



OnasemnogeneAbepravovec (Zolgensma®) for the Treatment of Spinal Muscular Atrophy

Mr. Ganesh Suryakant Pawar¹, Ms. Trupti A. Thange²

¹B.Pharmacy Student , PratibhataiPawar College Of Pharmacy , Wadala , Shirampur, ²Department Of Pharmaceutical Chemistry , PratibhataiPawar College Of Pharmacy , wadala , Shirampur

Correspondence: Email:pawarganesh741@gmail.com

ABSTRACT

Spinal muscular atrophy (SMA) is a debilitating disease characterised by means of degeneration of giant motor neurons. It is a heterogeneous crew of problems induced with the aid of a homozygous deletion in the survival motor neuron (SMN) gene on chromosome 5, ensuing in a SMN protein deficiency. Small quantities of SMN protein are additionally produced by way of the SMN2 gene, which that differs from SMN1 through a single nucleotide. Spinal muscular atrophy sorts and phenotypic severity rely on the wide variety of variants of the SMN2 gene and the quantity of SMN2 protein produced. Because the SMN protein deficiency is the root motive of the disease, therapy techniques for SMA revolve round growing SMN protein production. Nusinersen (Spinraza, Biogen, Cambridge, MA) used to be the solely cure choice reachable for SMA till the FDA authorized onasemnogeneabepravovec-xioi (Zolgensma, AveXisInc, Bannockburn, IL), a one-time-administered adeno-associated viral vector-based gene remedy that can provide the SMN gene to the motor neuron cells. Data from medical research exhibit sizable enchancement in motor milestone achievements and ventilator-free survival however are constrained via about 5 years' really worth of results. This one-time intravenous injection of this new gene remedy additionally bears a hefty charge tag; however, it can also be greater value high quality in the lengthy run versus the more than one intrathecal administrations wished with nusinersen. Drug get admission to and use are hindered with the aid of drug cost, payer compensation issues, and lack of long-term statistics from medical studies. Questions additionally stay related to the security and efficacy of repeated drug administration for sufferers with superior disease.

Keywords: adeno-associated viral vector, AVXS-101, gene therapy, motor neuron disease, occupational health and safety, onasemnogeneabepravovec-xioi, spinal muscular atrophy

INTRODUCTION

Spinal muscular atrophy (SMA) is a neuromuscular sickness notably characterised with the aid of degenerating alpha motor neurons (MNs) brought on with the aid of defects in the gene Survival Motor Neuron 1 [1]. SMA is the 2nd most frequent autosomal recessive disorder after Cystic Fibrosis [2] and is additionally the most frequent genetic ailment ensuing in childish demise [3]. MN loss outcomes in atrophy of skeletal muscles, paralysis and denervation of neuromuscular junctions [3]. SMA in general influences children, with signs along with muscle weakness, reflexia, problem swallowing and feeding, and in the most extreme instances is fatal, with childish demise most often attributed to respiratory failure [4].

Although MNs are the cells particularly affected in this disease, systemic pathology exists. Muscular [5], vascular [6] and cardiac defects [7] have been reported.

95% of SMA sufferers exhibit deletions of SMN1, with the final 5% carrying mutations in this gene. Homozygous deletions or mutations lead to no SMN protein manufacturing from SMN1, alternatively this can be in part compensated for by way of the duplicated SMN2 gene. Within SMN2, a C to T mutation 6-bp into exon 7 preferentially effects in an then again spliced transcript missing exon 7, recognised as SMNΔ7, which, when translated, leads to a truncated protein unexpectedly degraded. SMN2 produces a small quantity of full-length transcript and therefore protein. The quantity of SMN2 copies correlates inversely with the severity of SMA [8].

Two SMA treatments, Spinraza and Zolgensma, have been accepted for advertising via the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) inside the final few years. Spinraza is an antisense oligonucleotide focused on SMN2 splicing, aiming to promote inclusion of exon 7 inside transcripts and as a result the synthesis of full-length SMN protein. Spinraza binds to SMN2 pre-mRNA at an intronic splicing sequence in intron 7, stopping bad splice elements from binding this site. This reasons consciousness of exon 7 by means of U1snRNP and inclusion in the mature SMN2 mRNA transcript [9]. Zolgensma is a self-complementary AAV9 vector encoding SMN1.

