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Review Article

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CAUSES MANAGMENT AND PERCEPTION OF SPINALMASCULAR ATROPHY AMONG INFANTS

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ABSTRACT

Now-a-days, people are facing various kind of stress in the fast daily life and most of the people in the world are suffering from various neurological disorder. Spinal muscular atrophy (SMA) is one of the most common autosomal recessive diseases with progressive weakness of skeletal and respiratory muscles, leading to significant disability.In the most severe cases and when left untreated, leads to death within the first two years of life. Recent therapeutic advances have given hope to families and patients by compensating for the deficiency in survival motor neuron (SMN) protein via gene therapy or other genetic manipulation. We then explore recent preclinical research that is identifying and targeting dysregulated pathways secondary to, or independent of, SMN deficiency that may provide adjunctive opportunities for SMA. These additional therapies are likely to be key for the development of treatments that are effective across the lifespan of SMA patients. In this review, we discuss the three currently licensed therapies for SMA, briefly highlighting their respective advantagesand disadvantages. Recently, Food and Drug Administration (FDA) and European Medical Agency (EMA) approved the antisense oligonucleotide nusinersen, the first SMA disease-modifying treatment and gene replacement therapy by onasemnogene abeparvovec. However, the availability of effective approaches has raised up ethical, medical and financial issues that are routinely faced by the SMA community. This review covers the available data and the new challenges of SMA therapeutic strategies.

KEYWORDS: Spinal Muscular Atrophy, Motor Neuron, Survival Motor Neuron, Autosomal recessive diseases.

INTRODUCTION TO SMA

What is spinal muscular atrophy?

Spinal muscular atrophy (SMA) is a genetic disease affecting the central nervous system, peripheral nervous system, and voluntary muscle movement (skeletal muscle). It is a devastating childhood **motor neuron disease** that, in the most severe cases and when left untreated, leads to death within the first two years of life.

Most of the nerve cells that control muscles are located in the spinal cord, which accounts for the word spinal in the name of the disease. SMA is muscular because its primary effect is on muscles, where they don't receive signals from these nerve cells. Atrophy is the medical term for getting smaller, which is what generally happens to muscles when they're not stimulated by nerve cells. SMA involves the loss of nerve cells called motor neurons in the spinal cord and is classified as a motor neuron disease.

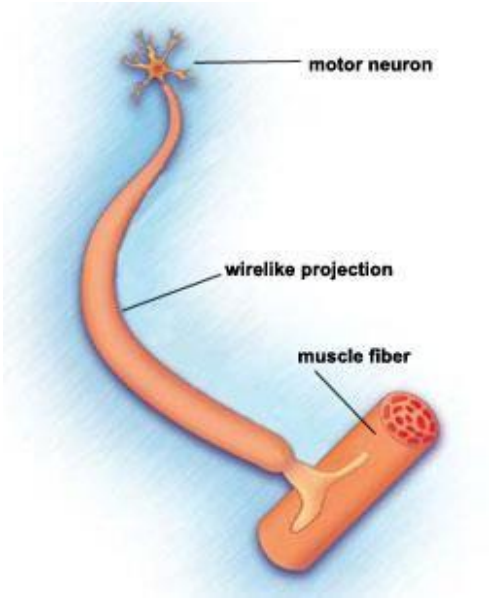

Figure 1.1: Muscle-controlling nerve cells (motor neurons) are located mostly in the spinal cord. Long, wire-like projections connect the motor neurons to muscles in the limbs and trunk. Normally, signals

from the neurons to the muscles cause muscles to contract. In SMA, motor neurons are lost, and muscles can't function.

In the most common form of SMA (chromosome 5 SMA, or SMN-related SMA), there is wide variability in age of onset, symptoms, and rate of progression. In order to account for these differences, chromosome 5-related SMA, which often is autosomal recessive, is classified into types 1 SMA (infantile SMA, Werdnig-Hoffmann disease).

The age at which SMA symptoms begin roughly correlates with the degree to which motor function is affected: The earlier the age of onset, the greater the impact on motor function. Children who display symptoms at birth or in infancy typically have the lowest level of functioning (type 1). Later-onset SMA with a less severe course (types 2 and 3, and in teens or adults, type 4) generally correlates with increasingly higher levels of motor function.

