Spinal Muscular Atrophy (SMA): Disease for the world's expensive therapy

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Abstract

The most frequent genetic cause of new born death is spinal muscular atrophy, a hereditary degenerativecondition of lower motor neurons characterised by increasing muscle weakening and atrophy. It is brought on by a drop in the "Survival of Motor Neuron" (SMN) protein level. Its autosomal recessive inheritance pattern, caused by mutations in the SMN1 gene on chromosome 5q13, is the outcome of these mutations. However, the SMN gene has a unique structure (an inverted duplication) that providesprospective treatment targets, unlike many other autosomal recessive illnesses. In the past four years, three new disease-modifying medications have been made available: Nusinersen, Onasemnogene Abeparvovec (Zolgensma) and Risdiplam. Although these drugs have shown to be safe and effective, further research is still needed to determine how long-term advantages will work. However, respiratory care and other supportive measures continue to play a crucial role in the management of spinal muscular atrophy. Newborn screening programmes are enabling earlier diagnosisand treatment as well as better results. A very modest quantity of full-length, functional SMN mRNA is produced by the SMN2 gene by alternative splicing in addition to a majority of truncated, unstable SMN messenger RNA (mRNA). A reliable predictive indicator of SMA clinical severity is the SMN2 gene copy number. Clinical therapyof SMA is helpful, but ongoing and upcoming studies aiming to raise SMN expression levels in motorneurons show significant promise.

Key Words: *SMA; Motor neurons; SMN1; SMN2; SMN gene; Zolgensma; Nusiresen; Risdiplam.*

Introduction:

A group of genetic disorders collectively known as "spinal muscular atrophy (SMA)" are characterized by the degeneration of anterior horn cells, which causes muscle atrophy and weakness and is linked to the degeneration of spinal and (in patients with the most severe cases) lower bulbar motorneurons.[1]

A homozygous deletion affecting exon 7 of the "survival of motor neuron" (SMN) gene at locus 5q13 causes the autosomal- recessive condition that causes more than 95% of instances of SMA. On each of the two copies of chromosome 5 that make up the SMN gene, SMN1, and SMN2, an inverted duplication is present. SMN2 and SMN1 vary from each other by five nucleotide alterations that do not alter the amino acids. Exon 7 of SMN2 is excluded from most transcripts by a crucial single nucleotide alteration in an exonic splice enhancer. As a result, the (SMN2) gene's duplication makes less functional SMN protein.[2]

The majority of people who have spinal muscular atrophy (SMA) have homozygous deletions of

the SMN1 gene, but they still have at least one copy of the SMN2 gene. The population-normally varying SMN2 gene copy number, the concentration of SMN protein, and the degree of illness are roughly correlated. Investigations on the function of the SMN protein are still ongoing. There also seem to be genes that modify, which may play additional functions in motor neuron function. In addition to decreased motor neurons, abnormalities of the neuromuscular junction (NMJ) have been seen in animal models of spinal muscular atrophy, and in the most seriously afflicted humans, aberrant muscle growth has also been reported.[3]

Based on the age of onset and the highest level of motor function attained, clinical aspects of SMA may be divided into four basic phenotypes. Although there is no known treatment for SMA, knowledge of the disease's molecular genetics has sparked the creation of many different prospective.[4] therapeutic strategies and preclinical models. These treatment modalities have just started early phase clinical studies, which has sparked a lot of interest in the SMA community. Focus has been placed on understanding the natural history of this condition, early diagnosis, and clinical intervention, along with the development of an active pharmaceutical pipeline. Clinical standards of care have been developed as a result of this. The most severe form of SMA (type 1) has received a lot of attention because of its unique natural history, which is marked by a fast loss of motor and respiratory function in the first year of life. Studies have demonstrated that early use of noninvasive ventilatory support and enteral feeding can increase survival in these infants beyond the first year by 70% or more. In addition, Studies on the natural history of the less severe varieties of SMA (types 2 and 3) have revealed a minimal decline in motor and respiratory function over the course of a year.[5]

In order to increase the expression of SMN2 or have an impact on other modifying genes to create more functional SMN protein, pharmacological substances are being developed as potential therapeutic agents. In addition to employing stem cells to replace deteriorated motor neurons, researchers are attempting to accomplish this aim using gene therapy, antisense oligonucleotides, and other methods. Recommendations in a consensus statement for the multidisciplinary supportive treatment of people with spinal muscular atrophy have helped many patients survive longer and live better lives during the past ten years.

