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Review on zolgensma: Milestone in spinal muscular atrophy

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***Abstract*---**Disease and disorders are outlined as disablement of the normal state of living organism and annoyance of normal functioning of the body respectively. The ideal causes of the disorders are genetic factors, disease, stress or trauma. Genetic disorders are a pathological state provoked by one or more monstrosities in the genome. Spinal Muscular Atrophy is a rare genetic disease and most common monogenic cause of infant mortality. Hypotonia and weakness are most common manifestations of Spinal Muscular Atrophy delineated by degeneration of anterior horn cells of the spinal cord. SMA is originated due to mutations and deletions of SMN1 (Survival Motor Neuron) gene on Chromosome 5q. Disease modifying therapy and Gene replacing therapy are the common gene therapy used to treat genetic disorders. Zolgensma is an Adeno virus associated gene therapy restored a gene which is functional one. Children under the age of 2 are benefited from a single time intravenous (IV) infusion of Zolgensma. In future Gene therapy can treat all the illness associated with Genetic disorders.

***Keywords*---**genetic disorder, spinal muscular atrophy, survival motor neuron, gene therapy, zolgensma.

Introduction

Disease usually defined as deviation or imbalance that occurred between normal structural states of organism. It possesses some sign and symptoms in order to specify their state. The science which involve in study of disease and their related is known as pathology. They involve in giving information related to the development, and the changes that happens after the wide spread of disease in body.

If the disease caused to an individual organism, then it is said to be idiopathic. Sometimes if it is caused by any external agents, they are known as non-communicable. In case, if it multiplies within the host and infects the other organism, then it is called communicable disease. [1] Spinal Muscular Atrophy is also known as Kennedy disease, which is hereditary motor neuron disease. It is characterized by slow progressive muscle weakness, atrophy of bulbar, facial and limbs muscles. As they never learn to sit without any support and won't survive beyond 2 years. Gene therapies were well known for long term effectiveness. For studying gene therapy on treatment for hemophilia A, clinical trial was conducted as it shown a decrease in effect of 3 years after treatment.[2]

History

It was first found in 1891, which has been considered as more common genetic killer in infants and in toddlers. It affects at around 1 in 10,000 newborns and which accounted for more than 1000 pediatric deaths. It is caused by two versions of SMN1, which is the most important one involved in controlling muscle movement. If it is hault, whole body becomes paralyzed and it may leads to death. The people suffering from SMA, the working protein amount and the severity of the disease mainly depends on number of SMN2 copies that are formed in genome naturally. If the patients were treated earlier, their walking, sitting and motor skills will be developed. [3]

Causes and Diagnosis Of SMA [4]

SMA is originated due to mutations and deletions of SMN1 (Survival Motor Neuron) gene on Chromosome 5q. Anomalous change in SMN1 gene leads to poor reflection of the survival motor neuron (SNM) protein. Wasting away of muscles and fragility are the most features of SMA due to decreased level of SMN protein level. This also leads to respiratory and feeding difficulty.

