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Onasemnogene Abeparvovec: Revolutionizing Spinal Muscular Atrophy Treatment Landscape

Diana A, Lavanya M[1]*, Nallappan G[2], Sanjay S[3], Saran Raj T[4], Gowarthanan Ranganathan[5] and Saranya Thamuraj[6]

[1,2,3] Faculty of Pharmacy, Karpagam academy of Higher Education, Coimbatore
[4,5]CAS in Marine Biology, Faculty of Marine Sciences, Annamalai University Parangipettai

***Corresponding author:** Lavanya M, Faculty of Pharmacy, Karpagam academy of Higher Education, Coimbatore.

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Abstract

This content introduces spinal muscular atrophy (SMA) gene therapy with onasemnogene abeparvovec, focusing on its development, mechanism of action, and impact on patients. Loss of motor neuronee is a genetic condition known as SMA, and onasemnogene abeparvovec aims to provide a working copy of the gene for survival motor neuronee SMN. The article explores the severity grades of SMA, the current treatment landscape, management strategies, and nutritional challenges faced by patients. It explores the economic considerations of gene therapy, comparing costs with other SMA treatments. Safety profiles, adverse events, patient selection criteria, and clinical studies are also discussed. The document concludes with insights into the future direction of SMA therapy, emphasising ongoing advancements and emerging treatments like Zolgensma.

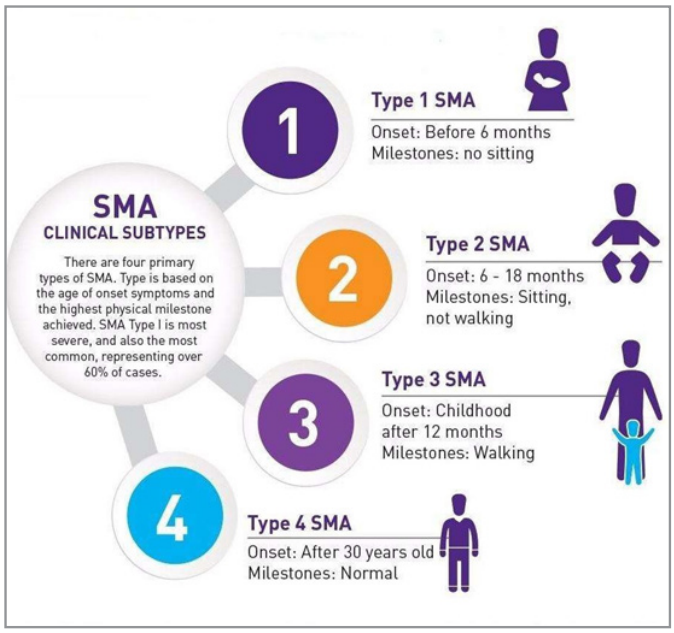
Keywords: Spinal Muscular Atrophy (SMA), Onasemnogene Abeparvovec, Gene Therapy, Zolgensma, Motor Neuron Disease, SMN1 Gene, SMN2 Gene

Introduction

Adeno related viral vector based genetic treatment called onasemnogene abeparvovec, aims to provide patients with werdnig hoffmann diseases a functional copy of the human survival motor neuron werdnig hoffmann (Day, J.W., et al.,2018) Young infants and children experience compromised and deteriorating voluntary muscles due to a hereditary disorder called spinal muscular atrophy (SMA) [1]. SMA is proven to be the most frequent inherited cause of newborn transience [2]. Put more accurately, SMA is caused by a deficiency of the SMN1 gene [3].

Symmetric muscular weakness is caused by progressive death of smaller motor neurons in the brain stem and spinal cord Dosage recommendations are 1.1 × 1014 vector genomes per kg of bodyweight, given as a sole injection into the vein over sixty minutes It was developed by AveXis, a Novartis firm, and accepted in the US in May 2019 [4]. the initial gene therapy was known as onasemnogene abeparvovec agree to for SMA in the United States [5]. A genetic condition called autosomal recessive spinal muscular atrophy results in steadily declining spinal cord motor neuron cell in the spinal cord, leading to paralysis and weakening of the muscles [6, 7].

The incidence is one baby for every 6000–10,000 live births. In the US, there are one or two cases per day [8].