Recent therapeutic advances have given hope to families and patients by compensating for the deficiency in survival motor neuron (SMN) protein via gene therapy or other genetic manipulation. However, it is now apparent that none of these therapies will cure SMA alone. In this review, we discuss the three currently licensed therapies for SMA, briefly highlighting their respective advantages and disadvantages, before considering alternative approaches to increasing SMN protein levels. We then explore recent preclinical research that is identifying and targeting dysregulated pathways secondary to, or independent of, SMN deficiency that may provide adjunctive opportunities for SMA. These additional therapies are likely to be key for the development of treatments that are effective across the lifespan of SMA patients.

Causes of SMA ?

What are the genetic causes of SMA?

Humans normally have 46 chromosomes in each cell, divided into 23 pairs. Two copies of chromosome 5, one copy inherited from each parent, form one of the pairs. Chromosome 5 spans about 181 million DNA building blocks (base pairs) and contains approximately 1700 genes which represents almost 6 percent of the total DNA in cells. The most common form of SMA (types 1-4) is caused by a defect or mutations in the SMN1 gene on chromosome 5.

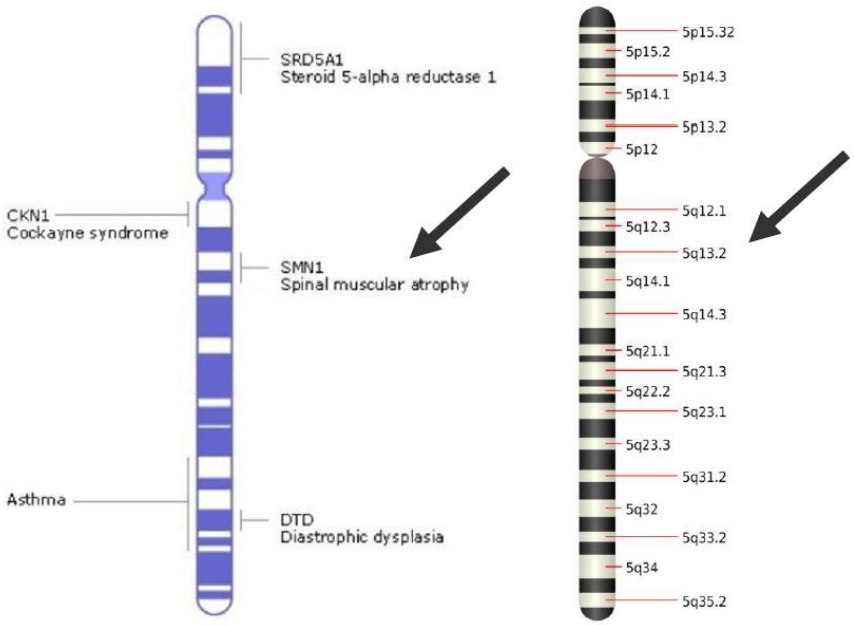

Figure 1.2: Shows Ideogram of the human chromosome 5 and 5q13.2 region.

People have two SMN1 genes — one on each chromosome 5. In 94% of all SMA cases, this mutation involves a deletion in a segment known as exon 7. This area is located in the long arm of the chromosome 5, in the **5q13.2 region.** chromosomes have two "arms": a short one, identified by the letter **"p,"** and a long one, identified by the letter **"q".**

A mutation in the SMN1 gene leads to a deficiency of a motor neuron protein called SMN, which stands for **"survival of motor neuron."** As its name implies, this protein is responsible for gene expression necessary for normal motor neuron function.

Very rarely, a mutation in an X-chromosome gene called UBE1 causes X-linked SMA. The UBE1 gene carries instructions for ubiquitin-activating enzyme 1,This enzyme is necessary for the **ubiquitin-proteasome system**, which targets damaged or unneeded proteins to be broken down (degraded) within cells

Another rare form of SMA called SMA-LED which

stands for **Spinal muscular atrophy with lower extremity predominance** is characterized by muscle weakness in the lower limbs, most severely affecting the thigh muscles. This type of SMA is caused by mutations in the **cytoplasmic dynein 1 heavy chain 1 (DYNC1H1) gene** on chromosome 14.

What causes the wide variation in symptom severity seen in SMA?

Normally, SMN1 genes produce full-length and fully functional SMN protein. But when the SMN1 gene has mutations, as in the chromosome 5-related form of SMA, insufficient levels of SMN protein are produced. A neighboring gene on chromosome 5, called SMN2, also produces SMN protein. Most of the protein made from instructions carried by SMN2 genes is not functional, but a small percentage, around 10 to 15% is functional. People can have multiple copies of the SMN2 gene. Normally, the number varies between zero and eight copies. In the chromosome 5-related form of SMA, the more SMN2 gene copies a person has, the more functional SMN protein is available. As a result, the milder the disease course is likely to be. Having three or more copies of the SMN2 gene is associated with a less severe disease manifestation.Genetic testing can tell how many SMN2 genes a personhas and roughly predict the course of SMA that is likely to result.

