NEUROPHARMAC JOURNAL 6 (2021) 145-149

NeuroPharmac Journal

Journal Homepage: https://www.neuropharmac.com

Editorial

Onasemnogene Abeparvovec-xioi: World's most expensive and approved therapy for spinal muscular atrophy

Aslam Pathan[1], Vinod Bairagi[2]

[1]Editor-in-Chief, NeuroPharmac Journal

[2]Department of Pharmacology, KBHSS Trust's Institute of Pharmacy, Malegaon; Savitribai Phule Pune University, India

ARTICLE INFO

Article history:
Received 22 April 2021
Accepted 26 April 2021
Available online
30 April 2021

Keywords:
Spinal muscular atrophy
Zolgensma
Onasemnogene
Abeparvovec-xioi

ABSTRACT

On May 24, 2019, the U.S. Food and Drug Administration approved Onasemnogene Abeparvovec-xioi (Zolgensma), the first gene therapy approved to treat children less than two years of age with spinal muscular atrophy (SMA), the most severe form of SMA and a leading genetic cause of infant mortality. It is priced in the United States at $2.1m (£1.6m; €1.9m) the world's most expensive drug.

Children with SMA experience difficulty performing essential functions of life. Most children with this disease do not survive past early childhood due to respiratory failure. Patients with SMA now have another treatment option to minimize the progression of SMA and improve survival. This review summarized the clinical guidelines for the Onasemnogene Abeparvovec-xioi use and may be useful to healthcare professionals.

Introduction:

Spinal Muscular Atrophy (SMA) is a hereditary disease that damages and kills specialized nerve cells in the brain and spinal cord (called motor neurons). Motor neurons control movement in the arms, legs, face, chest, throat, and tongue, as well as skeletal muscle activity including speaking, walking, swallowing, and breathing. The most common form of SMA is caused by an abnormal or missing gene known as the survival motor neuron gene 1 (SMN1), which is responsible for the production of a protein essential to motor neurons.[1-8]

This form of SMA has four types:

Type l, also called Werdnig-Hoffman disease or infantile-onset SMA, is usually evident before 6 months of age. The most severely affected children will have reduced movement and chronic shortening of muscles or tendons (called contractures). Other children may have symptoms including reduced muscle tone, lack of tendon reflexes, twitching, skeletal abnormalities, and problems swallowing and feeding. Without treatment, many affected children die before age 2 years.[9]

SMA Type ll is usually first noticed between 6 and 18 months of age. Children can sit without support

Corresponding author at: Department of Pharmacology, College of Medicine, Shaqra University, Shaqra-11961, Saudi Arabia
E-mail address: dr.aslam@su.edu.sa
https://orcid.org/0000-0002-6569-2306; https://orcid.org/0000-0003-0897-0696
https://doi.org/10.37881/1.612

but are unable to stand or walk unaided. Children also may have respiratory difficulties. Life expectancy is reduced but most individuals live into adolescence or young adulthood.[9]

SMA Type lll (Kugelberg-Welander disease) is seen after age 18 months. Children can walk independently but may have difficulty walking or running, rising from a chair, or climbing stairs. Other complications may include curvature of the spine, contractures, and respiratory infections. With treatment, most individuals can have a normal lifespan.[9]

Persons with SMA Type IV develop symptoms after age 21 years, with mild to moderate leg muscle weakness and other symptoms.[9]

SMA is a rare genetic disease caused by a mutation in the survival motor neuron 1 (SMN1) gene. The gene encodes the survival motor neuron (SMN) protein, a protein found throughout the body, which is critical for the maintenance and function of specialized nerve cells, called motor neurons. Motor neurons in the brain and spinal cord control muscle movement throughout the body. If there is not enough functional SMN protein, then the motor neurons die, leading to debilitating and often fatal muscle weakness. SMA caused by mutations in the SMN1 gene is generally classified into several subtypes, based on the age of onset and severity; infantile-onset SMA is the most severe and most common subtype. Children with this condition have problems holding their heads up, swallowing, and breathing. These symptoms may be present at birth or may present by the age of 6 months.[10, 14]

Onasemnogene Abeparvovec-xioi is indicated for the treatment of children less than two years of age with SMA. The product is an adeno-associated virus vector-based gene therapy that targets the cause of SMA. The vector delivers a fully functional copy of the human SMN gene into the target motor neuron cells. A one-time intravenous administration of Onasemnogene Abeparvovec-xioi results in the expression of the SMN protein in a child's motor neurons, which improves muscle movement and function, and the survival of a child with SMA. Dosing is determined based on the weight of the patient.[11,12, 14]