About Sma

Eventually lowering proximal muscle and subsequent paralysis are caused by alpha nerve cells in the spinal cord in weirding and Hoffmann diseases, a severe neuromuscular disorder. Hoffmann as well as Werdnig provided the earliest descriptions of the illness in the 1890s [9]. When these motor neurons are absent, signals to the skeletal muscle inside the spinal cord are stopped, causing an increase in adjacent muscular lassitude and immobility. it has a 4-severity degree linked with SMA phenotype (SMA I, SMA II, SMA III, and SMA IV) etermined by the age at which beginning takes place at the level of motor function developed [10, 11].

The Worst Range,

- **TYPE 1**

TYPE 1 keeps the patient from sitting. kids that have SMA type I exhibit extreme weakness and hypotonia along with sparing of the face muscles, which are always linked to a normal breathing pattern. Lower limbs are typically weaker than upper limbs, and the fragility typically equal and more proximal than the distal [12]. Paradoxical breathing is caused by a compromised diaphragm and weak intercostal muscles [13]. When swallowing increases, tongue fasciculation and poor sucking and swallowing are frequently caused by the involvement of bulbar motor neurons [14].

- **TYPE 2**

It impairs them from walking. The extreme type II patients can have joint contractures and kyphoscoliosis in their early years of life [15]. Symmetric muscular weakness is caused by a progressive death of smaller motor neurones in the brainstem and spinal cord. This condition is characterised by an initial in a span of 7 to 18 months [16].

- **TYPE 3**

Every patient can walk to a certain extent.Another name for spinal muscular atrophy type 3 is Kugelberg-Welander syndrome. SM spinal muscle atrophy beginning between the ages of two and seventeen SMA3 usually appears after the age of 18 months, though subtle symptoms may appear before [17, 18] Examining a youngster with SMA3 reveals limb girdle and proximal muscle atrophy. When compared to more distal locations (forearm, calf), there is a noticeable reduction in muscle bulk. The distribution of weakness is the same as that of muscle wasting.

- **TYPE 4**

The adult-onset SMA occurs, the most prevalent neurological findings were fasciculation and missing tendon reflexes, while the most common clinical complaint was limb-girdle muscle weakness [19]. SMA type 4, or mature beginning SMA, is uncommon. The most common type of spinal muscular atrophy, accounting for 45–60% of cases, is type 1.this hallmark of Werdnig Hoffmann diseases is chronic symmetric muscle weakness, which can be exacerbated by failure to grow, scoliosis, joint tightness, Mitochondrial functionality decreases with age, which also impairs the symptoms of SMA The stimulation of p53-mediated apoptosis as a result of poor pre-mRNA processing after splicing is one of the primary factors in the growth of SMA [20-22]. A recessive autosomal inheritance pattern characterizes SMA [23]. Each time a couple with a child diagnosed by SMA becomes pregnant, there is a about 25% risk that the unaffected child will not be a carrier, a 50% probability that the carrier will not exhibit symptoms, and a 25% chance that the affected child will be affected [24, 25]. If a family member's diagnosis of SMA has been verified through molecular genetic testing, then carrier screening for at-risk relatives and prenatal testing for pregnancies at elevated risk are feasible [26, 27].

Current Landscape Treatment for Sma:

Modifications to the survival motor neuron gene cause A mutation or reduction SMN1 is the reason behind the illnesses however, the objective picture is altered by a inconsistency known as SMN2, which is nearby in all individuals at attending opies [28, 29]. In general, there is less full-length SMN protein in the presence of additional SMN2 copies. All eukaryotic cells depend on the SMN protein Maybe as a result of its essential role as a partner in the synthesis of the spliceosomal unit of proteins About 5 million years ago, there was a duplication event that resulted in the human-specific SMN2 gene and a little upsurge in full length SMN [30, 31]. Normally, homozygous deletion of the normal

SMN1 gene would result in death [32, 33].

SMN2 splicing regulation is an important target for therapy because it may be possible to halt motor neuron degeneration with a slight grow in the full-length SMN protein. Nusinersen, often referred to as Spinraza, is a 2'-O-methoxyethyl (2'MOE) altered antisense oligonucleotide that is sketch to bind to the SMN2 pre-mRNA in order to corresponding to intronic fusion silencer found inside intron 7 As a result, the negative splicing factors hnRNP A1 and A2 are displaced and are unable to interact with the SMN2 pre-mRNA. In order to recognise exon 7 during splicing and produce complete RNA and a protein with function, this encourages the presence of codon 7 in an U1snRNP [34-38].