Epidemiology-

According to estimates, the prevalence of spinal muscular atrophy ranges from 1 in 6000 to 10,000 live births [2-4], or 7.8 to 10 per 100,000 live births, with spinal muscular atrophy type I expected to occur in 4.1 live births per 100,000. According to 2005 research from Cuba, type I spinal muscular atrophy is less common overall (3.53 per 100,000 live births) and more prevalent among people of African descent (0.89–0.93 per 100,000 live births) . Lower rates have also been observed, however, the estimated carrier frequency for SMN1 gene alterations was 1:38–1:50. In order to ascertain the carrier frequency in various ethnic groups in North America, an epidemiologic investigation was conducted in 2009. Caucasians had the greatest carrier frequency (1 in 37, or 2.7%), whereas Hispanics had the lowest carrier frequency (1 in 125, or 0.8%). African Americans (1 in 56,or 1.8%) and Ashkenazi Jews (1 in 46, or 2.2%) were both of intermediate frequency. Furthermore, the prevalence of spinal muscular atrophy is lower than anticipated despite the high carrier frequency.

A recent study in Japan (as of December 2017) shows that the actual number of SMA patients recorded was 658, and the percentage of genetic testing was 79.5 percent. The estimated patient population was 1,478 (95% confidence interval (CI), 1,122-1,834), with prevalence estimates of

1.17 (95% CI, 0.89-1.45) per 100,000 and 0.51 (95% CI, 0.32-0.71) per 10,000 live births, respectively. Instances with a confirmed diagnosis by genetic testing have incidence rates of 5q-SMA by clinical type of 0.27 (95 percent confidence interval, 0.17-0.38) an (95 percent confidence interval, 0.04- 0.11) per 10,000 live births for types 1 and 2, respectively. We discovered that 88 cases (20%) and 363 cases (82.7%), respectively, occurred in children under the age of two years and two months.[6]

Clinical Manifestation & Characteristics-[7]

Muscle withering and weakening are the main clinical signs of SMA. As in NP7, weakness is often symmetrical, with proximal muscle groups being more afflicted than distal ones. In the past 125 years, reports describing the clinical manifestations and wide spectrum of clinical severity have all identified and emphasized the seminal pathology as anterior horn cell degeneration, as well as the relevant clinical features of symmetric, proximal predominant extremity weakness that also affects axial, intercostal, and bulbar musculature. The Muscular Dystrophy Association-sponsored International Consortium on Spinal Muscular Atrophy in 1991 finally codified the many identified traits into a categorization scheme.

Although homozygous mutations in the SMN1 gene are the most common symptom of spinal muscular atrophy, there are three main clinical subtypes that may be distinguished based on the severity of the phenotypic variation, based on the age of onset, and the maximum degree of motor function (i.e., sitting or standing). Later additions included a type 4 for adult-onset instances, a type 0 for patients with prenatal onset who died within weeks, and a division of the type 3 group by age of onset. Even though there are variations in severity within a single type and up to 25% of patients cannot be accurately classified, this system is still effective in the genetic age and offers helpful clinical and prognostic data. The detailed classification of types is as follows-

- **SMA Type 0 (Outliers):**

At each extreme of the phenotypic continuum, a few cases stand out as outliers. Neonatal patients who have extreme weakness and significant hypotonia, likely of prenatal start, and who have a history of diminished foetal movements are referred to as having spinal muscular atrophy "type 0." Most people never reach any motor milestones. Areflexia, facial diplegia, atrial septal abnormalities, and joint contractures are other findings. Respiratory failure is a significant cause of morbidity and death in spinal muscular atrophy type 0, necessitating non-invasive ventilation and endotracheal intubation at delivery. Life expectancy is decreased, and the majority cannot live past the age of six months.

Three newborn siblings with deletions in the area of the chromosome linked to spinal muscular atrophy were reported to have congenital axonal neuropathy affecting the motor and sensory nerves, along with facial paralysis, joint contractures, ophthalmoplegia, and respiratory failure at birth. Most people who have SMN1 homozygous exon 7 deletions have the type 0 and type IV phenotypes of spinal muscular atrophy.

- **SMA Type I (Werdnig-Hoffman disease):**

Werdnig-Hoffman's illness, commonly known as type 1 SMA, affects infants and causes hypotonia, poor head control, and absent or diminished tendon reflexes before the age of six months. By definition, kids never develop the capacity to sit independently. When lying down, people with extreme hypotonia may adopt a "frog- leg" posture and have minimal to non- existent head control. The intercostal muscles are weak, and the diaphragm is relatively spared, which results in a bell- shaped chest and a paradoxical breathing pattern frequently referred to as "belly breathing." Tongue and swallowing weakness, as well as tongue fasciculations, are frequently found

in infants with type 1 SMA. Although this does not often show up early in the course of the disease, facial weakness does emerge. These newborn run the danger of aspiration and failing to thrive as their tongue and pharyngeal muscles deteriorate. Before the age of two, type 1 SMA infants typically have respiratory failure. Infants with type 1 SMA are frequently awake, attentive, and bright at the time of diagnosis, despite the severe weakness.