SMA severity also may depend on disease modifiers, which don't cause disease but can modify onset and severity by influencing various biological pathways. Levels of both **plastin 3 protein and ZPR1 protein** have been identified as modifiers of SMN-related SMA and could become therapeutic targets. In addition, testing for these protein levels could help predict disease severity, and insight into the activities of these proteins could shed new light on disease processes.

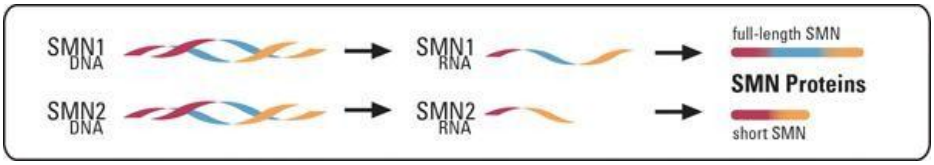

Figure 1.3: Genetic information moves from its storage form as DNA to a set of instructions known as RNA, from which protein molecules are made. Most of the RNA instructions from the SMN1 gene tell the cell to make full-length SMN protein. Most of the instructions from the SMN2 gene tell the cell to make short SMN protein.

Types of SMA

There are five types of spinal muscular atrophy (SMA): Types 0, 1, 2, 3, and 4. The type of SMA is based on the age that symptoms begin, and the highest physical milestone achieved. Even within each type, abilities can vary from person-to-person. In addition, individuals with SMA can lose function over time if muscles continue to weaken.

Type 0 (prenatal SMA)

SMA Type 0 is very rare and very severe. Symptoms begin prior to birth and is seen as decreased fetal movement in the weeks prior to delivery. At birth, the infant has severe weakness and often difficulty breathing, feeding, and may have joint contractures and cardiac defects. These infants typically require respiratory and feeding support prior to confirming the diagnosis. These infants may survive a few months.

Type I (Werdnig-Hoffman disease or SMA linked to chromosome 5)

SMA Type 1 is the most common (60%) and severe form, usually diagnosed during an infant's first 6 months. Babies with SMA Type 1 face many physical challenges, including muscle weakness and trouble breathing, coughing, and swallowing. They may need breathing assistance or a feeding tube. If not treated, Type 1 can be fatal early on in life.

Type II (Dubowitz disease or intermediate SMA)

Type 2 is usually diagnosed after 6 months of age, but before 2 years of age.Individuals with SMA Type 2 can typically sit up without help, though they may need assistance getting into a seated position, but they are unable to walk and will require a wheelchair. Feeding and breathing problems may also develop. SMA2 is caused by changes in the SMN1 gene and is inherited in an autosomal recessive manner.

Type III (Kugelberg-Welander disease or juvenile SMA)

Type 3 is usually diagnosed after 18 months of age, but before 3 years of age. However, SMA Type 3 can be diagnosed as late as the teenage years. Individuals with SMA Type 3 are initially able to walk, but have increasingly limited mobility as they grow and eventually, many need to use a wheelchair.SMA type 3 is caused by mutations in both copies — one inherited from each biological parent — of the SMN1 gene. This gene provides instructions to produce SMN, a protein essential for motor neuron and muscle health People with spinal muscular atrophy type III typically have a normal life expectancy.

Type IV (adult SMA)

SMA Type 4 is very rare, less than 1% of all diagnosed cases. It usually surfaces in adulthood, and it leads to mild motor impairment. While symptoms can begin as early as age 18 years, they usually begin after age 35 years.Spinal muscular atrophy (SMA) types 1 through 4 all result from a single known cause — a deficiency of a protein called SMN, which stands for "survival of motor

neuron.Affected individuals usually experience mild to moderate muscle weakness, tremors, and mild breathing problems.

Other types of SMA

Spinal Muscular Atrophy With Respiratory Distress (Smard)

SMARD1 is an inherited nervous system condition that causes muscle weakness and respiratory failure, usually beginning between the ages of 6 weeks and 6 months. SMARD1 is an extremely rare disease; the number of children affected is very small. Currently, it is not possible to collect accurate numbers of those affected but this may change as knowledge of the condition increases.

