. However, they have only shown in vivo efficacy, and the toxicity has yet to be tested in animal models of SMA. BBrm2 is a repurposed FDA-approved azithromycin acting on stop codon read-through, which was found to increase SMN in SMA patient cell lines and improve motor function and survival when intrathecally delivered in an SMA mouse model. Bortezomib is a ubiquitin proteasome inhibitor known to prevent SMN protein degradation. Bortezomib-treated animals had improved motor function, which was associated with reduced spinal cord and muscle pathology and improved neuromuscular junction size, but no change in survival. [16]

SMN-INDEPENDENT THERAPIES FOR SMA

For the patients with the chronic form of SMA with a substantial loss of MNs, it is more crucial to target the SMN-independent pathways disrupted downstream of SMN. Furthermore, emerging evidence has substantiated that SMA is a systemic disorder that goes beyond motor neurons. Identifying non-SMN targets to develop combinatorial therapeutic approaches is tempting because a comprehensive whole-lifespan approach to SMA therapy is required that includes both SMN-dependent and SMN-independent strategies that treat the CNS and periphery together [16]

NEUROPROTECTIVE AGENTS

Olesoxime (TRO19622) is a trophos cholesterol-oxime compound family of mitochondrial pore modulators with neuroprotective properties. Pre-clinical studies suggest that it improves the function and survival of neurons. A stabilized motor function at 24 months of treatment trial was shown in patients with types 2 and 3 SMA in phase 2 placebo-controlled. However, a subsequent follow-up study at 18 months did not demonstrate a significant clinical benefit.

Other potential neuroprotective agents, riluzole and gabapentin, have been investigated for their effects in treating SMA. Unfortunately, most of the results were not encouraging, or the studies were not adequate to show efficacy [16]

UPREGULATION OF MUSCLE GROWTH

Therapeutic approaches that do not directly target the genetic cause of SMA include the improvement of muscle mass and function. Two compounds are the most advanced: Myostatin-inhibitors and Fast Skeletal Muscle Troponin Activators (FSTA). Myostatin is a member of the TGF superfamily of growth factors that inhibits muscle over-growth and is primarily expressed in skeletal muscle. Myostatindeficient animals are known to have considerably increased muscle mass and strength, and the use of the myostatin-inhibitor SRK-015 in SMA-mice resulted in improved muscle mass and function.[12]

MYOSTATIN INHIBITORS

Muscleweakness is always prominent in SMA. Myostatin is a growth factor produced primarily in skeletal muscle cells to inhibit muscle growth. Theoretically, blocking the myostatin signalling pathway can induce increased muscle mass and consequently improve muscle strength and motor function. Follistatin is an endogenous antagonist of myostatin, and over-expression of recombinant Follistatin in SMA mouse muscle leads to increased skeletal muscle mass as well as survival. On the other hand, inhibition of activin receptor type IIB (ActRIIB) ligands can promote muscle growth, which suggests a potential therapy for neuromuscular disorders, including SMA. The systemic delivery of AAV-mediated soluble inhibitor of ActRIIB showed improvements in both muscle mass and muscle function in the SMA mouse model. [16]

SKELETAL MUSCLE TROPONIN ACTIVATOR: RELDESEMTIV

Reldesemtiv (CK-2127107) is a fast-skeletal muscle troponin activator which has been shown to improve muscle function and physical performance in SMA. Reldesemtiv was demonstrated to increase skeletal muscle force in response to nerve stimulation, associated with a calcium-sensitizing effect. With promising results

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demonstrating prolonged stamina and a modest improvement in pulmonary function, a double-blind phase 2 trial is ongoing to examine the efficacy of oral administration twice a day in non-type 1 SMA patients [16]

AGENTS TARGETING NEUROMUSCULAR JUNCTION, SYNAPSE, OR NEUROTRANSMITTER

Pyridostigmine is an anti-acetylcholinesterase drug approved for treating myasthenia gravis. Researchers believe that the medicine's ability to activate and strengthen muscles might benefit SMA patients. A placebo-controlled trial of pyridostigmine is ongoing to test the effects on muscle strength and fatigue in patients with types 2–4 SMA. 4-Aminopyridine (4-AP or Ampyra), a broad-spectrum inhibitor of potassium channels, is approved by the FDA for multiple sclerosis treatment. 4-AP was shown to improve the phenotypes of SMA in aDrosophila model, possibly through the pathway of motor circuits. A phase 2/3 clinical trial assessing the efficacy in walking ability and endurance of type 3 adult SMA patients was completed in 2017, and the results arepending. [16]

