THERAPEUTIC MODALITIES FOR SPINAL MUSCULAR ATROPHY

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ABSTRACT:

With a prevalence of 1 in 6000–10,000 live births, Spinal muscular atrophy (SMA) is a neurodegenerative illness that is common in children and a major cause of hereditary mortality globally and the carrier frequency estimated to be 1/40–1/60. [1, 2] SMA is a condition characterized by the degeneration of anterior horn cells in the spinal cord and motor nuclei in the lower brainstem, leading to progressive muscle weakness and atrophy. This review focuses on the different treatment modalities and equipment that assist spinal muscular atrophy (SMA).

INTRODUCTION:

Spinal Muscular Atrophy (SMA) is a progressive neuro muscular disorder characterized by the degeneration of the alpha motor neurons in the spinal cord. Alpha motor neuron loss causes muscle weakness, atrophy, and low tone, primarily in proximal muscles like shoulders, hips, and back, affecting the body's trunk.

The neurons controlling most voluntary muscles can be affected, including those that control muscles involved in feeding, swallowing and breathing. Based on their greatest motor milestones and age of start, they are classed as having SMA type 1–4 (SMA1–SMA4), and the number of SMN2 copies is inversely correlated with the clinical severity of the disease phenotype.[3]

PATHOGENESIS:

SMA is an autosomal recessive genetic disorder linked to mutations in the survivor motor neuron 1 (SMN1) gene, located on chromosome 5 in the long arm region, often referred to as 5q SMA.

On chromosome 5q13, humans have two inverted SMN genes. The homozygous deletion of the SMN1 gene has been linked to SMA. Because of the C>T alteration, 90% of SMN2 transcripts miss exon7, resulting in an isoform that is truncated, unstable, and rapidly degrades. Some full-length SMN protein is produced by alternative splicing processes.[4]

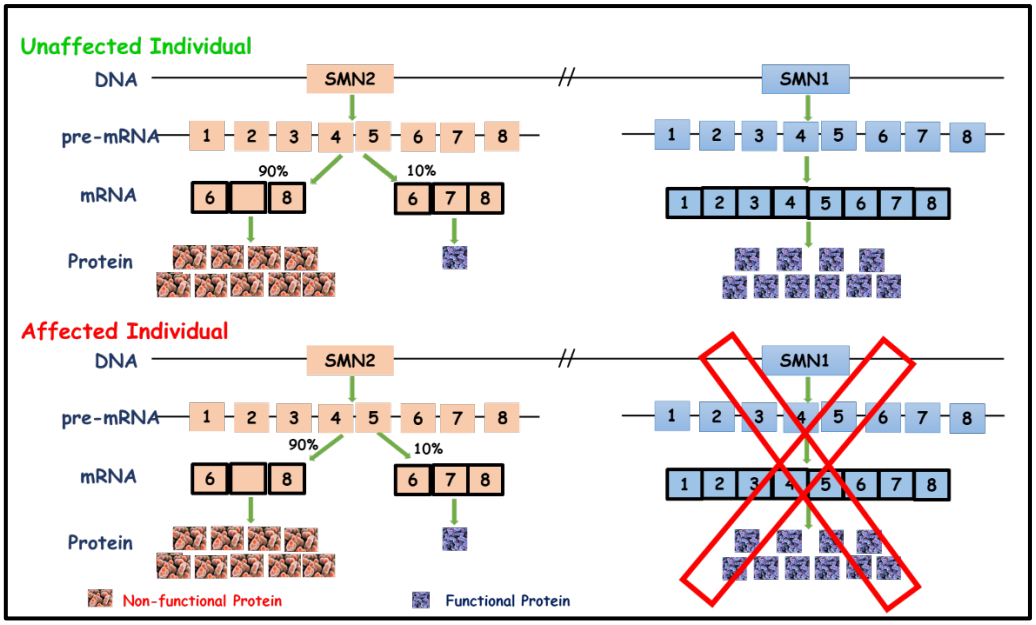

Figure: 1

MEDICAL AND SUPPORTIVE MANAGEMENT:

The severity of the disease varies depending on the kind of SMA, with more severe forms needing more intensive treatment.[4]

MEDICAL MANGEMENT FOR SMA:

Nusinersen, Risidiplam and Onasemnogene abeparvovec are the currently approved drug options for the treatment of SMA. These are targeted therapies for SMA, targeting the underlying disease mechanism. These treatments may prevent or slow SMA progression, with better efficacy when initiated before symptom onset. However, the long-term effects and potential emergence of new phenotypes remain unclear.

➢ WORKING OF NUSINERSEN:

Nusinersen is an ASO (Antisense Oligonucleotide) that alters SMN2 gene splicing to increase SMN protein synthesis by correcting the disease's underlying cause.

Nusinersen that belongs to a group of medicines known as antisense oligonucleotides (ASO). Treating 5q Spinal Muscular Atrophy (5q SMA) is the only application for Nusinersen. The "survival motor neuron" (SMN) protein is deficient in people with SMA. The nerve cells that assist movement of muscles are called motor neurons, and they depend on this protein to function.