Kennedy's disease, or spinobulbar muscular atrophy (SBMA)

Spinal and bulbar muscular atrophy mainly affects males and is characterized by muscle weakness that usually begins in adulthood and worsens slowly over time. Muscle wasting in the arms and legs results in cramping; leg muscle weakness can also lead to difficulty walking and a tendency to fall. Certain muscles in the face and throat (bulbar muscles) are also affected, which causes progressive problems with swallowing and speech.spinal and bulbar muscular atrophy is the abnormal expansionof a DNA segment called a CAG triplet repeat.

Spinal muscular atrophy with lower extremity predominance (SMA-LED)

It is characterized by muscle weakness and wasting (atrophy) in the lower limbs, most severely affecting the thigh muscles . The loss of motor neurons leads to atrophy of the muscles in the lower limbs. Affected individuals often have unsteady walk and walk on the balls of their feet. They may have difficulty rising from a seated position and climbing stairs. Some people with SMA-LED also have weakness in upper limb muscles.This type of SMA is caused by mutations in the **cytoplasmic dynein 1 heavy chain 1 (DYNC1H1) gene** on chromosome 14.

Distal Spinal Muscular Atrophy(DSMA)

The distal form of SMA is an extremely rare disorder, which presents in the adults and has a relatively slow progression with almost no effect on the patients' life-span. characterized by muscle wasting, particularly of distal muscles in legs and hands, and by permanent shortening of a muscle or joint of the hip, knee, and ankle. Affected individuals often have shorter lower limbs relative to the trunk and upper limbs Congenital distal spinal muscular atrophy is caused by a mutation of the TRPV4 genein chromosome 12.

X-linked infantile spinal muscular atrophy

It is a condition that affects only boys and is characterized by severe muscle weakness and absent reflexes Mutations in the UBA1 gene cause X-linked infantile spinal muscular atrophy. The UBA1 gene provides instructions for making the ubiquitin-activating enzyme E1. This enzyme is necessary for a process that targets damaged or unneeded proteins to be broken down.

SIGNS AND SYMPTOM

Type 0 (prenatal SMA)

The first sign may be a decrease or loss of fetal movement during late pregnancy. Symptoms of SMA type 0 are apparent at birth and include severe weakness and hypotonia. In addition, joint deformity and tightening (contractures) and congenital heart defects are common. As a result, infants do not achieve developmental motor milestones. Because of severe respiratory muscle weakness, affected infants rapidly progress to respiratory failure often by the first month of life.

Type I (Werdnig-Hoffman disease or SMA linked to chromosome 5)

Infants with SMA type 1 usually appear normal at birth but experience severe weakness before 6 months of age. Developmentally they do not achieve independent sitting and may achieve very few developmental motor milestones. Because of lower motor neuron loss, affected infants have poor suck and swallow reflexes and respiratory muscle weakness. Historically without intervention, affected children die before two years of age due to progressive respiratory muscle weakness and respiratory failure.

Type II (Dubowitz disease or intermediate SMA)

Affected children can sit independently at some point in their development. However,this ability is usually lost by the mid-teens or later and affected individuals never achieve independent standing and walking. Additional associated symptoms include difficulty swallowing (dysphagia) and respiratory difficulties. Trembling (tremor) of the fingers is also common. In addition, weakness of the muscles supporting the spine leads to curvature of the spine (scoliosis)

Type III (Kugelberg-Welander disease or juvenile SMA)

Affected individuals have hip and leg weakness and may fall frequently, they are able to walk independently at some point in their development. However, the ability to walk and stand may be lost as they grow and with disease progression, and many become wheelchair dependent. Long-term prognosis depends on the degree of motor function attained as a child, and respiratory muscle weakness is typically mild or absent.

Type IV (adult SMA)

Symptoms are less severe than in other subtypes and onset typically occurs in adulthood and most commonly after 35 years of age. All motor developmental milestones are achieved and most individuals with SMA type 4 can walk throughout their life. Patients with SMA type 4 have a normal life expectancy.

Diagnosis of SMA

The first steps in diagnosis of a neuromuscular disease are usually an in-office physical examination and family history, with some simple tests to distinguish spinal muscular atrophy from similar conditions. Muscle weakness and hypotonia should be the first signs that raise suspicion for SMA in babies. Other signs can help to confirm the diagnosis, such as a history of motor difficulties, loss of motor skills, proximal muscle weakness, hyporeflexia, tongue fasciculations (involuntary twitches), and signs for low motor neuron disease.