Recent research suggests that severe type I spinal muscular atrophy, in addition to affecting spinal cord motor neurons, can also affect other organs, such as the brain, heart, blood vessels, and even sensory nerves. Recent post-mortem investigations have shown growing evidence of congenital cardiac diseases, the most prevalent of which is hypoplastic left heart syndrome, in patients with severe spinal muscular atrophy. There is no indication of dilative or congestive cardiomyopathy in patients with molecularly proven spinal muscular atrophy, and Brady arrhythmias are the only known atrioventricular conduction defects. Studies using several mouse models have shown that vasculopathy might be a symptom of severe SMN protein depletion. This vasculopathy is considered to be mostly caused by autonomic dysfunction. In a biopsy analysis by Rudnik-Schöneborn et al. of 19 patients with juvenile spinal muscular atrophy, patients with severe spinal muscular atrophy type I could exhibit both clinical and morphologic involvement of their sensory nerves. In contrast, patients with spinal muscular atrophy types II and III did not exhibit any sensory involvement.

- **SMA Type II (Intermediate SMA):**

Patients with type II spinal muscular atrophy, also known as intermediate spinal muscular atrophy, can occasionally sit alone but never walk. They have hypotonia, areflexia, and increasing proximal weakness that mostly affects the legs rather than the arms. Along with intercostal muscular weakness, individuals also experience developing scoliosis, which as they age causes severe restrictive lung disease. Their hands tremble or have polyminimyoclonus. High functioning, nonambulatory kids have a higher relative fat mass index than normal children, putting them at risk of weight gain even if their body mass index may be modest (at the third percentile or below, compared with normal children). Cognitive functioning is feasible, and verbal IQ may be above average. Despite the possibility of living into their third decade, respiratory compromise shortens life expectancy.

- **SMA Type III (Kugelberg-Welander disease):**

At some time, people with Kugelberg- Welander disease, also known as type III spinal muscular atrophy, can walk ("walkers"). They develop little to no respiratory muscle weakness or scoliosis, but they do show gradual proximal weakness that eventually affects the legs more than the arms and may require a wheelchair. They could have hand tremors or polyminimyoclonus. Their life expectancy is not appreciably less than that of the general population. Type III also includes its subtypes IIIa & IIIb.

- **SMA Type IV (Adult SMA):**

SMA type 4 is categorized as being on the moderate end of the spectrum. They have the mildest type of SMA and account for less than 5% of cases. These people are ambulatory and comparable to type 3, but the beginning occurs in maturity and is frequently thought to occur at or after the age of 30, however it can also occur in children.

Because, as previously indicated, patients within these categories display phenotypes of varying severity, there has been considerable discussion on the proper classification of patients into these three kinds of spinal muscular atrophy. To more precisely represent the clinical spectrum of these individuals, a categorization system based on a continuous rather than discrete variable was

developed (e.g.- spinal muscular atrophy "type 1.8" in the case of a less seriously afflicted type I patient).

SMA type	Common Name	Age of Onset	Highest Achieved Motor Function	Life Span (Expectancy)	Other Symptoms	SMN 2 gene
Type 0	Congenital SMA, Prenatal type	Prenatal/Birth	In Majority Unable to achieve Motor functions (Respiratory supported)	Less than 6 months	Born with severe weakness, Extreme Hypotonia, Facial paralysis, Areflexia (Reflex absent), etc.	1
Type I	Werdnig-Hoffman disease, severe SMA "or'' Non-sitters	0-6 Mo.	Never Sits (Support required)	Less than 2Yrs (without Respiratory support)	'FrogLeg' Posture, respiratory failure, hypotonia, Areflexia Dysphagia, Tongue twitching, etc.	2-3
Type II	Intermediate SMA "or" sitters	6-18 Mo.	Individually Sits but Never Stand or walk	In the 25-year age group, approx. 70% are alive	Weakness(Proximal), Hand tremor (Postural), Scoliosis, Hyporeflexia, etc.	2-4
Type III	Kugelberg-Welander disease, mild SMA "or" walkers	More than 18 Mo.	Walk & stand alone	Nearly Normal	Hand tremor may occurs, Muscular dystrophy-like	3-5
Type IIIa	"	18 Mo.- 3 Yrs.	Walk & stand	Nearly Normal	Hand tremor may occurs,	3-5

			alone		Muscular dystrophy-like	
Type IIIb	”	More than 3Yrs.	Walk & stand alone	Nearly Normal	Hand tremor may occurs, Muscular dystrophy-like	4
Type IV	Adult SMA	More than 21Yrs.	Walk & stand alone (Normal)	Normal	Normal	4-8
Abbreviations	SMA- spinal muscular atrophy SMN- survival motor neuron Mo.- months; Yrs.- years - Without the use of disease-modifying treatments or mechanical ventilation.					