The safety and effectiveness of Onasemnogene Abeparvovec-xioi are based on an ongoing clinical trial and a completed clinical trial involving a total of 36 pediatric patients with infantile-onset SMA between the ages of approximately 2 weeks and 8 months at study entry. The primary evidence of effectiveness is based on results from the 21 patients treated with Onasemnogene Abeparvovec-xioi in the ongoing clinical trial. In this trial, there are 19 remaining patients, who range in age from 9.4 to 18.5 months; 13 of these 19 patients are at least 14 months of age. Compared to the natural history of patients with infantile-onset SMA, patients treated with Onasemnogene Abeparvovec-xioi also demonstrated significant improvement in their ability to reach developmental motor milestones (e.g., head control and the ability to sit without support).[13, 14]

The most common side effects of Onasemnogene Abeparvovec-xioi are elevated liver enzymes and vomiting. It has a boxed warning that acute serious liver injury can occur. Patients with pre-existing liver impairment may be at a higher risk of experiencing a serious liver injury. Clinical examination and laboratory tests to assess liver function should be completed before treatment with Onasemnogene Abeparvovec-xioi, and patients' liver function should be monitored for at least three months after Onasemnogene Abeparvovec-xioi administration.

Certain vaccines are contraindicated for patients on a substantially immunosuppressive steroid dose. Therefore, caregivers should consult with their healthcare professional to determine if adjustments to the patient's vaccination schedule are necessary to accommodate concomitant corticosteroid administration.[13]

Treatment:

There is no cure for SMA. Treatment consists of managing the symptoms and preventing complications. The U. S. Food and Drug Administration has approved the drug Nusinersen

(Spinraza) to treat children and adults with spinal muscular atrophy. The drug is designed to increase the production of the full-length SMN protein, which is critical for the maintenance of motor neurons. In May 2019, the FDA approved Onasemnogene Abeparovec-xioi gene therapy for children less than 2 years old who have infantile-onset SMA. A safe virus delivers a fully functional human SMN gene to the targeted motor neurons, which in turn improves muscle movement and function, and also improves survival. In August 2020, the FDA approved the orally administered drug Risdiplam (Evrysdi) to treat patients age two months of age and older with SMA. Physical therapy, occupational therapy, and rehabilitation may help to improve posture, prevent joint immobility, and slow muscle weakness and atrophy. Stretching and strengthening exercises may help reduce spasticity, increase range of motion, and keeps circulation flowing. Some individuals require additional therapy for speech, chewing, and swallowing difficulties. Applying heat may relieve muscle pain. Assistive devices such as supports or braces, orthotics, speech synthesizers, and wheelchairs may help some people retain independence. Proper nutrition and a balanced diet are essential to maintaining weight and strength Non-invasive ventilation at night can prevent apnea in sleep, and some individuals may also require assisted ventilation due to muscle weakness in the neck, throat, and chest during daytime.[13]

Formulation:

Onasemnogene abeparvovec-xioi suspension, for intravenous infusion.[14]

Indications & Usage:

Onasemnogene abeparvovec-xioi is an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.[14]

Limitations of Use:

The safety and effectiveness of repeat administration have not been evaluated. The use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.[14]

Dosage & administration:

Single-dose intravenous infusion only.

The recommended dosage is 1.1×10^{14} vector genomes (vg) per kg of body weight. For the patient weight of 10 kg, a 55 ml dose is required.[14]

Administer as an intravenous infusion over 60 minutes. Starting one day before infusion, administer systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight per day for a total of 30 days. At the end of the 30 days of systemic corticosteroid treatment, check liver function by clinical examination and by laboratory testing. For patients with unremarkable findings, taper the corticosteroid dose over the next 28 days. If liver function abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until findings become unremarkable, and then taper the corticosteroid dose over the next 28 days. Consult expert(s) if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone.[14]

Dosage forms & Strengths:

It is a suspension for intravenous infusion, supplied as single-use vials. It is provided in a kit containing 2 to 9 vials, as a combination of 2 vial fill volumes (either 5.5 mL or 8.3 mL). All vials have a nominal concentration of 2.0×10^{13} vector genomes (vg) per mL. Each vial of contains an extractable volume of not less than either 5.5 mL or 8.3 mL.[14]

Warnings & Precautions:

Thrombocytopenia: Monitor platelet counts before infusion, and weekly for the first month and then every other week for the second and third month until platelet counts return to baseline.

