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Review Article

Zolgensma: World's most expensive drug of choice; Survival of Motor Function for the Treatment of Spinal Muscular Atrophy Type 1

[1]Dr. Dhananjoy Saha, [2]Kushal Nandi, [2]Amrita Chakraborty and [2]Dr. Dhrubo Jyoti Sen

[1]Deputy Director, Directorate of Technical Education, Bikash Bhavan, Salt Lake City, Kolkata–700091, West Bengal, India.
[2]Department of Pharmaceutics & Pharmaceutical Chemistry, School of Pharmacy, Techno India University, Salt Lake City, Sector–V, EM–4, Kolkata–700091, West Bengal, India.

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ABSTRACT

Onasemnogene abeparvovec, sold under the brand name Zolgensma, is a gene therapy medication used to treat spinal muscular atrophy (SMA). It is used as a one-time infusion into a vein. Onasemnogene abeparvovec works by providing a new copy of the gene that makes the human SMN protein. The treatment must be accompanied by a course of corticosteroids of at least two months. Common side effects include vomiting and increased liver enzymes.
Onasemnogene abeparvovec was first approved for medical use in the United States in 2019 as a treatment for children less than two years old. It was later approved in other jurisdictions with similar scope. The approval scope in certain jurisdictions, including the European Union and Canada, is somewhat different. Zolgensma TM uses harmless, genetically engineered viruses to increase SMN protein levels. Once the virus is introduced into a person, it is able to travel around the body and get to a variety of different cells to help restore some of the SMN protein that is missing in SMA. Clinical studies have shown Zolgensma to be effective for treating SMA caused by genetic mutations in the SMN1 gene. The drug works by replacing an abnormal SMN1 gene with a normal SMN1 gene. However, Zolgensma won't reverse any effects of SMA that happened before your child received the drug.

Keywords: SMA; SMN1; SMN2; AAV9; capsid; viral DNA.

INTRODUCTION

Onasemnogene abeparvovec, sold under the trade name Zolgensma, is a gene therapy medication used to treat spinal muscular atrophy (SMA). SMA is a neuromuscular disorder caused by a mutation in the SMN1 gene, which in turn reduces the amount of SMN protein necessary for survival of motor neurons. Onasemnogene abeparvovec is a biologic drug consisting of AAV9 virus capsids that have been deprived of the original viral DNA and instead contain a SMN1 transgene along with promoters [1]. The drug is administered intravenously or intrathecally. Upon administration, the AAV9 viral vector delivers the SMN1 transgene to cell nuclei where the transgene begins encoding SMN protein, thus addressing the

Address for Correspondence: Dr. Dhrubo Jyoti Sen, Department of Pharmaceutics & Pharmaceutical Chemistry, School of Pharmacy, Techno India University, Salt Lake City, Sector–V, EM–4, Kolkata–700091, West Bengal, India; Email: dhrubosen69@yahoo.com

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root cause of the disease. Since motor neurons do not divide, it is thought that a single dose of the drug will have a lifelong effect [2]. The medication was developed by a US biotechnology company AveXis, a subsidiary of Novartis, based on an earlier discovery by French researchers. The intravenous formulation was approved in May 2019 in the United States for use in children under 2 years. It carries a list price of US$ 2.125 million per dose (one-time treatment), making it the most expensive medication in the world as of 2019 [3]. Onasemnogene abeparvovec is the international nonproprietary name (INN) and US adopted name (USAN). It was previously known under compound name AVXS-101.