Table 1- Classification of SMA & its Characteristics.

Info: There are also the non-5q13- associated spinal muscular atrophies, which comprise a heterogeneous group of motor neuron diseases affected by mutations in a variety of different genes, e.g., X-linked and autosomal dominant or recessive spinal muscular atrophies, distal spinal muscular atrophies or distal hereditary motor neuropathies, spinal muscular atrophy with respiratory complications ("spinal muscular atrophy respiratory distress" or "diaphragmatic spinal muscular atrophy," resulting from mutations in the IGHMBP2 gene on chromosome 11q), and pontocerebellar hypoplasia with infantile spinal muscular atrophy.

Molecular genetic & mechanism-[8]

SMA presented a conundrum in terms of severity before the genetic etiology was discovered: how can a single gene defect cause such a wide range of clinical severity? The answer to this conundrum began with the Melki laboratory's 1995 discovery that a homozygous deletion in the SMN1 gene on chromosome 5q13.26 is the root cause of 95% of cases of SMA, regardless of type. Each human SMN allele has two distinct versions of the gene: a telomeric form (SMN1) and a centromeric form (SMN2). Full-length messenger RNA (mRNA) transcripts encoding the SMN protein are generated during transcription of the SMN1 gene.

The SMA gene:

All three types of spinal muscular atrophy map to chromosome 5q11.1–13.3, according to linkage analysis studies. The SMN (survival of motor neuron) gene, which was lost or interrupted in 98.6% of the patients in Lefebvre et al.'s group, was discovered in this area in 1995. This region has a complicated structure that includes a sizable inverted duplicate of a 500 kb fragment. The SMN1 gene, which is older in evolution and is present in this duplication, is located in the telomeric section of the area, while the SMN2 gene, a duplication of SMN1 that varies from SMN1 by only five nucleotides, is located in the centromeric region. A C-to-T transition in an exonic splicing enhancer found in exon 7 of SMN2 is the key distinction between SMN1 and SMN2. Exon 7 is often spliced out of or omitted from most SMN2 messenger RNA transcripts despite the fact that this modification is translationally silent (i.e., it does not alter the amino acid sequence).

95–98% of those who have spinal muscular atrophy have telomeric SMN1 gene deletions. The remaining individuals have minute intragenic changes or have undergone SMN1 to SMN2 gene conversions. The breakage of exon 7 in the latter situation causes SMN1 to become SMN2 as a

result of a frameshift or point mutation of SMN1. Because of the instability of this area of chromosome 5, which contains not only the inverted repeat of SMN1 and SMN2, but also nearby low copy number repeats, de novo mutations happen at a rate of around 2% (which is relatively high). Normal people differ in the number of copies of SMN2 on chromosome 5, and 10- 15% of people have no copies of SMN2. A direct relationship between SMN2 copy number and phenotypic severity was found in patients with spinal muscular atrophy. According to Feldkotter et al research's from 2002, SMN2 was present in one or two copies in 80% of the patients in their series with type I spinal muscular atrophy, three or more copies in 82% of those with type II, and three or more copies in 96% of those with type III. However, a patient with one copy of SMN2 is often more likely to have severe type 0 or type I spinal muscular atrophy. Unaffected family members with homozygous deletions of SMN1 and five copies of SMN2 have been described. This is intriguing because it suggests that the SMN2 copy number cannot be the only variable modifying disease severity. Some individuals with type III spinal muscular atrophy also have five copies of SMN2.

In asymptomatic SMN1-deleted females who carried the same number of SMN2 copies as their afflicted siblings, a greater expression of plastin 3 was also discovered as a sex-specific protective modulator of spinal muscular atrophy. However, a later study found that the expression of the gene was highest in postpubertal females with spinal muscular atrophy type III, intermediate in spinal muscular atrophy type II, and lowest in spinal muscular atrophy type I, underscoring an association with disease severity. Plasmin 3 may also be an age-, puberty-, or sex-specific modifier. Although there is often an inverse relationship between the amount of SMN protein and the severity of the disease, this relationship does not appear to be as strong as that between SMN2 copy number and phenotypic.

