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Zolgensma : A curative treatment for a severely debilitating disease

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ABSTRACT

Spinal Muscular Atrophy, a fatal genetic neuromuscular disease is distinguished by progressive muscular weakness , atrophy and paralysis . The 5q SMA is characterized by the degeneration of alpha motor neurons in the ventral horn of the spinal cord. It has a clinical spectrum that ranges from premature death of an infant to a normal life with slightly expressive muscular weakness. Onasmogene Abeparvovec is one of the three FDA approved treatment options for this disease. It is a gene therapy that is non replicating and self complementary in nature . It is an Adeno Associated Virus -9(AAV 9) vector that delivers a completely functioning SMN gene that encodes the SMN protein to the neurons, thus addressing the root cause of SMA by delivering the missing SMN1 gene to the neurons. This drug can enhance the motor functioning of the infants but it cannot reverse any disabilities appeared before the administration of the drug. Although clinical trials have revealed a tremendous information about the drug, it is imperative for these studies to continue to gather knowledge on its long term use.

INTRODUCTION

Onasmogene Abeparvovec , marketed under the trade name of Zolgensma is an orphan drug that paved a way to novel treatment options in medical care for targeted minority population affected with rare diseases[1].It is indicated for type 1 5q SMA . Spinal Muscular Atrophy , a fatal genetic neuromuscular disease is distinguished by progressive muscular weakness , atrophy and paralysis[2] .It is a recessively inherited monogenic neurodegenerative disease that severely enervate the patient [3]. The 5q spinal muscular atrophy is characterized by the degeneration of alpha motor neurons in the ventral horn of the spinal cord [4,5] .The degeneration being caused by the homozygous deletion or the mutation of the Survival Motor Neuron (SMN1) gene . The loss of SMN1 gene results in drastic reduction in the synthesis of SMN protein needed for survival of motor neurons [3]. It is found to be the second most prominent autosomally recessive disorder after cystic fibrosis with an approximate estimate of 1 in 11,000 occurrence [2,6] .It has a clinical spectrum that ranges from premature death of an infant to a normal life with slightly expressive muscular weakness. There also exist non 5 q associated spinal muscular atrophy which is not caused by the mutation in SMN gene and makes 5% of all SMA cases .[7].

The severity of 5q SMA is mostly varying and patients can be clinically classified into five (Table .1) [2,6]. The classification depended on the onset time, clinical manifestations and motor function. SMA 0 which is usually diagnosed in utero with the manifestations like respiratory distress and diffuse hypotonia on birth might obligate the mechanical ventilation [8]. SMA 1 is the most common type of the disease with about 60% of the patients being diagnosed with this type. Patients might face difficulty in breathing and feeding .The disease onset is within 6 months and infants usually express extremely deficient head control . Survival time of such infants without mechanical

Table 1 : Classification of SMA

Type	Name	Age onset	SMN2 copy number	Clinical manifestations	Implication
0	Prenatal	In utero onset	1	Joint contractures, Respiratory distress, Diffuse hypotonia	Not able to survive neonatal period without intervention
1	Acute infantile/ Werdnig Hoffman disease	0-6 months	2	Hypotonia, Difficulty breathing, motor delays, Scoliosis, Bulbar dysfunction, Dysphagia	Never be able to sit , Pulmonary complications persists
2	Chronic infantile/ Dubowitz disease	<18 months	3-4	Inability to walk, Respiratory symptoms	Feeding support required
3	Chronic juvenile/ Kugelberg Welander disease	>18 months	3-4	Ability to stand and walk but not retained for long	Gradual loss of ability to stand and walk
4	Adult onset	>21 years	4	Slow decline in the strength	Mild form of disease

ventilation is said to be approximately 2 years. Along with the pulmonary complications, scoliosis and bulbar dysfunction can manifest.. SMA 2 , where the clinical symptoms become evident in 7-18 months render the need for feeding support. Patients may be able to sit independently but may not be able to walk. They might develop scoliosis and might require bracing for the purpose [8]. Patients with SMA 3 might be able to stand and walk but it may not be retained for a long time as progressive loss of muscle function can occur. SMA 4 is the mildest form of disease that is of adult onset and might result in mild impairment in motor function and have standard life expectancy [6,9].