HISTORY

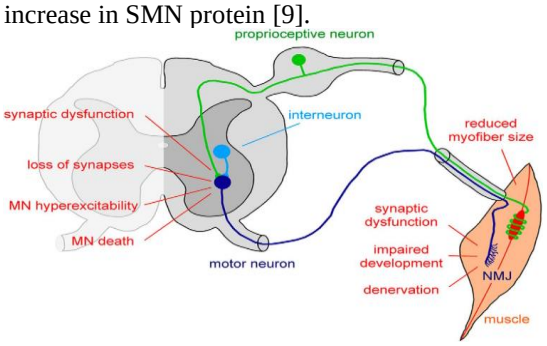
Onasemnogene abeparvovec was developed by the US biotechnology startup AveXis, which was acquired by Novartis in 2018, based on the work of Martine Barkats from the Institut de Myologie in France. The U.S. Food and Drug Administration (FDA) granted the application for onasemnogene abeparvovec-xioi fast track, breakthrough therapy, priority review, and orphan drug designations. The FDA also awarded the manufacturer a rare pediatric disease priority review voucher, and granted the approval of Zolgensma to AveXis Inc. In June 2015, the European Commission granted orphan designation for the drug [4]. In July 2019, the drug was removed from the Committee for Medicinal Products for Human Use (CHMP) accelerated assessment program. In May 2019, onasemnogene abeparvovec received US FDA approval as a treatment for children less than two years old [5]. Since 2019, the treatment has been reimbursed in Israel and Qatar. In March 2020, onasemnogene abeparvovec was granted regulatory approval in Japan with the label identical to the US one. Also in March 2020, the European Medicines Agency recommended a conditional marketing authorization for use in people with SMA type 1 or with any SMA type and having no more than three copies of the SMN2 gene. In May 2020, Onasemnogene abeparvovec was conditionally approved in Europe. In August 2020, onasemnogene abeparvovec was granted regulatory approval in Brazil by the Brazilian Health Regulatory Agency (ANVISA). In December 2020, onasemnogene abeparvovec was approved for medical use in Canada. Onasemnogene abeparvovec was approved for medical use in Australia in February 2021. NHS England treated its first patient in May 2021 [6].

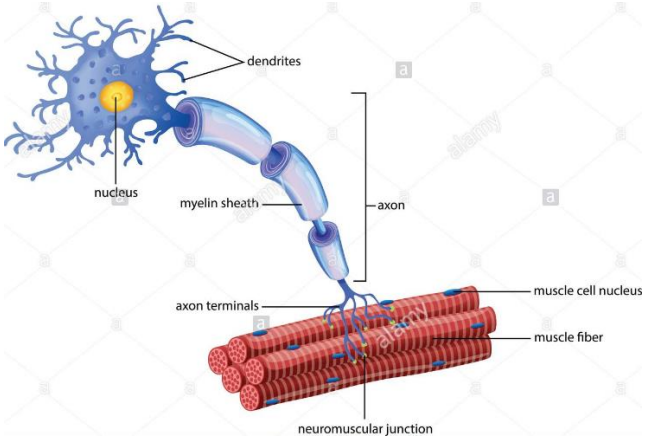
Medical Uses

Onasemnogene abeparvovec has been developed to treat spinal muscular atrophy, a disease linked to a mutation in the SMN1 gene on chromosome 5q and diagnosed predominantly in young children that causes progressive loss of muscle function and frequently death. The medication is administered as an intravenous infusion. The treatment is approved in the United States and certain other countries for use in children with SMA up to the age of two, including at the presymptomatic stage of the disease [7]. In the European Union and Canada, it is indicated for the treatment of patients with SMA who either have a clinical diagnosis of SMA type 1 or have up to three copies of the SMN2 gene. The medication is used with corticosteroids in an effort to protect the liver. While marketed as a one-time treatment for SMA, it is unknown how long the onasemnogene abeparvovec-delivered transgene will persist in people. Since motor neurons do not divide, it is expected that the transgene may have long-term stability [8].

Mechanism of Action

SMA is a neuromuscular disorder caused by a mutation in the SMN1 gene, which leads to a decrease in SMN protein, a protein necessary for survival of motor neurons. Onasemnogene abeparvovec is a biologic drug consisting of AAV9 virus capsids that contains a SMN1 transgene along with synthetic promoters. Upon administration, the AAV9 viral vector delivers the SMN1 transgene to the affected motor neurons, where it leads to an increase in SMN protein [9].





How is Zolgensma used?