The brain and spinal cord include motor neurons, which are responsible for contacting muscles. Human cells need the SMN1 and SMN2 genes to make the SMN protein. The SMN2 gene, which typically generates just 10% of the SMN protein and is not as functional as a full-length protein. The SMN1 gene is mutated or deleted in the SMA patients. Nusinersen assists these patients making the SMN2 gene to produce full length (100%) SMN protein essential for normal function of motor neurons.

- **WORKING OF RISDIPLAM:**

Risdiplam, an orally bioavailable molecule, and targets the genetic cause of SMA by facilitating the inclusion of exon 7 in the mature transcript during SMN2 pre-mRNA splicing. This helps produce functional SMN proteins to compensate for the loss of SMN1 function in SMA patients.[8] Risdiplam, an oral solution, is prescribed daily based on a child's age and weight, and should be given after feeding, crossing the blood-brain barrier, and metabolized by enzymes like CYP 3A4.[9]

The SMN2 risidiplam splicing modifiers bind to two sites within exon 7 of the SMN2 transcript, exonic splicing enhancer 2 (ESE2) and 5' splice site (5'ss). This interaction enhances U1 snRNA binding, leading to dislocation of hnRNP G and binding of the U1 snRNP complex. This results in the inclusion of exon 7 and full-length SMN2 mRNA production.[10]

- **WORKING OF ONASEMNOGENE ABEPARVOVEC:**

Onasemnogene abeparvovec is a gene therapy using a viral vector to deliver a functional copy of the human survival motor neuron gene to patients with spinal muscular atrophy. Infantile-onset SMA patients treated with onasemnogene abeparvovec showed significant improvement in developmental motor milestones like head control and sitting without support compared to their natural history.[11]

Recombinant AAV vectors are ideal for gene therapy due to their ability to transduce both dividing and non-dividing cells, allowing long-term transgene expression in non-dividing cells.[12] One of the most intriguing and well-studied methods for delivering transgenes is the adeno-associated virus (AAV) vector, which makes it a desirable choice for gene therapy. AAVs are distinguished by a number of characteristics, including their nonpathogenicity, resistance to immunological responses, capacity for strong transgenic expression, and diverse tropism for a number of bodily tissues.[13]

The SMN gene is delivered to motor neuron cells using the AAV9 vector as self-complementary DNA. This leads to the fast activation and ongoing expression of the SMN gene, which is caused by a circular episome that remains in the nondividing nucleus of motor neuron cells.[14]

SUPPORTIVE CARE FOR SMA:

Palliative, supportive, and rehabilitative treatment can change the normal course of SMA and minimise the disease burden. Orthopaedic care, rehabilitative therapies, dietary assistance, end-of-life care, and management of pulmonary problems are all included in the treatment plan.

SPECIALIZED EQUIPMENT USED TO MAINTAIN GOOD RESPIRATORY HEALTH AND MOBILITY ASSISTANCE:

For assistance with breathing, coughing, and swallowing difficulties, as well as to support them in everyday activities, people with spinal muscular atrophy (SMA) may require specialised equipment. Following are the treatments that focus on the disease's underlying aetiology can aid in managing the illness.

Mobility challenges for individuals with SMA require assistive equipment for tasks like sitting, dressing, eating, and stairs management. Specialized equipment like adaptive strollers and wheelchairs optimize care and independence. Support is crucial for younger children to prevent respiratory issues and hospitalization.

Individuals with SMA may face orthopaedic issues due to poor body alignment, requiring support devices like braces and standers to stabilize various body parts.

- **BiPAP machine:**

A BiPAP is a non-invasive ventilation device that adjusts air pressure during inhalation and exhalation, making it easier for patients with SMA to breathe by providing higher pressure and automatically adjusted pressure.[6]

- **Cough assist machine:**

A cough assist machine, adaptable and used as a mouthpiece or face mask, helps clear airways in patients with weak chest muscles. It uses positive and negative pressure to expand lungs and remove airway secretions.

- **Braces:**

SMA, a common spinal condition, often affects spinal alignment due to weakness in supporting muscles. It can impact comfort, balance, and breathing, necessitating surgical treatment. Braces can improve function, independence, and quality of life.

- **Standers:**

Standers aid SMA patients in standing, promoting bone and muscle strength, digestion, circulation, breathing, social interactions, self-confidence, and mental health by supporting their legs.

- **Pulse oximeter:**

A pulse oximeter is a non-invasive device used to monitor blood-oxygen levels, detect respiratory distress, and measure oxygen efficiency in extremities, alerting users to low oxygen levels or coughing assistance.

Figure: 2[7]

CONCLUSION:

Spinal Muscular Atrophy (SMA) is a neurodegenerative disorder caused by mutations in the survivor motor neuron 1 (SMN1) gene. It results in muscle weakness and atrophy, and is a major cause of hereditary mortality globally. Treatment options include assistive equipment, adaptive strollers, and support devices. Target therapies like Nusinersen, Risidiplam, and Onasemnogene abeparvovec target the disease mechanism and may slow or prevent SMA progression.

Disease-modifying treatments for SMA provide significant improvements in motor function and life expectancy, while phenotypes are evolving due to their non-cure nature. The SMN2 gene splicing treatment approach for SMA has been significantly modified by the development of antisense oligonucleotides (nusinersen), small-molecule medications (risdiplam), and gene replacement therapy (onasemnogene abeparvovec).

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