A doctor probably will recommend genetic testing if SMA is suspected because this is the least invasive and most accurate way to diagnose chromosome 5-related SMA (types 1-4). Genetic testing requires only a blood sample. However, it has implications for the whole family that must be considered.

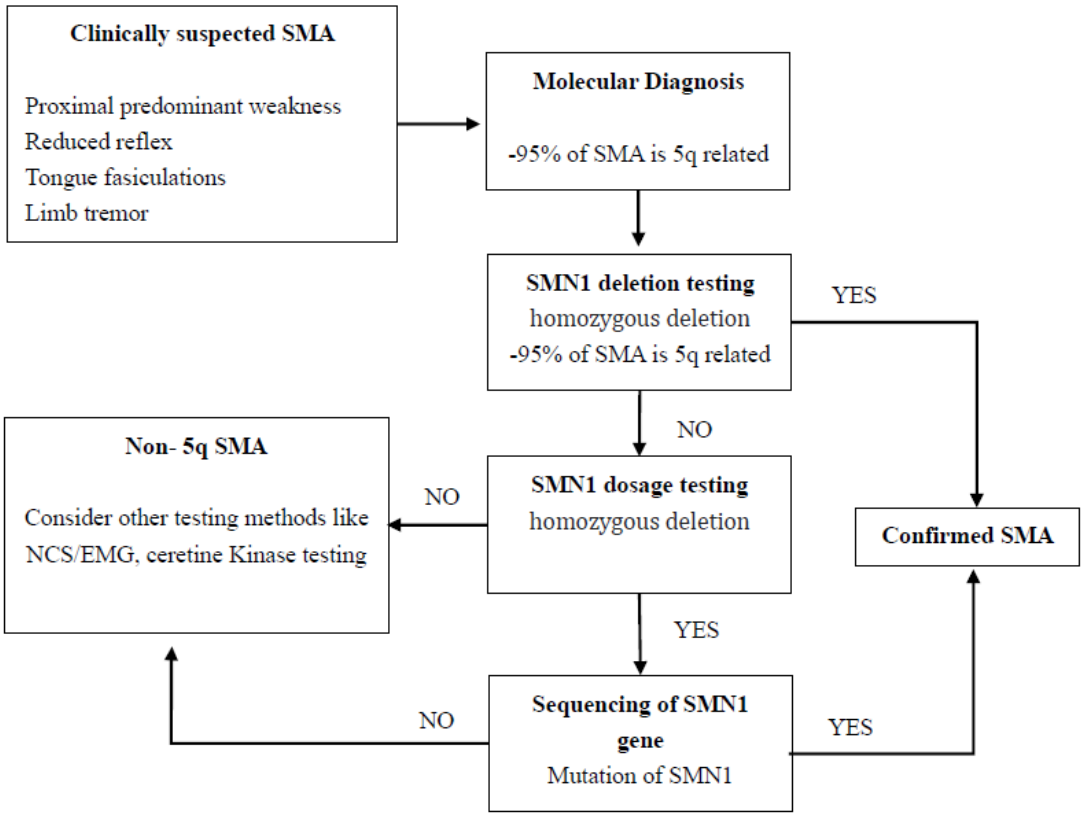

Figure 1.4: Chart Represents the General Diagnostic Procedure for SMA.

MANAGEMENT OF SMA

Gene-targeting SMN replacement therapies

There are three treatment approved by the US Food and Drug Administration (FDA)and the European Medicines Agency (EMA)

1. Nusinersen (Spinraza; Biogen)
2. Onasemnogene abeparvovec (Zolgensma; Novartis)
3. Risdiplam (Evrysdi; Roche)

Table 1.1: Approved therapy for SMA-Nusinersen (Spinraza; Biogen).

Approved therapy	Mechanism of action	Stage of Development	Route of Administration and protocol	Population targeted by license	Cost
Nusinersen (Spinraza; Biogen)	Splicing modefier of SMN2 (antisense oligoeucleotide)	Approved by FDA and EMA (december 2016 and May 2017)	Intrathecal Administration Of 3 loading dose at 14 day interval 4th dose after 30 days of 3rd dose, Maintenance dose at every 4 months.	All ages andall types of SMA	Upto 125000$per dose. Drug cost for firstyear 750000$ then 375000$ Annually

Table 1.2 Approved therapy for SMA-Onasemnogene abeparvovec (Zolgensma; Novartis).