Zolgensma is given once as an infusion (drip) into a vein lasting about 1 hour. The infusion should take place in a clinic or hospital under the supervision of a doctor experienced in managing spinal muscular atrophy. Before and after receiving the infusion, the patient will have a number of tests, including liver and blood tests, and will be given corticosteroid medicines to reduce the risk of side effects. The medicine can only be obtained with a prescription. For more information about using Zolgensma, see the package leaflet or contact your doctor or pharmacist [10].

What benefits of Zolgensma have been shown in studies?

A main study showed that Zolgensma reduces the need for artificial ventilation in babies with spinal muscular atrophy. In this study, 20 out of the 22 babies given Zolgensma were alive and breathing without a permanent ventilator after 14 months, when normally only a quarter of untreated patients would survive without needing a ventilator. The study also showed that Zolgensma can help babies sit unaided for at least 30 seconds. 14 out of the 22 babies given Zolgensma were able to do so after 18 months, a milestone that is never achieved in untreated babies with severe forms of the disease [11].

Adverse Effect

Common adverse reactions may include nausea and elevated liver enzymes. Serious adverse reactions may include liver problems and low platelets. Transient elevated levels of cardiac troponin I were observed in clinical trials; the clinical importance of these findings is not known. However, cardiac toxicity was seen in studies of other animals. As the medication may reduce the platelet count, platelets may need to be checked before the medication is started, then weekly for the first month and every two weeks for the next two months until the level is back to baseline. Liver function should be monitored for three months after administration [12].

Controversies

In the months leading up to the medication's approval by the U.S. Food and Drug Administration (FDA), a whistleblower informed Novartis that certain studies of the medication had been subject to data manipulation. Novartis fired two AveXis executives it determined responsible for the alleged data manipulation but informed the FDA of the data integrity issue only in June 2019, a month after the drug's approval [13]. The delay drew strong condemnation of the FDA. In October 2019, the company admitted to not having informed the FDA and the European Medicines Agency (EMA) for seven months about toxic effects of the intravenous formulation observed in laboratory animals. Due to data manipulation issue, the EMA withdrew their decision to allow an accelerated assessment of the medication. In December 2019, Novartis announced that it would donate 100 doses of onasemnogene abeparvovec per year to children outside the US through a global lottery. The decision, which has been claimed by Novartis to be based on a recommendation by unnamed bioethicists, was received with much criticism by the European Commission, some European healthcare regulators and patient groups (e.g., SMA Europe or the UK's TreatSMA) who see it as emotionally burdening, suboptimal, and ethically questionable. Novartis did not consult with families or doctors before announcing the scheme. Alan Regenberg, a bioethicist at Johns Hopkins Berman Institute of Bioethics, said that the scheme was perhaps the best available since it may be impossible to reliably establish prognosis for children under two years of age [14].

Research

AveXis is developing an intrathecal formulation of onasemnogene abeparvovec; however, trials in humans were halted by the US Food and Drug Administration (FDA) in October 2019, due to observed animal toxicity [15].

Conclusion

The main study of Zolgensma showed that a one-time infusion can improve survival in these patients and reduce the need for a permanent ventilator to breathe. It can also help them reach development milestones. As for its safety, the side effects of Zolgensma are considered manageable; the most common side effect in the study, raised liver enzymes, resolved after treatment with a steroid. The European Medicines Agency therefore decided that Zolgensma's benefits are greater than its risks and it can be authorised for use in the EU. Zolgensma has been given 'conditional authorisation'. This means that there is more evidence to come about the medicine, which the company is required to provide. Every year, the Agency will review any new information that

becomes available and this overview will be updated as necessary. Since Zolgensma has been given conditional authorisation, the company that markets Zolgensma will provide additional data on its benefits and risks. These include data from 2 studies in patients younger than 6 months with SMA type I and one study in patients younger than 6 weeks who do not have symptoms but for whom the diagnosis of SMA is confirmed based on genetic testing.

The company that markets Zolgensma will conduct a long-term study of the medicine's safety and effectiveness and provide data from another study to improve the consistency of the batches of the medicines. Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Zolgensma have also been included in the summary of product characteristics and the package leaflet. As for all medicines, data on the use of Zolgensma are continuously monitored. Side effects reported with Zolgensma are carefully evaluated and any necessary actions taken to protect patients.

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