Diagnosis: Genetic-[9]

With targeted mutation analysis based on polymerase chain reaction and an exon 7- digesting restriction enzyme, spinal muscular atrophy may be genetically tested. A band won't be seen on the gel if SMN1 exon 7 is homozygously deleted, which happens in 95–98% of patients. In this case, there won't be any restriction fragments, DNA won't be amplified, and there won't be any restriction fragments. A lighter band will be visible if a person is a carrier (i.e., a heterozygous deletion). Many DNA diagnostic laboratories use multiplex ligation probe amplification for deletion investigations of the SMN1 gene's exon 7 in putative probands and carriers. However, this sequencing analysis cannot identify exonic deletions or duplications, nor can it tell if the point mutation is in the SMN1 gene or the SMN2 gene (if one of these genes is not deleted). The discovery of a previously reported mutation confirms its pathogenicity and placement in the SMN1 gene since a few point mutations were fortunately found in several patients with spinal muscular atrophy.

Using a polymerase chain reaction-based dosage assay known as "SMN gene dose analysis," carrier testing is practical and reliable in parents of patients with homozygous exon 7 deletions or compound heterozygosity. Point mutations in nondeletion carriers will be found by the sequencing of the SMN gene. Rarely, carriers (sometimes known as "2 + 0 carriers") may show two copies of SMN1 on one chromosome. The spinal muscular atrophy dose carrier test will give falsely normal results in "2 + 0 carriers," and one may need to use other strategies, like family linkage analysis, to find the disease- associated genotype in families where a deletion mutation was passed down more than once from a parent with two copies of the SMN1 gene. One of the parents might not be a carrier because de novo mutations occur in 2% of individuals with spinal muscular atrophy.

New born screening-

The possibility of birth screening for spinal muscular atrophy has drawn a lot of attention since the best moment to begin treatment would come before the beginning loss of motor neurons, and new born screening could assist identify individuals who are pre symptomatic. Swoboda et al. conducted a prospective study in infants with type I spinal muscular atrophy who had been prenatally diagnosed, and they discovered electrophysiologic evidence of precipitous denervation (assessed with serial measurements of compound motor action potential amplitude and motor unit number estimation) that was associated with the initial onset of signs or decline in function in these young infants, indicating that motor neuron loss occurs very early. Should a treatment option become available, this discovery lends more evidence to the potential value of new born screening in identifying individuals before their time of maximum motor neuron loss.

Other tests-[10]

Serum creatine kinase levels in persons with spinal muscular atrophy may be two- to four- to ten-fold higher than normal. Studies on nerve conduction show normal sensory potentials, but they may also show reduced compound motor action potential amplitudes. In type II and type III patients, needle electromyograms show a neurogenic pattern with high amplitude and motor unit potentials of extended duration with a diminished recruitment pattern. In type I patients, needle electromyograms show denervation alterations but may not show signs of reinnervation because there may not have been enough SMN protein or time for reinnervation to take place.

Muscle biopsies in all types of spinal muscular atrophy demonstrate a neurogenic pattern, with grouped atrophy. For the same reasons as previously stated, this pattern is less consistently observed in patients with type I. Although electromyograms are still occasionally used to diagnose spinal muscular atrophy in unusual instances, muscle biopsy is now effectively worthless.

Clinical Care & Therapeutic Approaches-

Clinical Care-[11]

The comprehensive approach to therapy is extremely beneficial for patients with spinal muscular atrophy and their families. Practitioners from the fields of neurology, neuromuscular medicine, orthopaedics, physical therapy, occupational therapy, pulmonology, nutrition, and gastrointestinal are involved in this strategy. The early participation of paediatric advanced care or a palliative care team can offer parents support and guidance in making decisions according with their values and help enhance their child's quality of life for severely afflicted kids with type I spinal muscular atrophy. In 2007, a Multidisciplinary team released a Statement for Standard of Care in SMA-

- Gastrointestinal:

  Patients with type I spinal muscular atrophy get fatigued when eating, which can result in aspiration and failure to thrive along with recurring respiratory infections. Silent gastric reflux, which can lead to aspiration, is believed to occur often in patients with spinal muscular atrophy. In a short retrospective research, Durkin et al. found an association between early laparoscopic Nissen fundoplication and gastrostomy and improved nutritional status and maybe a tendency toward fewer long-term aspiration occurrences in patients with type I spinal muscular atrophy. Last but not least, individuals with spinal muscular atrophy run the risk of constipation, which, if severe (particularly in young individuals with type I), can exacerbate respiratory symptoms or even reflux.