This remedy objectives to exchange the lacking SMN1 gene in SMA patients, accordingly restoring ordinary SMN protein characteristic [10]. Both of these healing procedures had been significantly examined in pre-clinical experiments earlier than progressing to medical trials. The approval of Spinraza used to be generally underpinned through facts from ENDEAR and CHERISH scientific trials, whilst solely the START scientific trial the usage of Zolgensma was once executed prior to licensing. It is necessary to nation that, technically, oligonucleotides are now not classed as gene treatment options by using FDA or Advanced Therapy Medicinal Products by way of the EMA, whilst viral vectors like Zolgensma are. We consequently refer to each of them as "genetic" treatment options in the cutting-edge analysis. One greater therapy for SMA, Risdiplam (Evrysdi)

has been these days authorized with the aid of each FDA and EMA. It is primarily based on a small molecule in a position to alter the splicing of SMN2 [11]; no longer being a genetic therapy, we will no longer talk about it further.

Here, we overview all research that have used a genetic remedy method to deal with SMA rodent fashions the use of meta analytic strategies to furnish quantitative records pertaining to cure efficacy. This data is beneficial as it can supply insights into the most profitable techniques in pre-clinical research, keeping off useless and unethical repetition of animal experimentation [12], and pick out gaps in know-how that can be addressed in the future. Potential sources of bias and heterogeneity inside pre-clinical research had been also explored. We talk about how correctly pre-clinical statistics can predict scientific trial outcome.



Fig-zolgensma



HISTORY

Spinal muscular atrophy (SMA) is a team of heterogeneous autosomal-recessive neuromuscular problems that had been first pronounced in the Nineties with the aid of Hoffman and Werdnig as a situation characterised through hypotonia, muscle atrophy, and paralysis, located in neonates. Spinal muscular atrophy impacts about 1 in 11,000 newborns and stays the main genetic reason of childish death. It is brought about with the aid of mutations in the survival motor neuron (SMN) gene determined on chromosome 5 that effects in SMN protein deficiency. Most commonly, the sickness happens due to the fact of a homozygous deletion in the gene that debts for the majority of the SMN protein expression. SMN2 gene is nearly an same replica of SMN1, with the exception of a single nucleotide that consequences in the exclusion of exon 7 from the gene. This version effects in flawed splicing of the SMN protein transcript, which predominantly produces a non-functional SMN protein. There are 0–8 editions of the SMN2 gene that might also produce a small quantity of practical SMN protein. Increasing the variety of copies of SMN2 genes reasons an extend in the quantity of useful SMN protein produced, main to decreased phenotypic severity of the disease. Non-SMN1-related SMA contributes to much less than 5% of instances that involve extra medical features, such as arthrogyriposis, ordinary extraocular movements, and cardiomyopathy.¹

The disorder is categorised widely into proximal SMA and distal SMA, characterised with the aid of degeneration of massive motor neurons of the spinal wire and intelligence stem.^{1,2} Based on the age of onset and medical severity, there are 5 subtypes (Table); SMA kind zero has an in utero onset

and is a very extreme structure that requires mechanical air flow at start and in the end consequences in demise earlier than the age of 6 months. Type 1 SMA, additionally known as Werdnig Hoffman disease, is the most frequent subtype that money owed for about 60% of all cases

DOSE AND ADMINISTRATION

Table 1: Dosing

Patient Weight Range (kg)	Dose Volume (mL)
2.6 – 3.0	16.5
3.1 – 3.5	19.3
3.6 – 4.0	22.0
4.1 – 4.5	24.8
4.6 – 5.0	27.5
5.1 – 5.5	30.3
5.6 – 6.0	33.0
6.1 – 6.5	35.8
6.6 – 7.0	38.5
7.1 – 7.5	41.3
7.6 – 8.0	44.0
8.1 – 8.5	46.8
8.6 – 9.0	49.5
9.1 – 9.5	52.3
9.6 – 10.0	55.0

The recommended dose of ZOLGENSMA is 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight.

Preparation

- Thaw ZOLGENSMA before use. The contents of the ZOLGENSMA kit will thaw in approximately 12 hours if placed in a refrigerator, or in approximately 4 hours if placed at room temperature. If thawed in a refrigerator, remove from refrigerator on day of dosing.
- When thawed, ZOLGENSMA is a clear to slightly opaque, colorless to faint white liquid, free of particles. Visually inspect vials for particulate matter and discoloration prior to infusion. Do not use vials if particulates or discoloration are present.
- **DO NOT SHAKE.**
- Draw the appropriate dose volume from all vials into a syringe, remove air from the syringe, cap the syringe, and deliver the syringe at room temperature to the patient infusion location.
- Use ZOLGENSMA within 8 hours of drawing into syringe. Discard the vector-containing syringe if the drug is not infused within the 8-hour timeframe.
- **DO NOT REFREEZE.**

PHARMACOLOGIC TREATMENTS

Because SMA is precipitated by means of low stages of SMN protein, ongoing efforts for new cure techniques revolve round strategies to extend SMN protein degrees via SMN2 splicing modulation and gene substitute therapy, amongst others.