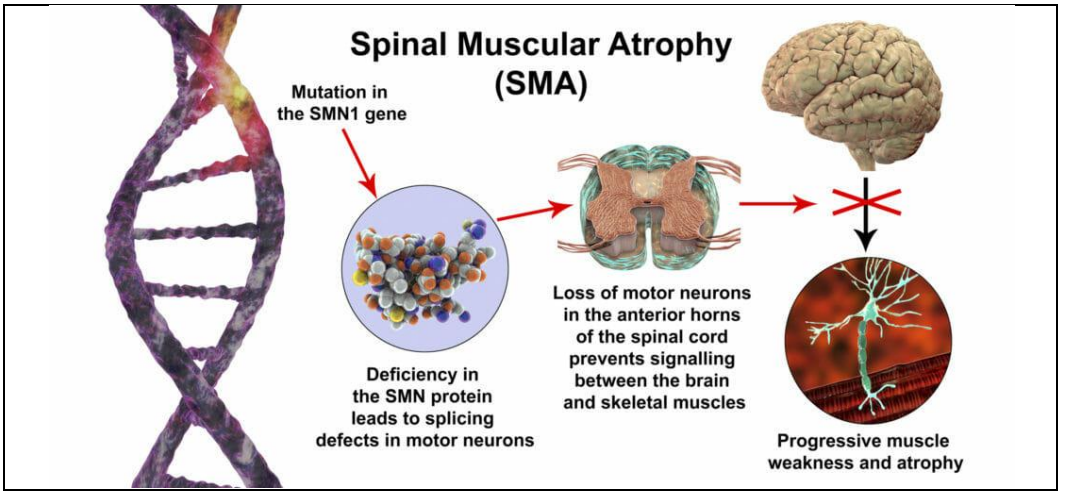


Fig: 1 Causes of Spinal Muscular Atrophy

Clinical Features of Spinal Muscular Atropy (SMA)

One of the clinical features of SMA was weakness of muscle and atrophy. The weakness of muscle was usually symmetric with which the proximal muscles were affected more when compared with distal groups. They were divided into three types based on onset of age in which type 0 is for patients who had prenatal onset and death occurs within weeks, type 3 and type 4 were on adult oriented. Moreover 25% of patients showed precise classification, which seems related to genetic era and which gives more information for clinical purposes.[5]

Classifications of Spinal Muscular Atrophy [4, 8]

5 most important clinical phenotypes of SMA is described in the year of 1992.

Spinal Muscular Atrophy Type 0

It occurs in neonates who experiences severe weakness, hypotonia accompanied with decreased fetal movement. The weakness involved in this due to prenatal onset. While examining, the neonate's experiences areflexia, atrial septal defects, facial diplegia and contractures in joints. In this instance, respiratory failure develops. The one suffer in this condition could not survive beyond 6 months.

Spinal Muscular Atrophy Type 1

This type called by other name as "Werdnig-Hoffman" disease. It occurs with poor head control, reduced or absent tendon reflexes occurs before 6 months of age. Infants would feel weakness in their tongue while swallowing and fasciculation present. Infants suffer from respiratory failure before two years. It was regarded as motor neuron disorder. Recent research has revealed that spinal muscular atrophy can induce various symptoms affecting motor neurons in the spinal cord, as well as those in the brain, heart, and all sensory nerves.

Spinal Muscular Atrophy Type 2

Patients who were suffering from type 2 spinal muscular atrophy children can able to sit without any support but they could not able to walk. There occurs progressive scoliosis accompanied with intercostal muscle weakness which causes lung disease when they grow old. They could experience areflexia and hypotonia on examination.[6]

Spinal Muscular Atrophy Type 3

Spinal muscular atrophy type 3, otherwise known as "Kugelberg welander" disease, in which there will be progressive weakness in legs compared to arms. There would be no pain or experience weakness in respiratory muscle.

Spinal Muscular Atrophy Type 4

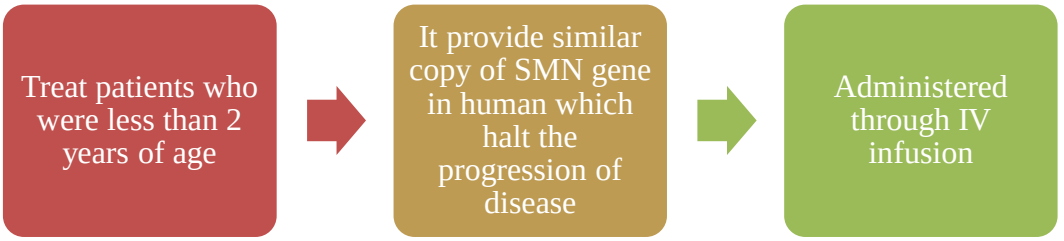
In this type, less than 5% of individuals were affected. They experience side effect similar to type 3. It occurs at the age of 30 or above, but can be found at very young state.[8]