TREATMENT CHOICES OF SMA

In the year of 2005 SMA standard of care committee was formed and subsequently a standard consensus on the treatment and care of the patients were brought about[7]. Management of SMA obligates a multidisciplinary approach that comprise of supportive care, intense nutritional support , symptomatic management and foresighted rehabilitation programmes that ensures enhanced musculoskeletal functioning . Though the clinical diagnosis, classification, supportive management, family education and counseling were proposed, discussed and reviewed numerous times, it was with the advent of Nusinersen , an Antisense Oligonucleotide drug that the selective treatment of 5q SMA became possible.

Nusinersen (Spinraza) works by modulating the SMN2 pre - mRNA splicing there by including exon 7 in the messenger RNA . This guarantees the production of ample SMN protein required for the survival of neurons and elongation of dendrons and axons .It is administered intrathecally (12 mg dose equivalent) and has potential to modify pre symptomatic patient condition along with improving motor functions in a symptomatic infant. It is considered to be a lifelong therapy with 4 loading doses initially and maintenance dosing in every 4 month interval. It is indicated in all types of SMA and is recommended in both the pediatric as well as the adult population [9,10].It was the only drug in the market approved by FDA for SMA since its approval in 2016 till 2019 when FDA approved Zolgensma [9].

Unlike Nusinersen which modulates the mRNA splicing Onasmogene Abeparvovec (Zolgensma) is a gene therapy that is non replicating and self complementary in nature . It is an Adeno Associated Virus -9(AAV 9) vector that delivers a completely functioning SMN gene that encodes the SMN protein to the neurons. This drug was developed by an US company AveXis which now became a subsidiary of Novartis . It is the very first drug approved by the FDA which is an AAV gene therapy that is administered intravenously [11].While it can improve the disease progression , it cannot reverse any of the effects that occurred prior to its administration [12].

Risdiplam (Evrysdi) is the first orally administered drug molecule that is distributed systemically, to be approved by US FDA for Spinal Muscular Atrophy[13,14]. It is approved to be used in infants who are two months of age and older [15] . It is a drug that is available in the liquid form and acts on the pre mRNA splicing. The action on the site of exonic splicing enhancer two, helps in including exon 7 in the mRNA thereby resulting in enhanced production of SMN protein[14] .This action comparable to mechanism of Nusinersen which also acts on mRNA as a splicing modifier [16].

CLINICAL TRIALS

Prevalence of humoral immunity after an exposure to the wild type Adeno Associated Virus can result in the presence of antibodies that can neutralize this virus in the body [17]. This in

fact can be a hindering factor in the transduction process of the viral vector thus effecting the efficacy of the gene therapy . This made it mandatory to assess the AAV titers before the commencement of the therapy. Hence trials excluded every patients with an anti -AAV9 antibody titer greater than 1:50 [9,18]. Phase 1 and 2 clinical trails for Onasmogene Abeparvovec were conducted for assuring the safety of the drug in human population as well as the efficacy of the treatment [9,19]. It was initiated as Gene Transfer clinical trial for Spinal muscular atrophy type 1(START NCT02122952) where symptomatic patients were enrolled who had two SMN 2 gene copies present and had Bi- allelic mutations in SMN1 gene. A total of 15 patients (mean age was 3.4 months) were thus enrolled in two cohorts as a part of the study. Patients with onset of symptoms before 6 months of age were included as part of the study. The study was