ONASEMNOGENEABEPARVOVEC (AVXS-101)

Previously recognised as AVXS-101, is a non-replicating, self-complementary, adeno-associated viral vector-9-based (scAAV9) gene remedy that gives you a utterly useful gene encoding the SMN protein to the motor neuron cells. An adeno-associated virus (AAV) is a non-enveloped, single-stranded DNA virus that generally requires the presence of a helper virus for the completion of its lifestyles cycle and can efficiently bear transduction in neurons. Multiple serotypes of AAV have been remoted from people and primates over the years and are recognised to differ in their capsid homes due to the fact of the presence of wonderful neutralizing antibodies. These variations outline the receptor affinity of the AAV capsid to the cellphone floor glycan receptor and decide tissue tropism of the vector.¹⁴ The scAAV9 vectors are special due to the fact they are packaged with double-stranded, self-complementary DNA to enable quicker protein synthesis after transduction into host cells. Gene transduction into the CNS has remained a undertaking with different viral vectors due to the fact of the presence of a blood-brain barrier. When studied in new child and grownup mice, cats, rats, and non-human primate models, AAV9 vector-based gene remedy has shown the best transduction to the CNS in contrast with different AAV serotypes. Initial in vivo checking out of AAV9 vector-based injection containing inexperienced fluorescent protein in new child and person mice showed profitable expression, notably in the motor neurons of the intelligence and spinal cord. Transgene expression used to be most advantageous when injected intravenously in contrast with intraperitoneal and intramuscular routes of delivery, with expression lasting at least 5 months. These findings have additionally been translated to cynomolgus macaque fashions from delivery up to three years of age and in the end led to the development of human trials.^{15–18}

NUSINERSEN

Businessmen (Spinraza, Biogen, Cambridge, MA), the first FDA-approved drug for SMA treatment, is a SMN2-directed antisense nucleotide that works through modulation of SMN2 messenger RNA splicing to consist of exon 7 in the transcript, inflicting improved manufacturing of full-length SMN protein.¹² Nusinersen is authorized for all sorts of SMA in each pediatric (newborn to 17 years) and grownup populations at a encouraged dose of 12 mg, administered intrathecally.

It is a lifelong remedy that involves four preliminary loading doses, observed by way of protection doses each four months, requiring at least three lumbar punctures per year.¹³ In scientific trials, nusinersen has been proven to make bigger cerebrospinal fluid tiers of SMN protein, in the end ensuing in motor characteristic improvement. Since its approval in December 2016, nusinersen remained the solely drug on the market for SMA treatment, till May 2019, when the FDA accepted onasemnogenebeparovecxiol (Zolgensma, AveXis Inc, Bannockburn, IL), the first gene remedy for pediatric SMA sufferers <2 years of age with bi-allelic mutations in the SMN1 gene.

CLINICAL TRIALS

The protection and efficacy of onasemnogenebeparovec have been evaluated in section I Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 (START) (NCT02122952) that enrolled and observed two cohorts of sufferers (n = 15) between December 2014 and August 2017. All protected sufferers had homozygous SMN1 exon 7 deletion and two copies of the SMN2 gene (mean age: 3.4 months [range, 0.9–7.9 months]).¹⁹ Patients had been blanketed if they had an onset of medical signs earlier than 6 months of age with a genetically validated diagnosis. Humoral immunity is widely wide-spread in human beings after publicity to wild-type AAV, main to the improvement of anti-AAV neutralizing antibodies. These antibodies can have an effect on vector transduction and normal efficacy of gene transfer, making it essential to measure AAV titers earlier than remedy is rendered.^{20,21} Hence, the trial excluded sufferers with improved AAV9 antibody titers of >1:50 at baseline. The foremost consequence used to be to decide protection based totally on any treatment-related destructive occasions of grade three or higher. Infants protected had been between the a long time of zero to about eight months at the begin of the trial. Secondary effects blanketed time till demise or the want for everlasting ventilatory help (at least sixteen hours of respiratory help per day for at least 14 days in the absence of any acute, reversible sickness or perioperative state). Motor milestones and the CHOP INTEND rankings have been additionally assessed as section of the exploratory outcomes. The first cohort of sufferers (n = 3) enrolled over the preliminary four months acquired a low dose of gene remedy (6.7 × 10¹³ vector genomes per kilogram [vg/kg]), whilst the latter (n = 12) acquired a excessive dose (2.0 × 10¹⁴ vg/kg), administered intravenously thru a venous catheter inserted into a peripheral vein.