TREATMENT OR MANAGEMENT OF SMA [7, 9]

There is not a cure for Spinal Muscular Atrophy. Symptomatic and supportive treatment based upon type of SMA and symptoms of the patient. Orthopaedic braces, walkers and wheel chairs are plays major role as an assisted devices for uplifting the life style of SMA patients. Physical and Occupational therapy provides beneficial and supportive effect in the management of SMA Symptoms.
Disease Modifying Theraphy: Nusinersin is the drug which is administered through Epidural site of drug administration for the children ages 2 to 12 to stimulate production of SMN protein.
Gene Replacement Theraphy: Gene replacement therapy replaces a faulty gene with a functioning gene. Children under the age of 2 are benefited from a single time intravenous (IV) infusion of Zolgensma.

Zolgensma

Zolgensma, well known as Onasemnogene. Zolgensma (Onasemnogene abeparvovec-xioi, AVXS-101, Avexis, Novartis, Bannockburn, IL, USA) is a proprietary gene therapy approved by the USFDA that treats paediatric patients under 2 years of age with Spinal Muscular Atrophy (SMA) with bi-allelic mutations in the surviving motor gene for neuron 1.[7]



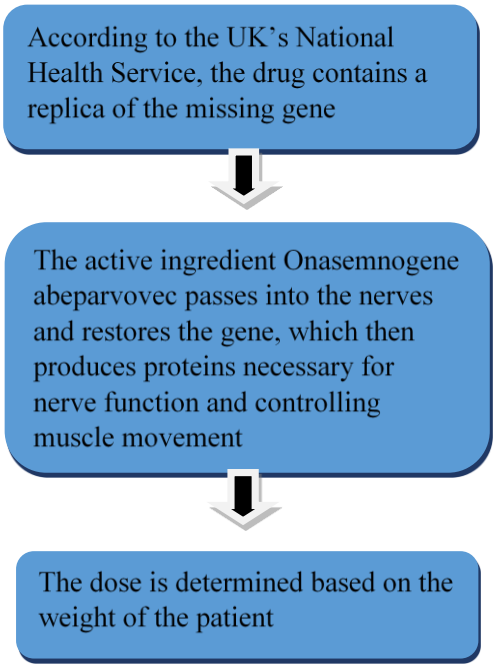
Zolgensma refers to the first approved site on the proprietary site for the treatment of rare, monogenic disease using gene therapy.[10,11,12]

Drug Details [13]

Drug name	Zolgensma® (Onasemnogene abeparvovec-xioi)
Developer	Avexis
Therapy class	Gene therapy
Product description	Adeno associated virus vector based gene therapy

Table: 01- Details of Zolgensma

How Will Zolgensma Treat SMA [14]



Zolgensma's Mechanism of Action [15]

Zolgensma is a gene therapy based on the Adeno-Associated Virus (AAV) 9 that delivers a copy of the SMN1 gene that encodes for human growth hormone SMN protein. It's a self-complementary AAV9 recombinant that includes a human SMN protein-encoding transgene. The Zolgensma drug will be available in single use vials, each containing a nominal concentration of 2×10^{13} vector genomes (vg) per millilitre for intravenous infusion.

Adult Dosage [16]

≥ 2 years-not applicable

Children Dosage and Cost

Give as a slow IV infusion over 60minutes. < 2 years: 1.1×10^{14} vg/kg. Give systemic corticosteroids equivalent to oral prednisolone 1mg/kg/day for 30 days starting one day before Zolgensma infusion, then reduce dose gradually over the next 28 days if LFTs are ordinary.[16]

The expected cost of Zolgensma is around €2 000 000. .[6]

Figure 02: Image of Zolgensma

Indications

Zolgensma is an Adeno associated virus vector based gene therapy that treats paediatric patients less than 2 years of age with bi-allelic mutations in the motor neuron 1 gene for survival with SMA.