Management Strategy for Sma Patients

Currently, supportive and multidisciplinary care is the cornerstone of Spinal muscular atrophy management, with an emphasis on lowering complications and enhancing quality of life. For Spinal muscular atrophy types I and II, pulmonary illness is each primary cause as concern death, while for SMA type III, it affects a small percentage of individuals [39]. The four main management techniques are continuous non-invasive breathing, nocturnal non-invasive ventilatory support cough help, and airway clearance [40]. Constipation, delayed stomach emptying, and gastro-oesophageal reflux are examples of digestive dysfunction Prokinetic agents and acid neutralizers are used in medical management Laparoscopic Nissen fundoplication and gastrostomy tube implantation have being sometimes done in arrangement to lessen The main interventions used to raise patients' both functional level and standard living are pain management, limb orthotics, assistive technology, physical therapy, occupational therapy,nutrition assistance ,as well as posture be head of Managing optimum nutrition, particularly for children, is a top challenge in spinal muscular atrophy types I and II because feeding difficulties include GOR, aspiration, chewing and eaten are common In SMA populations, height, body weight, and body mass index are low to usual; few people are obese or overweight [41-44].

In individuals with various neuromuscular illnesses and chronic respiratory failure altered body composition, especially reduced lean body mass, has been linked to more adverse results, such as a lower quality of life and more respiratory work [45]. Vagaries in body composition, especially low lean body mass, have been linked to worse outcomes in individuals with various neuromuscular illnesses and chronic respiratory failure [46]. These include lower quality of life and higher respiratory work. SMA patients may be exposed for malnutrition, vitamin deficits, and altered body composition, hence dietary support is crucial [47]. Consuming and ingestion Particularly in light of more recent therapies that may have an impact on their metabolic states, individualised nutrition therapy for SMA patients could enhance their quality of life, change their body composition, and lower morbidity [48,49].

Furthermore, children with SMA are more susceptible to acidosis in this situation due to metabolic abnormalities they have shown to be consistent with an extensive deficiency in fatty acid metabolism [50]. Observational studies aim was to evaluate each appropriateness of using standardised growth spinal muscular atrophy and, to provide an account of body composition, calorie intake, and macro- and micronutrient intakes and the amount of bone minerals those with type 1 spinal muscular atrophy Over time, nearly half of the cohort showed signs of nutritional deterioration. For most of the cohort, energy, protein, and the antioxidant vitamin D intakes were insufficient [51,52].

Mechanism Action Onasemnogene Abeparvovec

Onasemnogene abeparvovec, previously identified as AVXS-101, represents a non-replicating, self-complementary gene therapy utilising an adeno-associated viral vector–9 (scAAV9) [53]. This therapy carries a fully functional survival motor neuron protein-encoding gene to motor neuron cells. AAV, a non-enveloped, single-stranded DNA virus, relies on helper viruses for its life cycle completion and demonstrates successful transduction in neurons [54]. Various AAV serotypes, differing in capsid properties due to distinct neutralising antibodies, affect receptor affinity and determine vector tissue tropism. Notably, scAAV9 vectors, containing double-stranded, self-complementary DNA, enable rapid protein synthesis post-transduction into host cells [55].

Overcoming the blood-brain barrier challenge, AAV9-based gene therapy exhibits superior CNS transduction in non-human primates' cats, rats, and neonatal and adult mice CNS transduction exist. In vivo studies, using AAV9 vectors carrying green fluorescent protein, demonstrated successful expression, particularly in brain and spinal cord motor neurons [56]. Intravenous injection outperformed intraperitoneal and intramuscular routes, with transgene expression lasting at least 5 months [57]. These findings, validated in cynomolgus macaque models, paved the way for human trials, showcasing the promising potential of AAV9 vector-based gene therapy [58].

Onasemnogene Abeparvovec-Xioi (Zolgensma®), an FDA-approved and EMA-approved gene replacement therapy, utilises intravenously administered AAV9 for a single-dose SMN1 GRT, [59]. enhancing SMN creation of proteins in both the central region of brain and peripherally. Approved in 2019 by the FDA and 2020 by the EMA for children under two with SMA, Zolgensma® employs self-complementary AAV9 technology and a hybrid CMV-enhanced chicken β-actin booster, ensuring high and persistent SMN expression in CNS motor neurons [60]. The AAV9 serotype's ability to cross the hematoencephalic barrier facilitates aim at critical cells in SMA pathogenesis. Zolgensma®'s self-complementary feature, delivered as dsDNA, allows for rapid episome formation, resulting in a swift onset of effect [61]. With MNs being long-lived, a single administration of AAV9 GRT is anticipated to provide lifetime episomal transgenic mice expression [62].