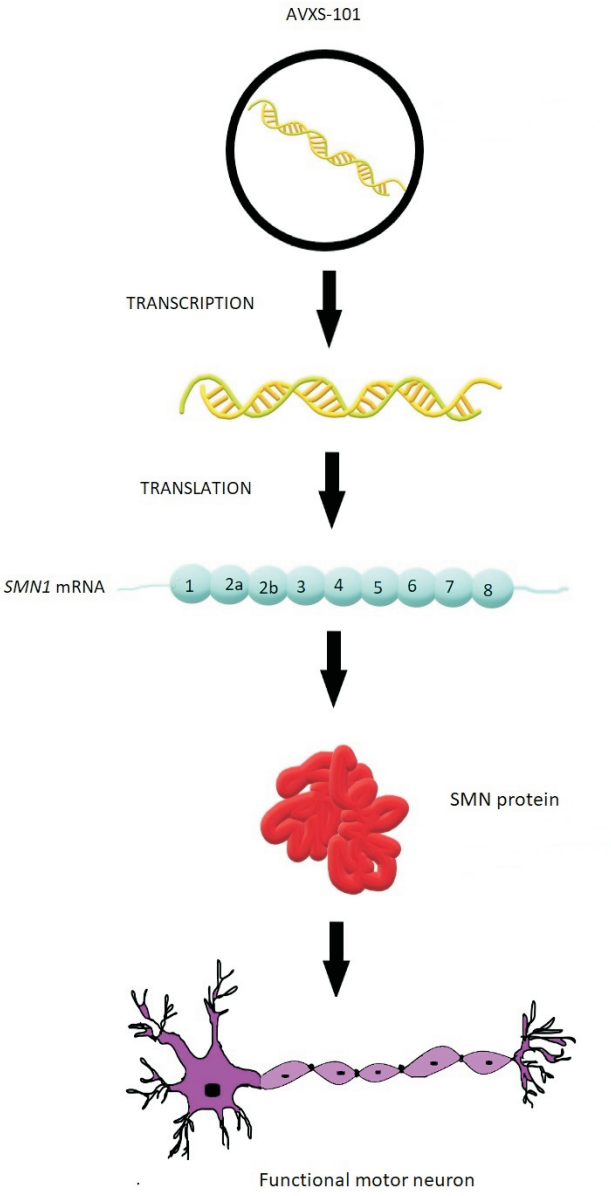

Fig 1 : Mechanism of Action of Onasmogene Abeparavovec

open label and single site and 12 patients were treated with a higher dose of Onasmogene Abeparvovec Xioi (2.04 e 14 vg/kg) and three infants with a lower dose (6.7 e 13 vg/kg) . Comparing the study with the historical cohorts were untreated patients with SMA were include, this therapy showed significant improvement in motor functioning and patients seemed to achieve numerous developmental milestones such as steady oral feeding , rolling over , ability to sit without support and further speaking and walking abilities .It was found that the infants who received higher dose had faster achievement of the motor function milestones than the other cohort [20]. Motor functioning was assessed using CHOP INTEND(Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scale and all infants were found to have an increase in the score from baseline [9,21]. Primary outcome of the trial was to determine the safety and to find any therapy related side effects as well as the adverse events of grade three or higher [9].The secondary outcome were determining the time interval between birth and death and the time required for assisted ventilation for more than sixteen hours per day[19]. Prednisolone was appended to the study protocol afterwards due to the findings of elevated serum transaminase levels in patients after 9 day of therapy and owing to serious hepatic injury in one of the patients [11].This uncharacterized elevation in the liver transaminase levels was hypothesized to be due to a massive immune related response to the bulk of viral peptides[20] .Participants of the START trial were followed as an observational study (NCT03421977) for a period of 15 years for a more elaborate safety assurance.

While the START trial and following long term observational study were single centre studies a global multicentre Phase 3 clinical trial of this drug known as the Gene Replacement Therapy clinical trial for Spinal Muscular Atrophy type 1 (STR1VE) were conducted with three regional specifications STR1VE-US in United states , STR1VE EU in Europe and STR1VE AP in Asian Pacific. These studies enrolled patients who were less than 6 months of age. STR1VE US (NCT03306277) was an open label, single dose and single arm study were 20 participants were planned and 22 were treated [22]. The study reported a survival devoid of serious events in 91% of the patients enrolled after 14 months of constant follow up [9]. STR1VE EU (NCT03461289) which was also an open label study with single dose infusion, planned 30 study subjects .But 33 patients were enrolled in the study of which 32 were followed up to 18 months of age. The primary outcome of this study was independent sitting of the infant for at least 10 seconds.14 of the 32 patients observed, achieved the primary endpoint where they were able to sit independently for at least 10 seconds.31 of these patients were freed from the use of mechanical ventilation[23].STR1VE AP (NCT03837184) study which submitted its primary report in January 2021, enrolled only 2 patients despite having planned on enrolling at least 6 patients .The study included three periods : screening , the gene replacing and follow up [24].

The study of AVXS 101 in pre symptomatic individuals intravenously was performed as SPR1NT(NCT03505099) were patients who were less than 6 weeks of age were enrolled [25] .A total of 29 infants were enrolled in two cohorts of which 10 patients who could sit independently achieved this milestone within standard developmental window as per WHO-MGRS(World Health Organization Multicentre Growth Reference Study)[22,26,27] .The safety and subsequently the tolerability of Onasmogene Abeparvovec on Intrathecal