STEM CELL THERAPY

The potential of cell therapy in SMA is related to the ability of stem cells to provide support to endogenous degenerating MNs. Two currently available stem cell transplantation studies for SMA showed that primary neural stem cells injected into the spinal canal engrafted to the spinal cord, improved motor function, and extended survival. However, these results have only reflected benefits likely with trophic support but without evidence of functional cell replacement. Accurate validation of therapeutic impact and a precise definition of the mechanism of action is still pending. [16]

COMBINATION THERAPY FOR SMA

A combined approach using SMN-dependent ASO-inducing SMN2 exon inclusion and SMN-independent myostatin inhibition have shown a favourable result in an SMA animal model. Combined treatment with Zolgensma and Nusinersen has recently been investigated in a small group of patients, although the long-term benefit is still unclear. Zolgensma and Nusinersen have different mechanisms of action, so the drug-to-drug interaction is less likely. Nusinersen works by targeting an intron sequence to enhance exon 7 inclusion. However, a transferred gene of Zolgensma does not contain any introns, so its translation should not interfere with Nusinersen. Because thrombocytopenia has been reported as an adverse event in association with Nusinersen, caution is required when Zolgensma treatment is considered. Longer-term follow-up data, especially in the treatment of pre-symptomatic patients, should be accumulated to assess the efficacy and risks of combination therapy. [16]

OPTIMIZING SMA THERAPEUTICS.

Challenges remain for SMN inducing approaches in terms of optimizing drug timing, dosage, delivery route, distribution and uptake in vulnerable neuronal populations. The importance of targeting cells and tissues other than motor neurons remains unclear. In addition, long term durability and potential toxicities remain to bedefined. It is clear that while patients treated very early in disease can show markedimprovements, many patients haveonly modest responses. The institution of neonatal testing for SMA will increase the number of patients who receive therapy soon after birth. In addition, identification of biomarkers of disease progression and methods to quantify SMN levels in target tissues are keys for progress. Studies of combinatorial treatment that includes more than one SMN-inducing drug as well as SMN induction with SMN-independent strategies such as drugs to improve muscle growth and contractility are ongoing. [16]Patient-centered multidisciplinary care should continue after treatment to optimize outcomes for patients and families [18]

NEED FOR PRESYMPTOMATIC OR EARLY SYMPTOMATIC TREATMENT

Clinical studies have consistently demonstrated the benefits of early treatment initiation in SMA, before irreversible loss of motor neurons.Although the clinical benefits of early treatment in the presymptomatic phase are known, diagnostic delays occur. To expedite treatment initiation, the United States, Europe, Taiwan, Japan, and Australia, among other countries and regions, have introduced new born screening programs or pilot studies. Current guidelines recommend immediate treatment for all infants with two, three, or four copies of SMN2. Treating physicians should discuss timing of therapeutic initiation with families, highlighting treatment urgency given that motor neuron degeneration largely occurs in the first few months and rapid decreases in motor unit number estimation and maximum compound motor action potential amplitude occur within 2 postnatal months, demonstrating irreversible loss of motor units. Widespread adoption of new born screening will facilitate early SMA diagnosis and treatment

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initiation, which holds the potential to improve outcomes.[18]

II. CONCLUSION

Spinal muscular atrophy is a progressive, autosomal recessively inherited monogenic neurologic disease, the genetic cause of which is the absence of a functional survival motor neuron 1 (SMN 1) gene. SMN2 is a potent disease modifier for SMA, hence it represents the primary target for potential therapies. The two novel therapeutics using antisense oligonucleotides (ASOs) or virus-mediated gene therapy have a common objective, i.e., to increase the production of Survival Motor Neuron (SMN) protein in Motor Neurons and thereby improve motor function and survival. Since SMA is such a devastating disease, it is reasonable to assume that a unique therapeutic solution may not be sufficient. Zolgensma and Nusinersen combination is the most commonly investigated treatment approach.It is important to consider patient perspectives and expectations during SMA treatments development and discussions on treatment. Patient-centered multidisciplinary care should continue post treatment to optimize the therapeutic outcomes. It is also concluded that new born screening and an early initiation of treatment can bring miracles in the SMA treatment. Evidence based and research driven strategy need to be developed to personalize medicine, so that each individual patient may have access to the therapy that provides individual optimal therapeutic benefit.

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