- Nutrition:

  Infants with type I spinal muscular atrophy and certain severely afflicted type II patients sometimes exhibit failure to thrive or growth failure. Nevertheless, despite the fact that many type II patients show a body mass index that is "normal" (sometimes as low as the third percentile for healthy children of their age), they may really have too much fat mass in comparison to their muscle mass. Compared to both low-functioning non-ambulatory (Hammersmith score 12) and ambulatory patients, clinically high-functioning, non-ambulatory individuals with spinal muscular atrophy (Hammersmith score 12) were more likely to be obese. These patients are at risk of gaining weight as a result. For some kids and teenagers with type 2 SMA, malnutrition—a issue brought on by reduced oral intake—can be sneaky. It is best to avoid undereating and fasting since these actions can lead to a loss of muscle mass and subsequently reduced performance. Each kid should be assessed individually by a dietitian during routine visits with the aim of preserving the development curve and avoiding inadequate or excessive intake in order to treat these issues. It's important to have enough calcium and vitamin D because as people age, their bone mineral density tends to decline.

- Pulmonary:

  The main cause of death in persons with types I and II spinal muscular atrophy is respiratory failure. With somewhat maintained diaphragm strength and weak intercostal muscles, infants with type I spinal muscular atrophy might have underdeveloped lungs, pectus excavatum, and bell-shaped chests. Hypoventilation in the midst of sleep is brought on subtly by restrictive lung disease. The initial indication of respiratory muscle weakness in neuromuscular diseases is frequently sleep-disordered breathing.

  O'Hagen et al. reviewed 143 type I patients registered in the International Spinal Muscular Atrophy Registry and found that those born between 1995 and 2006 had significantly higher survival rates compared to those born between 1980 and 1994, with a 70% lower risk of passing away over the course of a mean follow-up of 49.9 months. Increased use of ventilation (invasive and non- invasive, i.e., bilevel positive airway pressure or BI-PAP), mechanical cough assist devices, and gastrostomy feeding had a substantial negative impact on survival.

  When BI-PAP is used correctly, with the appropriate pressure changes and mask positioning, there are no noticeable negative effects on the patient's hemodynamics. Patients who also have respiratory muscle weakness and spinal muscular atrophy have weak coughs that make it difficult for them to empty their airways of secretions. Due to their vulnerability, they are more susceptible to repeated infections and hypoxemia from mucus plugging (particularly during periods of severe sickness). Assisted airway clearing techniques should be performed, and patients who are at risk for mucus clogging should be monitored with nocturnal oximetry during acute infections. Due to the possibility of pneumonia, these patients should also have a low tolerance for the use of antibiotics during acute infections, with regular Pulmonologist check-up.

- Muscoskeletal & Orthopedic:

  Numerous musculoskeletal problems are predisposed to by weakness and restricted motion. Contractures are frequent in nonambulatory SMA patients, and regular stretching and bracing regimens to maintain flexibility and avoid contractures are the key therapeutic objectives. Patients who have spinal muscular atrophy of types II and III frequently get fractures. The most frequent fracture sites are the distal femur, lower leg, ankle, and upper arm. Most fractures are amenable to conservative treatment. Nearly of SMA patients who are nonambulant have scoliosis. Scoliosis results in chest cage abnormalities that limit breathing if left untreated. The preferred therapies for scoliosis include spinal fusion and bracing, however there is no universal agreement on whether these methods are effective. Through the use of exercises like swimming, aquatic therapy, and adapted sports, physical therapy may help patients achieve their highest levels of endurance, fitness, and safety.

Therapeutic Approaches:[12]

- ❖ GENE THERAPY-

  The replacement of the SMN1 gene, the disorder's primary cause, may be the most straightforward method of SMA treatment. A significant initial step in this area was made by Foust and colleagues, who used a self-complementary adeno-associated viral vector, serotype 9 (scAAV9), to successfully rescue a mouse model of severe SMA. The chosen agent for monogenic illnesses getting human gene therapy has been adeno-associated virus (AAV). AAV is a nonpathogenic virus that may produce transgenes for a long time without integrating into the host genome and with low innate immune response activation.

  15 babies with SMA, aged 1 to 8 months, participated in a crucial clinical research to assess the efficacy of gene therapy using AVXS-101. The SMA type I phenotype was predicted by the presence of 2 copies of SMN2.

  Compared to only 8% of historical controls, gene therapy allowed all 15 treated people to survive without a ventilator for more than 20 months. The motor function of every patient who received treatment also improved. 11 of the 12 patients in the higher-dose group could sit on their own, whereas just two could walk by themselves. Only the oldest patient in the experiment who had received treatment couldn't talk and safely swallow. Onasemnogene abeparvovec-xioi, the commercial version of AVXS-101(Zolgensma) was approved by the FDA in 2019 as a consequence of these findings. The FDA has given its permission for the treatment of kids up to age 2. A slightly different licencing process in Europe permits treatment of any infants weighing under 21 kg, regardless of age.