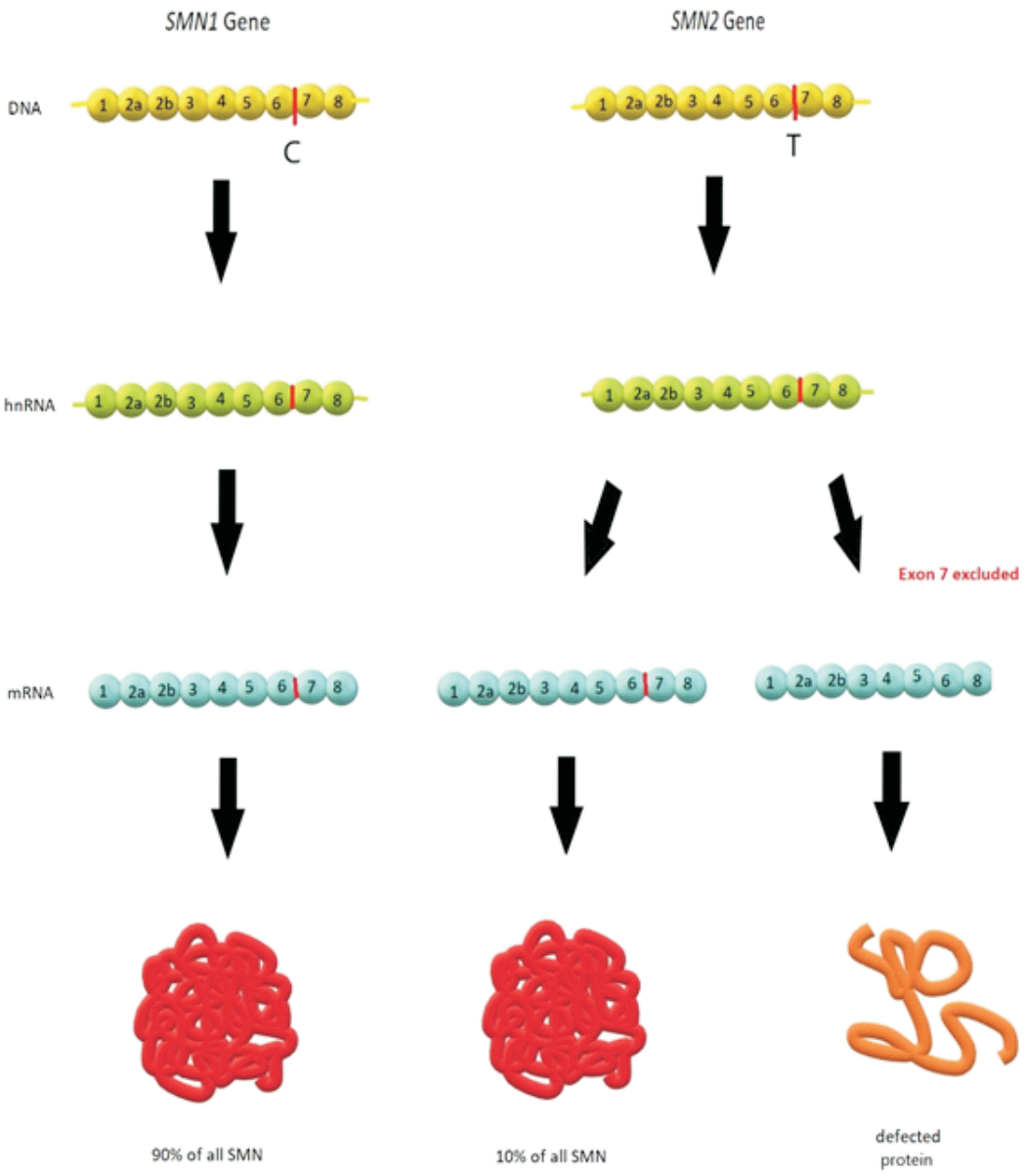

Fig 2 : SMN protein expression

administration was supposedly evaluated in the STRONG trial (NCT03381729)[28] . It was conducted in patients with at least 3 SMN2 copies and SMN 1 deletion. 32 infants were enrolled for the purpose of the study. This clinical trial was partially restricted by FDA in 2019 due to the concerns of Dorsal Root Ganglia injury and further Novartis declared its re initiation in 2021 after FDA lifted its partial hold owing to the non clinical toxicological study evidences in non human primate put forth by the company[29]. An additional study was planned to be initiated in Type 2 SMA patients known as STEER (NCT05089656) by Novartis. It is a multicentre , sham controlled study that is randomized with an overall trial duration of about 64 weeks[30].