Economical Consideration: Cost And Access

The report's main focus was on the two SMA medicines that the US Food and Drug Administration had accepted [63]. At $2.125 million, zolgensma has earned the title of "most expensive drug in the world." For a $100,000 investment per QALY achieved, the price of Zolgensma should be $310,000, which is 6.9 times cheaper than the stated price [64, 65]. The wholesale purchase cost of Spinraza, an intermittent intrathecal infusion, is $805,000 for initial year of counselling and $380,000 for each additional the year that followed [66]. At the $100,000 per quality adjusted life year investment point, the Spinraza SMA type 1 presymp-

tomatic cost-effective modelling revealed a cost of $72,800 per QALY in year 1 and $36,400 every QALY gained in year 2 and beyond. Consequently, for a reasonable pricing at, the current Spinraza price should be decreased by ten times.

The maximum annual cost of Spinraza is $36,400 because of its statistically significant but limited therapeutic efficacy [67]. 29% of treated newborns in the Spinraza infant onset SMA of type 1 were permitted to sit independently, and 100% of treated infants had complete head contro l [68]. At 24 months, 92% of infants in Zolgensma were able to manage their heads, and 17% were able to walk on their own Assessing the financial worth of each incremental cost Comparing the best supportive care (BSC) or nusinersen (Spinraza®) against onasemnogene abeparvovec in symptomatic SMA1 patients, and contrasting the year of quality adjusted life (QALY) to the ICER model [69, 70]. In the US -value based pricing incremental saving ratio utilizing conventional criteria for general pharmaceuticals are contrasted with nusinersen, an antisense oligonucleotide, and onasemnogene abeparvovec, a –one time use of gene replacement therapy.

The Model Predicted an Undiscounted

updated survival of 37.60 years for onasemnogene abeparvovec, vs 12.10 years for nusinersen and 7.27 years for BSC. The revised quality adjusted survival was determined by utilizing ICER's utility ranking and discounted at 3% led to discounted QALYs of 13.33, 2.85, and 1.15 for onasemnogene abeparvovec, nusinersen, and BSC. The ICER model predicted that in the people with and without symptoms of SMA, the cost per QALY gained would be $139,000 for onasemnogene abeparvovec compared to nusinersen and $243,000 for BSC. When comparing nusinersen to standard of therapy in SMA1, the incremental cost- effectiveness ratio (ICER) varied from $210,095 to $1,150,455 each a year of quality-adjusted living (QALY) gained. Similarly, when comparing onasemnogene abeparvovec to standard of care, the ICER varied from $32,464. An ICER value of $206,409 to $735,519 was found for individuals who were not symptomatic. For spinal muscular atrophy the ICERS for types 2,3, and 4 of spinal muscular atrophy varied ranged from $275,943 to $8,438,049, indicating a greater degree of diversity [71].

Safety Profile and Adverse Event

Onasemnogene abeparvovec, a gene therapy linked to specific adverse events, necessitates vigilant monitoring for effective management [72]. Understanding potential correlations between adverse events and viral vector dose is crucial, prompting the need for further research to identify specific risk factors [73]. Patient selection, evaluating recent infections, active infections, and signs of indication of prior liver imbalance, is pivotal for protection and treatment suitableness. Liver monitoring post-infusion is imperative, with baseline tests and ongoing assessments. Dosing caution is advised if liver enzyme levels exceed limits. Prednisolone treatment, initiated before and after infusion, is recommended [74]. Thrombocytopenia requires regular platelet count monitoring, especially during the initial months post-infusion, with early recognition of thrombotic microangiopathy (TMA) symptoms.

Cardiac events demand baseline Troponin I assessment and continued monitoring. For DRG cell inflammation, a detailed neurological examination is crucial [75]. Onasemnogene abeparvovec demonstrates consistent safety for SMA patients over six months old. While intravenous administration is common, ongoing studies explore intrathecal delivery. Common side effects encompass vomiting and elevated aminotransferases. Additional effects incorporate pyrexia, thrombocytopenia increased troponin, and upper respiratory infection. FDA approval extends to SMA patients under two years old, specifically with SMA type 1 symptoms and SMN2 gene mutations [76].

Treatment outcomes from 250 SMA patients, primarily SMA type 1, highlight the therapy's efficacy and safety. Clinical data, gathered over a minimum hospital stay and outpatient observation, emphasise the therapy's overall safety. Although hepatic transaminase activity increased universally, brief drops in platelet count occurred, and post-marketing observations noted thrombotic microangiopathy (TMA). Factors for example age, weight, SMA type, SMN2 copy number, and liver enzyme elevations are integral considerations in assessing therapy- related outcomes [77].