Approved therapy	Mechanism ofaction	Stage of Development	Route of Administration and protocol	Populationtargeted bylicense	Cost
Onasemnogene abeparvovec (Zolgensma; Novartis)	Replacement ofSMN1 gene.	Approved by FDA and EMA (May 2019 and May2020)	Intravenousinjection	Treatment of pediatric patient with < 2 years With SMA bi-allelic mutation in SMA1 gene	2125000$ Per single injection

Table 1.3: Approved therapy for SMA-Risdiplam (Evrysdi; Roche).

Approvedtherapy	Mechanism ofaction	Stage of Development	Route of Administrationand protocol	Populationtargeted bylicense	Cost
Risdiplam (Evrysdi;Roche)	Risdiplam Facilitates the Highly Specific Inclusion of Exon 7in the Mature Transcript to enableProduction of Sufficient Functional SMN Proteins	Risdiplam Wasfirst Approved by the FDA in August2020	Orally administered	Adults and children 2 years of ageand older weighing 20 kilograms (kg) or more— 5 milligrams (mg) once a day. Children2 years of ageand older weighing less than 20 kg	One bottle costs about Rs 6lakh, with a dosage of 0.75 mg/ml powder for oral solution

NUSINERSEN (SPINRAZA; BIOGEN)

Background

An antisense oligonucleotide that induces survival motor neuron (SMN) proteinexpression, it was approved by the U.S. FDA in December, 2016 as Spinraza for the treatment of children and adults with spinal muscular atrophy (SMA). It is adminstrated as direct intrathecal injection.

Biologic Classification

Gene Therapies, Antisense oligonucleotides

PHARMACOLOGY

Indication

Indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients

Mechanism of action

Nusinersen is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide (ASO) designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency.

Antisense Oligonucleotide. ASOs are single-stranded, highly-modified, synthetic RNA, DNA and sequences, designed to selectively bind via complementary base-pairing to RNA which encodes the gene of interest, The main pharmacological action mechanism of the 2-O-methoxyethyl phosphorothioate-modified drug nusinersen consists of an alteration of the SMN2 pre-RMA splicing process by inhibiting splicing factors. This facilitates the integration of exon 7 into the mRNA and thereby enhances full-length SMA protein levels.

Absorption

Intrathecal injection of nusinersen into the cerebrospinal fluid (CSF) allows it to be distributed from the CSF to the target central nervous system (CNS) tissues.

Metabolism

Nusinersen is metabolized via exonuclease (3'- and 5')-mediated hydrolysis primarily at the 3' end of the oligonucleotide

Volume of distribution

CSF: 0.4 L Plasma: 29 L

Route of elimination

Excreted by the kidney as chain-shortened oligonucleotides, which are not considered pharmacologically active.

Half-life

The mean terminal elimination half-life is estimated to be 135 to 177 days in CSF,and 63 to 87 days in plasma

IMPORTANT SAFETY INFORMATION

Increased risk of bleeding complications has been observed after administration of similar medicines. Your healthcare provider should perform blood tests before you start treatment with SPINRAZA and before each dose to monitor for signs of these risks. Seek medical attention if unexpected bleeding occurs.

Increased risk of kidney damage, including potentially fatal acute inflammation of the kidney, has been observed after administration of similar medicines. Your

healthcare provider should perform urine testing before you start treatment with SPINRAZA and before each dose to monitor for signs of this risk.

The most common side effects of SPINRAZA include lower respiratory infection, fever, constipation, headache, vomiting, back pain, and post-lumbar puncture syndrome.

ONASEMNOGENE ABEPARVOVEC (ZOLGENSMA;NOVARTIS)

Background

Onasemnogene abeparvovec is an adeno-associated virus vector-based gene therapy that has been approved by the FDA in May 2019 for the treatment of infant patients (less than 2 years of age) with spinal muscular atrophy (SMA) and a specific mutation in the survival motor neuron 1 (SMN1) gene

Biologic Classification

Gene Therapies

PHARMACOLOGY

Indication

Onasemnogene abeparvovec is indicated for the treatment of pediatric patients less than 2 years of age (neonatal and infant patients) with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene

Mechanism of action

A common mutation that causes spinal muscular atrophy involves a bi-allelic deletionof exon 7 in the SMN1 gene. Onasemnogene abeparvovec is gene therapy thatconsists of a recombinant self-complementary adeno-associated virus serotype 9 (AAV9) as a gene delivery vector, which contains a transgene encoding the human survival motor neuron (SMN) protein

After administration, this viral vector is shed and a copy of the gene encoding the human SMN protein is delivered, leading to cell transduction and expression of the SMN protein.

Absorption

There is limited pharmacokinetic information on onasemnogene abeparvovec.