Limitations of Use

Zolgensma repeatedly the safety and performance of the administration has not been evaluated. The use of Zolgensma in advanced SMA patients has not been evaluated. [15]

Adverse Reactions

The most common adverse reactions are elevated aminotransferase and vomiting.

Zolgensma Warnings/Precautions [18]

- Acute Serious Liver Injury
  Acute Serious Liver Injury and elevated amino transferase can occur with Zolgensma. Patients with already impaired liver function may be at higher risk. Prior to injection, evaluate the liver function of all patients through clinical trials and laboratory tests and administer the appropriate corticosteroid to all patients before and after the Zolgensma injection. Continue to monitor liver function for at least 3 months after injection
- Thrombocytopenia
  Temporary decreases in platelet count, which met the criteria of some thrombocytopenia, were observed at different time points after Zolgensma injection. Monitor platelet count on a regular basis before and after Zolgensma injection
- Elevated Troponin-I
  Clinical trials showed a transient increase in cardiac troponin 1 levels following the injection of Zolgensma. These findings aren't known to have any clinical significance. However in animal studies heart toxicity was found. Monitor troponin 1 before Zolgensma injection and on a regular basis for at least 3 months [18]

Clinical Studies on Zolgensma [19]

FDA approval for this drug was based on the positive results of two open label, non-randomized, single-group, single-dose clinical trials named STR1VE and START. STR1VE is an ongoing phase 3 clinical trials in 21 patients with infant-onset SMA and START is a phase 1 clinical trial. A 24 month clinical trial, START was conducted to evaluate the safety and efficacy of the drug in patients. Three subjects participated in the low dose cohort and the remaining three participated in the high dose group. The study's primary goal was to see how long people could live without permanent ventilation.

At an end of 24 months, the 12 patients who received high doses no longer needed permanent ventilation. This represents event free survival. During the study, about 91.7% of the tested patients were able to sit upright, 83.3 was able to sit for 10sec or longer without support and 75% were able to sit for 30sec or longer. In addition, 16.7% of patients were able to stand alone and walk with help. Event free survival and reclining for at least 30sec were the primary endpoints of the 24 month STR1VE trial. Out of the 21 patients, 19 no longer required continuous ventilation and 47.6% were able to sit unassisted for at least 30sec. The most commonly reported adverse events (AEs) in patients were elevated aminotransferase and vomiting. Avexis also reported positive interim data from the 1/11 strong trial investigating the intrathecal formulation of the drug on SMA patients aged 2-5 years.

In October 2019, the FDA partially clinically discontinued the trial for intrathecal Zolgensma after Avexis reported a safety event in a preclinical study. The drug Zolgensma has been observed in animal experiments to be associated with inflammation of the dorsal root ganglion (DRG) mononuclear cells and in some cases, with degeneration or loss of nerve cell bodies. The FDA also received a report from Avexis in August 2019 highlighting the issue of tampering with some data from animal studies. US regulators evaluate the data and at the same time recommend the availability of this drug in further markets.[19]

Advancement in Gene Therapy for Treating SMA [21]

According to the statement released by NOVARTIS on March 15- 2021, more than 1,000 SMA children have been treated with Zolgensma. Novartis has Global license with Nationwide Children Hospital for deliberating AAV9 gene therapy for the treatment of all types of SMA. Also has international agreement with AskBio for application of its self-complementary DNA technology for SMA Treatment.

Conclusion

Genetic disorders are well or not be heritable. There are overall 6,000 inarguable genetic disorders, and new genetic disorders are constantly being reported. More than 600 genetic disorders are remediable. In non- heritable genetic disorders are treated by advanced medicines like Zolgensma used in the treatment of Spinal Muscular Atrophy. Gene therapy may change the practice of medicine from a treatment-based to a prevention- based medicine. The hope in the coming years, advancement in technology in gene therapy every genetic disease will have gene therapy as its treatment.

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