PREPARATION AND ADMINISTRATION

Onasemnogenebeparovec is presently provided as a frozen package with the aid of the manufacturer; it wants to be thawed (4 hours at room temperature, 12 hours in the refrigerator) earlier than use. After thawing, contents of the medicinal drug vial need to be drawn up to the required dose into a syringe, capped, delivered to the patient location, and used inside eight hours of drawing. Of note, steadiness has solely been studied in polypropylene syringes, polyvinylchloride, and di(2-ethylhexyl)phthalate-free tubing and extensions. Storage in polystyrene or polycarbonate syringes and IV luggage need to be prevented due to the fact compatibility and balance are doubtful in these kinds of baggage or syringes. The agent is dosed via physique weight at a advocated dose of 1.1 × 10⁴ vg/kg. For most patients, IV administration is carried out in an outpatient setting, such as an infusion center. The producer recommends administering the drug solely as a single-dose gradual IV infusion over 60 minutes thru a peripheral venous catheter utilising an infusion pump. Infusion traces need to be primed with saline earlier than and after infusion. Because of the lack of compatibility information with different medications, a devoted IV line must be used for administration.

Adverse Effects

The most frequent negative outcomes of the drug encompass expanded aminotransferases and vomiting. Considering the detrimental outcomes and hazard for liver injury, the drug comes with a boxed warning for acute liver injury, with tips to examine liver characteristic earlier than infusion and extra often thereafter for at least three months. Baseline monitoring of liver characteristic and checking out of anti-AAV9 antibodies must be performed. Patients must acquire systemic corticosteroids equal to 1 mg/kg/day of oral prednisolone, beginning 1 day prior to onasemnogenebeparovec administration, for a whole of 30 days. Platelet counts and cardiac troponin-I concentrations need to additionally be carefully monitored after infusion due to the fact scientific trials have proven a transient minimize in each following infusion. It is essential to word that in animal models, onasemnogenebeparovec has proven dose-dependent cardiac and hepatic toxicities that have been additionally related with mortality at a dose of 2.4 × 10¹⁴ vg/kg or higher. At the completion of 30-day systemic corticosteroid treatment, liver characteristic have to once more be assessed. If physical examination and laboratory findings (AST, ALT <2 × top limits of normal, complete bilirubin, prothrombin time) are unremarkable, then corticosteroids have to be tapered off over the subsequent 28 days. If liver characteristic is abnormal, then corticosteroids have to be persevered and solely tapered off after all assessments are inside regular limits.

OCCUPATIONAL SAFETY

Vector DNA was once detected in saliva, urine, and stool in sufferers after onasemnogenebeparovec infusion. Shed stages had been extra centred in the stool, and concentrations swiftly declined logarithmically as the days progressed. It is encouraged that caregivers use acceptable managing methods for 1 month after onasemnogenebeparovec administration (e.g., sealing diapers in disposable luggage earlier than discarding them in ordinary trash and the usage of acceptable hand hygiene after managing bodily waste). In medical trials, the drug has been organized and dealt with in accordance to country wide aseptic approach beneath Biosafety Level 1 conditions, which suggests that it may additionally be secure to put together the agent in a horizontal laminar drift hood.²⁸ In a small variety of mice studies,²⁹ recombinant AAV remedy has resulted in improvement of insertional mutagenesis inflicting hepatocellular carcinoma. At this time, no unique security pointers have been furnished with the aid of the producer related to managing and coaching of the agent for administration. Because of the lack of hazardous chance statistics the drug can't be positioned into a National Institute of Occupational Safety and Health class at this point. However, given the hazard of mutagenesis in animal fashions with AAV vectors, it is vital to err on the aspect of warning and deal with it as a hazardous drug following USP 800 requirements for handling. It is additionally strongly really useful for

personnel coming into contact with the medicinal drug throughout transport and administration to use chemotherapy-tested gloves and disposable robes for non-public protection.

CONCLUSION

Spinal muscular atrophy is a debilitating disease that also accrues an insurmountable financial burden for the affected patients. Before the availability of onasemnogenebeparovec, nusinersen was the only treatment option for patients. Follow-up data now available from patients treated in the START trial reaching 5 years of age show sustained developmental milestones without the need for permanent ventilation after a one-time dose. Much remains undiscovered regarding whether this gene therapy is effective for older patients or whether patients with advanced disease would benefit from repeated administration of the drug. Even though this new gene therapy also carries a hefty price tag, the one-time administration makes it more cost effective in the long run, compared with lifelong maintenance treatment with intrathecal administration of nusinersen 3 times a year. While drug access and insurance coverage remain a barrier for many pediatric hospitals across the nation, approximately 27 sites in 19 states are now utilizing this drug. Access and use are anticipated to expand as more data become available, inciting approval in other countries across the globe.

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