MECHANISM OF ACTION

Zolgensma addresses the root cause of SMA by delivering the missing SMN1 gene to the neurons. Though Adeno Associated Viruses were proposed for similar gene therapies , Glybera in 2012 was the first the AAV based therapy approved by FDA[11] . Onasmogene Abeparvovec is a viral vector that contains a copy of human SMN1 transgene. The AAV9 vector delivers this copy of functional gene with the help of CMV (cytomegalovirus) enhancer/chicken beta actin hybrid promoters to the motor neurons which produces SMN protein[18] .This protein produced as a result of SMN gene translation is responsible for the survival and development of motor neurons (Figure 1). In patients with SMA , deletion of SMN1 gene or mutations within it can cause the reduced production of SMN protein [31] .On the very same chromosome is the SMN2 gene often represented as the backup gene for SMN1. While SMN1 produces SMN proteins in an ample quantity, the SMN2 produces only about 10%of functional proteins. The exon 7 exclusion due to splicing consequently prompt it to produce unstable or degraded protein

product after translation (Figure.2)[9].

PHARMACOKINETICS

Onasmogene Abeparvovec is a bioengineered vector that contains the genetic sequence of the protein that is needed for the proper functioning of neurons . AAV9 though has greater potential to traverse the blood vessels and penetrate blood brain barrier , cannot integrate itself into the host DNA . For the purpose it requires promoters sequences to assist transcription . As the intravenous injection guarantees a 100% bioavailability , even without any conclusive absorption study evidences , it is safe to assume the same bioavailability from the drug .Upon IV administration , the drug is rapidly distributed systemically. The 6 month IV safety and the bio distribution studies in mice assessed the bio distribution and expression of the transgene. The transduction of the viral vector into various tissues is dependent upon the tropism of the viral particle . Initial studies showed persistent and elevated tissue transduction on administration by IV. The transgene expression was found to be including major tissues (liver, heart, CNS). The persistence of the vector particles and transgene presence shows that drug was able to cross blood brain barrier with minimal obstacles. The autopsy report of two children who were being treated with the drug showed that kidney is a target organ for the vector[22] .Clinical trials also significantly collated data on vector shedding after infusion. The results showed that vector DNA is shed through saliva , urine and stool . But greater concentration of vector shed was found in stool [32].

ADMINISTRATION

Onasmogene Abeparvovec that is supplied by the manufacturers as a frozen kit needs to be thawed before use(4 hours at room temperature, 12 hours when kept in refrigerator). The drug that is taken into the appropriate syringe for administration should be given within 8 hours of drawing . Elaborate study on storage of the drug in syringes or tubings is not yet done. It is safer in polypropylene syringe and polyvinylchloride tubings and its extensions .Zolgensma is given as an one time infusion which lasts for about one hour , usually in an outpatient clinic .The dose is calculated according to body weight with a recommended dose of $1.1x10^{4}$ vg/kg [9].Prior to the administration assure that the receiving infant is not expressing any signs or symptoms of a concurrent infection. If found to be carrying any infection postpone the administration till it is resolved to avoid serious immune responses. Baseline test for the AAV9 viral vector gene therapy is anti AAV9 antibody titre .If it is above 1.5 , a retesting is recommended. Other clinical tests to be performed prior to the administration include , Liver function test, Serum creatinine , Troponin I and whole blood count. On the day before drug infusion systemic corticosteroids equivalent to about 1 mg/kg of the body weight is to be started[32].

CLINICAL SAFETY

The most commonly presented adverse events were asymptomatic transient rise in aminotransferase and vomiting .The rise in ALT and AST made it essential for the drug to be marketed with a boxed warning for Acute serious hepatic injury and liver failure. It was observed early , almost one week post AVXS 101 dose in the phase 1 safety clinical trial. Elevations that were rendered to be clinically significant were reported after three or four weeks [33]. This elevation makes it difficult for a patient with pre exiting liver injury to receive the treatment. It is for this purpose that mandatory liver function testing is done prior to the administration. The introduction of systemic corticosteroids as pre medication also serves a similar purpose of suppressing a potential liver injury or serious complications[9]. Therefore the constant liver function monitoring weekly in the first month and every other week in the second and third month is necessary [32]. Platelet count is to be monitored with great care as thrombocytopenia was reported as a serious treatment emergent adverse event in the four studies conducted in the initial stages [22] . Thrombotic microangiopathy that is manifested as thrombocytopenia , acute kidney injury , microangiopathic hemolytic anemia , bruising, seizures, hypertension and decreased output of urine was also reported as an adverse reaction . Troponin I elevation made the weekly testing of Troponin I value mandatory and after the first month , monthly monitoring was recommended as cardiac toxicity was reported in animal studies[12,32].In the initial clinical trail of zolgensma CL -101(START) 16.7% of the individuals experienced adenovirus and enterovirus infection, 8.3% manifested tachycardia .58.3% of the infants contracted pneumonia. STRIVE EU(CL-302) showed that 6.1% of infants showed pyrexia and bronchiolitis each. And another 9.1% showed respiratory tract infection[22]. Post marketing studies mostly reported the adverse events of acute liver injury, thrombotic microangiopathy , thrombocytopenia and pyrexia. The infusion of the drug before the fetus reaching full gestational age is not recommended by the manufacturer. The studies in mothers who are seropositive for the AAV9 antibody and are breastfeeding is not yet done[32].