  The immunogenicity of the viral vectors and hepatotoxicity associated with the anticipated hepatic clearance of AAV are important safety factors in gene therapy. In preclinical and clinical investigations of gene therapy for SMA and other reasons, the latter has been shown. Patients with SMA receiving gene therapy frequently experience asymptomatic thrombocytopenia and elevated serum transaminases, with the latter occurring more frequently in older adolescents. Patients who have baseline antibodies against AAV9 are not

included due to worries about the immune system's reaction to the therapy. Prednisolone 1 mg/kg is administered to all patients beginning the day of gene transfer and continuing for at least 30 days, and perhaps longer, if transaminase increases remain.

Onasemnogene abeparvovec-xioi (Zolgensma) was approved by the FDA, but there are still many unanswered issues about the best patients to treat, how to administer the medication, and its long-term consequences. Given that dosage is weight-based, the greater dosages that would be necessary for older individuals raise questions regarding systemic toxicity. Because of this, a clinical trial (NCT03381729) is being conducted to assess the effectiveness of intrathecal injection in these individuals. Unexpectedly, intrathecal treatment in nonhuman primates revealed indications of dorsal root ganglion toxicity, correlating with prior findings with highdose intravenous dosing. The intrathecal clinical trial was halted until this toxicity is examined even though this has not been seen in humans.

The possibility of long-term toxicity associated with over-expression is brought up by the restoration of SMN expression by gene therapy as opposed to SMN2 splicing. The virally transmitted SMN transgene is not susceptible to the same regulatory processes as SMN1 and SMN2 because it is not driven by the same endogenous promoter. The time frame for the transgene's expression is a related query. It is thought that gene therapy for SMA will have long-lasting effects since motor neurons continue to function throughout an individual's lifetime. Without the necessity for ongoing breathing or the loss of previously accomplished milestones, all patients are living. In a recent publication on a porcine model of SMA, researchers were able to show that gene therapy given to piglets while they were exhibiting symptoms was advantageous.[14] It is noteworthy that overall survival, ventilator-free survival, and achievement of motor milestones were all significantly higher in the pivotal trial of AVXS-101 than in the ENDEAR trial of Nusinersen in a similar age group, despite there being no head-to-head trials comparing Nusinersen, Risdiplam, and gene therapy to date. Therefore, combining several agents, especially those with various modes of action, may result in further benefits. Few individuals who underwent gene therapy also got or kept taking Nusinersen or Risdiplam. This implies that the method is secure, but its long-term advantages have not yet been established. If there are any further benefits to be gained in patients who have already had gene therapy, they may be determined by the results of an ongoing open-label research of Risdiplam in patients who have already received treatment with other drugs (JEWELFISH, NCT03032172). Now that participants in a Nusinersen extension trial (SHINE, NCT02594124) are also qualified for open-label Risdiplam therapy, it may be possible to combine two medications that affect SMN2 splicing.[15,16-44]

Info	ZOLGENSMA	RISDIPLAM	NUSINERSEN
category	AAV-delivered gene therapy	Small molecule	Antisense oligonucleotide

MoA	Delivers a functional SMN transgene	Enhancing splicing of SMN2 to full-length SMN protein	Enhancing splicing of SMN2 to full-length SMN protein
Route of administration	I.V.	Oral	intra-thecal
Duration	Single dose	Daily	4 loading doses in the first 2 mnths, thereafter in every 4 Mnths[20]
Age ranges (FDA-approved)	Less than 2Yrs.	More than 2mnths.	All age group
Treatment limitations	Baseline Presence of AAV9 antibodies	Drug interactions	Inability to undergo lumbar puncture
Baseline evaluation	LFT, platelet count, trop-I, AAV9 antibody titer, prednisolone treatment for 30 days	-	Platelet count, urinalysis, coagulation studies
ADRs/Events	Acute liver injury, transaminitis, troponemia, thrombocytopenia	Fever, diarrhoea, rash	Thrombocytopenia, lumbar puncture complications, proteinuria
Vitals Monitoring	LFT, platelet count, trop-I		Platelet count, coagulation studies, urinalysis
Abbreviations- MoA: Mechanism of Action FDA: Food & Drug Administration AAV: Adeno-associated virus LFT: Liver function test			

Table 2- various Gene therapies.

Other treatments-[17,18]

SMN2 gene-upregulating substances that encourage the inclusion of exon 7.

Histone deacetylase inhibitors were the subject of substantial research as possible treatments for spinal muscular atrophy. It has been shown that the histone- deacetylase inhibitor phenylbutyrate raises the amounts of full-length SMN messenger RNA, SMN protein, and nuclear gems in vitro in fibroblast cells from type I, II, and III patients. Other pilot trials found that oral phenylbutyrate therapy improved the Hammersmith Functional Motor Scale and enhanced SMN gene expression in peripheral leukocytes.