Volume of distribution

When biodistribution was evaluated in autopsy studies, the highest levels of vector DNA were found in the liver. Vector DNA was also detected in the spleen, heart, pancreas, inguinal lymph node, skeletal muscles, peripheral nerves, kidney, lung, intestines, spinal cord, brain, and thymus.

Metabolism

There is limited pharmacokinetic information on onasemnogene abeparvovec. The viral vector and the survival motor neuron (SMN) protein are expected to undergo normal nonspecific cellular degradation.

Route of elimination

There is limited pharmacokinetic information on onasemnogene abeparvovec.

Half life

There is limited pharmacokinetic information on onasemnogene abeparvovec.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know about ZOLGENSMA?

ZOLGENSMA can increase liver enzyme levels and cause acute serious liver injury or acute liver failure which could result in death.

Patients will receive an oral corticosteroid before and after infusion with ZOLGENSMA and will undergo regular blood tests to monitor liver function.

What should I watch for before and after infusion with ZOLGENSMA?

Infections before or after ZOLGENSMA infusion can lead to more serious complications. Caregivers and close contacts with the patient should follow infection prevention procedures.

Decreased platelet counts could occur following infusion with ZOLGENSMA. Thrombotic microangiopathy (TMA) has been reported to generally occur within the first two weeks after ZOLGENSMA infusion.

RISDIPLAM (EVRYSDI; ROCHE)

Background

Risdiplam is an orally bioavailable mRNA splicing modifier used for the treatment of spinal muscular atrophy (SMA). It increases systemic SMN protein concentrations by improving the efficiency of SMN2 gene transcription.Risdiplam was approved by the FDA in August 2020 for the treatment of spinal muscular atrophy (SMA).Set to be substantially cheaper than other available SMA therapies, risdiplam appears to provide a novel and relatively accessible treatment option for patients with SMA regardless of severity or type

Indication

Evrysdi is an approved treatment for spinal muscular atrophy (SMA) in adults, children and infants aged 2 months and older.

Mechanism of action

A secondary SMN gene (SMN2) can also produce SMN proteins, but a small nucleotide substitution in its sequence results in the exclusion of exon 7 duringsplicing in approximately 85% of the transcripts - this means that only ~15% of the SMN proteins produced by SMN2 are functional, which is insufficient to compensate for the deficits caused by SMN1 mutations. Emerging evidence suggests that manycells and tissues are selectively vulnerable to reduced SMN concentrations, making this protein a desirable target in the treatment of SMA.

Risdiplam is an mRNA splicing modifier for SMN2 that increases the inclusion of exon 7 during splicing, which ultimately increases the amount of functional SMN protein produced by SMN2. It does so by binding to two sites in SMN2 pre-mRNA: the 5' splice site of intron 7 and the exonic splicing enhancer 2 of exon.

Absorption
The Tmax following oral administration is approximately 1-4 hours.3,7 Following once-daily administration with a morning meal (or after breastfeeding), risdiplam reaches steady-state in approximately 7-14 days

Volume of distribution
Following oral administration, risdiplam distributes well into the central nervous system and peripheral tissues.The apparent volume of distribution at steady-state is 6.3 L/kg

Metabolism
The metabolism of risdiplam is mediated primarily by flavin monooxygenases 1 and 3, with some involvement of CYP1A1, CYP2J2, CYP3A4, and CYP3A7. Parent drug comprises approximately 83% of circulating drug material.

Route of elimination
Following the oral administration of 18mg risdiplam, approximately 53% of the dose was excreted in the feces and 28% was excreted in the urine.

Half-life
The terminal elimination half-life of risdiplam is approximately 50 hours in healthy adults.

IMPORTANT SAFTEY INFORMATION
Before taking Evrysdi, tell your healthcare provider about all of your medical conditions, including if you:
If you are pregnant or plan to become pregnant, as Evrysdi may harm your unborn baby. Ask your healthcare provider for advice before taking this medicine are a woman who can become pregnant:

Before you start your treatment with Evrysdi, your healthcare provider may test you for pregnancy

Talk to your healthcare provider about birth control methods that may be right for you. Use birth control while on treatment and for at least 1 month after stopping Evrysdi

If you are an adult male. Evrysdi may affect a man's ability to have children (fertility). Ask a healthcare provider for advice before taking this medicine

The most common side effects of Evrysdi include
For later-onset SMA:fever
Diarrhea Rash
Respiratory infection

PROBLEMS RELATED TO TREATMENTCOST
How much Does Spinal Muscular Atrophy Treatment Cost in India ?
It is important to note that Zolgensma isn't marketed in India, and has to be imported from the US if prescribed by a medical practitioner. At $2.125 million, it is touted to be the world's most expensive drug. The price, according to industry sources, is due to the low incidence of the disease, which means a smaller number of patients, aswell as the significant costs in the research in gene therapy and the drug development process.