Patient Selection and Preparation

Prior to AAV9 application, it is crucial to assess children for underlying health conditions such as severe liver disease, thrombocytopenia, or any genuine health related problems that might increase the peril associated with AAV9 therapy. Respiratory infection, as evidenced in the STR1VE-EU study, resulted in severe outcomes, emphasizing the potential impact of viral illness even in SMA-treated individuals [78, 79]. Age and weight restrictions for onasemnogene abeparvovec vary by authority, with there is a less data regarding reliability and efficacy in order, heaver patient, or those win an advanced a sickness [80]. Comprehensive research is necessary to evaluate the treatment for these populations, and a thorough risk-benefit analysis is essential before initiating therapy. Additionally, counselling on potential adverse events is mandatory pre- dosing, with diligent clinical and laboratory observation in the subsequent from weeks to months, despite the single-administration nature of gene therapy [81, 82].

Clinical Studies

Demographic and the study's subjects' base line clinical characteristics are described in Table 1 of the supplementary materials [83]. Almost all patients, 99 out of 102 (97%), encountered the minimum of one adverse event related to treatment emerges, with 56.9% of them linked to the treatment [84]. In 49% of patient, there where serious adverse event and 10.8% of these were considered treatment-related (refer to Table 3). Notably, commonly reported SAEs, such as pneumonia and respiratory distress, were not deemed treatment-related enhanced results on liver function test and pyrexia were among the treatment related SAES that where consistently reported (2.0% each) [85, 86].

In post marketing analysis, 660 case reports, comprising 2400 adverse events (AEs), were identified, with 703 being classified as SAEs. Predominant events with over 50 reports included pyrexia, vomiting, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), elevated hepatic enzymes, decreased platelet count, increased liver function test results, and thrombocytopenia [87]. Although occasional fluctuations in out of the vital sign values recorded, none were sustained or maintained clinical significance [88]. Utilizing prednisolone

was linked to higher blood pressure screens without adverse event AES did not reveal any clinically significant aberrant findings [89]. The report highlights deaths in young ones following onasemnogene abeparvovec oversight (see pages 6–8 of the supplementary materials). There were three recorded deaths in clinical trial by November 12, 2020, including two in STR1VE-US (one during screening, not treated) and one in STR1VE-EU [90]. It was a determined that two more death in the post marketing data were more likely to be caused by underlying SMA and less likely to be connected to onasemnogene abeparvovec [91].

Future Direction and Emergence Therapy

Even though the genetic underpinnings of SMA are well recognized it was possible to conclude from the scientific facts at hand that there are still many unknowns regarding its etiology, and that just three medications—Risdiplam, Nusinersen, and Onasemnogene Abeparvovec-Xioi— have recently received approval Using the available data, we examined the cost-effectiveness of Zolgensma® GRT and found that, for paediatric SMA patients, a single dose of Zolgensma® GRT was more affordable than chronic Nusinersen [92]. This was linked to decreased pulmonary support requirements and improved motor function during the follow-up period. Our investigation also led us to the conclusion that Risdiplam is a small molecular alteration of mRNA administration ornaments that allows the survival motor neuron 2 gene to create a effective SMN protein. Nusinersen is a completely gene expression modulator that facilitates the incorporation of the extra 7 nas transcribed from the mRNA of the SMN2 gene, with no effect on the functional expression of the SMN protein [93].

The novel genetic therapy drug Zolgensma® is made up of a viral AAV9 that binds to the person SMN1 gene beneath the resolution of the chicken β-actin promoter, allowing the amount of functional SMN protein to be present in motor neurons and, as a result, enhancing neuronal and muscular function [94]. A cutting-edge medication and gene therapy approach for SMA sufferers is called Zolgensma. [95]. Prolonged All SMA I infants in the therapeutic-dose group were active and did not demand continuous aeration, according to a follow-up study. An extra milestone of standing with help was attained by 20% of SMA I newborns, according to reports. The disease phenotype is being altered by these treatments, in addition to enhancing the lives of SMA patients and their families [96, 97]. When administered at an early stage of the illness, they are most beneficial. Therapy aimed at the Survival Motor Neuron (SMN)—Independent Factors include splicing modifiers of SMN2 (nusinersen, small compounds) and therapies that replace the SMN1 gene (onasemnogene abeparvovec [98].

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