ECONOMICAL PERSPECTIVES

Zolgensma was given the title of most expensive drug marketed ever with a value of 2.125 million dollars which amounts to about 16 crore rupees [34].There developed contradictory views on the ethical justice of pricing such an indispensable drug to this extreme extent . An earlier editorial by Rajiv Mahajan indicated that this pricing is beyond anything a commoner of India can raise[35].The health economic evaluation of the gene replacement therapy conducted in 2020 elucidated that the cost effectiveness analysis is assessing the Quality adjusted Life years in under a budget constraint. But the exclusion of time constraints (distribution of cost according to time) makes the evaluation complicated as the budget constraints can be exceeded or price can be reduced after the expiration of patent[36].Institute of Clinical and Economic Review compared the effectiveness of the two treatment options available for 5q Spinal Muscular Atrophy. It stated that though the long term effectiveness of the drug is yet to be detailed and studied , its short term benefits are indeed substantial . The added advantage of Zolgensma being a one time treatment and life long lasting compared to the Nusinersen was emphasized and stated that its value as 2.1 million dollars is fair considering its effectiveness[37].The ICER (Institute for Clinical and Effectiveness Review) QALY(Quality Adjusted Life Years) cost effective model for infants <8 months found out that the Zolgensma should be priced to about $ 3,10,000 for $1,00,000 investment per Quality Adjusted Life Years gained. This is 6.9 folds less than the listed price[34]. An early cost effectiveness analysis conducted in Netherlands calculated base ICER (Incremental Cost effectiveness ratio) for AVXS 101 and Nusinersen as € 53446/QALY. If the relapse happens 10 years, ICER can increase 6 folds. Zolgensma was not rendered to be cost effective according to the Dutch reference value of willingness to pay[3]. In Netherlands where the negotiations with Ministry of

health is the only way to sell an expensive medicine, Nusinersen was initially not available due to its exorbitant cost per QALY €60,000. Now the Ministry of Health is willing to pay € 80,000 for each QALY gained. When it was applied to Zolgensma to determine if it is cost effective when € 1.9 million have to be paid for each treatment ,it was found to be cost effective in € 1.7 million which is close to the actual price[38] .The systemic review on the economic evaluations which detailed the methodological approaches adopted by the various economic evaluations , also concluded the effectiveness of Onasmogene Abeparvovec over Nusinersen , when Nusinersen most often exceeded the cost effectiveness value calculated by various models throughout the world[39].The cost utility model of Zolgensma in comparison with the ICER (Institute for Clinical and Effectiveness Review) cost effectiveness model conducted by Rebecca Dean indicated the similarity of their results and effectiveness of Zolgensma over Nusinersen[40].

CONCLUSION

Gene replacement therapies have traversed a long way from tisagenlecleucel to Onasmogene Abeparvovec and finally to Idecabtagene vicleucel. Despite being named the curative treatment it does not literally cure the disease. It can suppress the pathophysiology of the disease to a certain extent. Onasmogene Abeparvovec being an AAV9 vector based gene therapy can modify the muscular functioning and day today life of many children .It is unique as it can improve the quality of life of the infants immensely and can rescue them from the clutches of disability and a gradual death. While this innovative therapy is enormously helpful to the patient it does not mean it was an effortless feat to manufacture and market such a drug . The huge cost of manufacturing , delivery and reduced patient population has made this therapy extremely expensive. The hope is that the effectiveness provided by the treatment is lifelong. If the gene expression wanes or wavers in the upcoming years in treated infants, another treatment option that is as effective will have to be researched upon.

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