The Novartis drug is one of the only three drugs in the world for SMA — Biogen's Spinraza and recently, Roche and Genentech's Evrysdi are the other

Spinraza costs $750,000 for the first year and $375,000 for every subsequent year.

Evrysdi, an oral drug which may be coming to India soon, requires the patient to take it for their entire lifetime, and can cost up to $340,000 per year.

Hurdles
Apart from the cost of the drug itself, customs duty and GST can both be levied on import, which comes up to roughly 30% of the cost of the drug. Finance Minister Nirmala Sitharaman said earlier this year that the customs duty on such lifesaving drugs is waived off, but will attract GST of 5%

Policymaking and accessibility
The Union government recently released the National Policy for Rare Diseases, 2021, which classified various rare diseases into three categories, based on level of treatment available and its cost. It states that the government will not be able to cover the high cost of treatment, and that it will set up a voluntary crowdfunding mechanism.

MEDICAL MANAGEMENT
Respiratory muscle weakness
When the respiratory muscles weaken, air doesn't move into and out of the lungs very well, with subsequent adverse effects on general health.

Many physicians advise starting out with **noninvasive ventilation**, which generally means that air is delivered under pressure through a mask or mouthpiece. This kind of system comes in many forms and can be used as many hours of the day and/or night as necessary.

When noninvasive ventilation isn't sufficient, ventilation assistance can be delivered through a **tracheostomy** — a surgical hole in the trachea, or windpipe. Air under pressure is then delivered through a tube in the tracheostomy site.

Other necessary aspects of respiratory care in SMA

include clearance of respiratory secretions, sometimes also achieved with a mechanical device, and prevention of infection. An **insufflator-exsufflator** is one type of device that can assist with clearing respiratory secretions from the airway. The device applies positive pressure to the airway and then rapidly reverses to negative pressure, mimicking a natural cough.

Swallowing muscle weakness

Babies with infantile-onset SMA usually have trouble swallowing and sucking. Sucking weakness can lead to dehydration and poor nutrition, while swallowing weakness can lead to obstruction of the airway and respiratory infections from inhaled food or liquids.

Babies with severe swallowing and sucking weakness can be fed by alternativemethods, such as a feeding tube, often called a **gastrostomy tube or g-tube.**

Anesthesia concerns

A child or adult with SMA who must undergo surgery needs to take special precautions. The surgical team, particularly the anesthesiologist, must thoroughly understand SMA.

Sometimes, especially in the early stages of SMA, the muscle cells that aren't receiving nerve signals develop certain abnormalities as they try to "reach out" to nerves. These abnormalities can lead to dangerous reactions to muscle-relaxing drugs often used during surgery. Doctors can get around this problem, if they're aware of it, by using different drugs

Back muscle weakness with progressive spinal curvature

Weakness of the muscles of the back that normally support the flexible, growing spine is a major problem in childhood-onset SMA. If it's not corrected, the child may develop **scoliosis**. The permanent solution to spinal curvature is almost always **spine-straightening surgery,** which can be done if the child's respiratory status is good enough to withstand the surgery.

The timing of back surgery is tricky. Doctors generally like to wait until maximum spinal growth has been achieved because that allows a simpler surgical technique to be used. On the other hand, if respiratory status is deteriorating, surgery often can't wait until growth is complete.

CONCLUSION

SMA is a genetic neuromuscular disease that can significantly affect quality of life and life expectancy. It's a progressive disease that gets worse over time. Symptoms may be present at birth (type 1), or develop during childhood (type 2 or 3) or in adulthood (type 4).

Despite major progress in our understanding of the biological consequences of SMN reduction, the pathogenic mechanism of SMA by which low levels of SMN protein lead to selective loss of motor neurons remains undefined. Regardless, preclinical development has led to several SMN-restoring therapies that have shown dramatic success in animal models of the disease, and several of these candidates are currently being testing in early phase clinical trials. Newer disease-modifying and gene replacement therapies offer promise. It's possible to carry the gene that causes SMA and not know it. If SMA runs in your family, talk to your doctor about ways to lower your future baby's chance of getting SMA.

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