LBH589 (hydroxamic acid), a different histone deacetylase inhibitor that is currently widely utilised in cancer clinical trials, might be a strong contender for the treatment of spinal muscular atrophy. In fibroblast cultures from individuals with spinal muscular atrophy, it causes a 10-fold increase in SMN levels, a two- to three-fold increase in full-length SMN2, and a noticeable increase in the number of gems. Even in fibroblasts from spinal muscular atrophy that were resistant to valproate, LBH589 was found to be active. Aminoglycosides may encourage the stop codon in exon 8 to be read through, stabilising the SMN protein and offering a different strategy to raise SMN protein levels in fibroblasts from patients. Heier and DiDonato administered the aminoglycoside geneticin (G418) to mice with spinal muscular atrophy, which improved motor function and led to higher levels of the SMN protein. Unfortunately, the animals experienced severe toxicity from this medication.

A signalling molecule called myostatin prevents the creation of new muscle. A monoclonal antibody that targets myostatin is SRK-015. Following therapy to restore SMN protein expression, it was discovered that muscle mass and strength increased in a mouse model of SMA. This implies a possible role for SRK-015 as an adjuvant therapy for SMA, and a phase 2 clinical study (TOPAZ, NCT03921528) is now assessing the drug's effectiveness. A phase 1 study is also examining the myostatin inhibitor BIIB 110 (ALG 801).

Fast skeletal muscle troponin activation is an alternative strategy to improve skeletal muscle function in SMA. 76 These medications are designed to increase exercise tolerance and postpone the onset of muscle tiredness. A troponin activator called tirasemtiv has been studied in the past to treat amyotrophic lateral sclerosis. The drug's poor tolerability may have contributed to its inability to show benefit in adults with amyotrophic lateral sclerosis. Reldesemtiv (CK2127107) is a second-generation medication that has improved tolerability and greater efficacy but does not penetrate the blood-brain barrier. Reldesemtiv was studied in a phase 2 study for SMA types II to IV, with the higher dosage potentially improving respiratory function and the 6-minute walk test compared to placebo.[21]

Another substance that has been looked into for its potential to increase endurance in SMA is albuterol (salbutamol). Albuterol is used to treat some congenital myasthenic disorders and is known to improve neuromuscular transmission. Numerous small open-label trials have revealed that albuterol may improve type II and type III SMA patients' motor and respiratory performance. Albuterol produced more SMN protein expression over placebo in the one randomised controlled study, along with a small improvement in performance on the 6-minute walk test, which did not achieve statistical significance. An intronic splicing suppressor element was constructed to be blocked by antisense oligonucleotides, which thus prevents exon 7 from being skipped. In mice models with spinal muscular atrophy, antisense oligonucleotides delivered intracerebroventricularly on a regular basis have been shown to enhance the motor phenotype.[24]

Another team created bifunctional RNAs that increased the quantity of full-length SMN in patients' fibroblasts by inhibiting an intronic repressor and attracting a serine/arginine-rich protein to the crucial exonic splice enhancer in exon 7.[23,25]

Conclusion-

There is no proven cure for the hereditary, persistent motor neuron illness known as spinal

muscular atrophy. However, there is reason for hope because the field is dynamic and we are learning more and more about the molecular genetics and aetiology of spinal muscular atrophy. Through the use of already-approved medications, the discovery of novel agents through high-throughput screening, or the creation of novel pharmaceutical substances, several organisations are actively investigating pharmacologic therapies.

Clinicians and academics are collaborating to plan multicenter studies and choose the most effective outcome metrics. The remarkable preclinical outcomes in SMA model systems have also sparked unprecedented worldwide collaboration between doctors, scientists, government, business, and volunteer groups to create the standards required for clinical trial preparedness.

Researchers are now able to successfully screen potential therapies in vitro, test them in precise animal models, and then advance promising agents to clinical trials in patients identified in an early or possibly presymptomatic stage of the disease. This is possible as a result of the remarkable progress made over the past 20 years in understanding the molecular pathogenesis of this disease. Under the direction of the US Food and Drug Administration and other regulatory authorities, it will be a tough task to select and progress the most promising medicines ahead to clinical trials in an effective, timely, and safe way.

Even while gene therapy significantly changes the course of SMA, some individuals may still exhibit symptoms, especially if they get treatment after becoming symptomatic. Therefore, more research is required to ascertain whether treatment efficacy might be increased, potentially by combination therapy. Further research will be needed to assess the effectiveness and effects of gene therapy over the long run.

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