Thrombotic Microangiopathy (TMA): If clinical signs, symptoms, and/or laboratory findings occur,

consult a pediatric hematologist and/or pediatric nephrologist immediately to manage as clinically indicated.

Elevated Troponin-I: Monitor troponin-I before infusion, and weekly for the first month and then monthly for the second and third month until troponin-I level returns to baseline.

Acute serious liver injury and elevated aminotransferases can occur. Before infusion, assess the liver function of all patients by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer systemic corticosteroid to all patients before and after infusion. Continue to monitor liver function for at least 3 months after infusion.[14]

Adverse reactions:

The most common adverse reactions (incidence ≥ 5%) were elevated aminotransferases and vomiting.[14]

Use in specific populations:

Pediatric Use: Use in premature neonates before reaching full-term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Delay infusion until full-term gestational age is reached.[14]

Follow the steps below for infusion:

Place a primary catheter into a vein (generally a peripheral vein in the arm or leg). Insertion of a backup catheter is recommended. Program syringe pump for saline priming, or prime tubing manually with saline. Administer as a slow infusion over 60 minutes. Do not infuse as an intravenous push or bolus. Flush line with saline following completion of the infusion.[14]

Preparation:

Thaw Onasemnogene Abeparvovec-xioi before use. The contents of the 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 it from the refrigerator on the day of dosing.

When thawed, It is a clear to slightly opaque, colorless to faint white liquid, free of particles. Visually inspect vials for particulate matter and discoloration before 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 it within 8 hours of drawing into a syringe. Discard the vector-containing syringe if the drug is not infused within the 8-hour timeframe. Do not refreeze.[14]

Mechanism of action:

Onasemnogene Abeparvovec-xioi is a recombinant AAV9-based gene therapy designed to deliver a copy of the gene encoding the human SMN protein. SMA is caused by a bi-allelic mutation in the SMN1 gene, which results in insufficient SMN protein expression. Intravenous administration of Onasemnogene Abeparvovec-xioi that results in cell transduction and expression of the SMN protein has been observed in two human case studies.[14]

References:

1. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [updated 2020 Dec 3]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2021.
2. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin. 2015 Nov;33(4):831-46. doi: 10.1016/j.ncl.2015.07.004.
3. Arnold ES, Fischbeck KH. Spinal muscular atrophy. Handb Clin Neurol. 2018;148:591-601. doi: 10.1016/B978-0-444-64076-5.00038-7.
4. D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. Orphanet J Rare Dis. 2011 Nov 2;6:71. doi: 10.1186/1750-1172-6-71.

5. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve. 2015 Feb;51(2):157-67. doi: 10.1002/mus.24497. Epub 2014 Dec 16.
6. Ross LF, Kwon JM. Spinal Muscular Atrophy: Past, Present, and Future. Neoreviews. 2019 Aug;20(8):e437-e451. doi: 10.1542/neo.20-8-e437.
7. Fitzgerald DA, Abel F, Jones KJ, Farrar MA. Spinal muscular atrophy: A modifiable disease emerges. Paediatr Respir Rev. 2018 Sep;28:1-2. doi: 10.1016/j.prrv.2018.07.001.
8. Kolb SJ, Kissel JT. Spinal muscular atrophy: a timely review. Arch Neurol. 2011 Aug;68(8):979-84. doi: 10.1001/archneurol.2011.74.
9. Spinal Muscular Atrophy. https://www.ninds.nih.gov/Disorders/All-Disorders/Spinal-Muscular-Atrophy-Information-Page. [Accessed April 20, 2021].
10. Farrar MA, Park SB, Vucic S, Carey KA, Turner BJ, Gillingwater TH, Swoboda KJ, Kiernan MC. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol. 2017 Mar;81(3):355-368. doi: 10.1002/ana.24864.
11. Waldrop MA, Elsheikh BH. Spinal Muscular Atrophy in the Treatment Era. Neurol Clin. 2020 Aug;38(3):505-518. doi: 10.1016/j.ncl.2020.03.002.
12. Bozorg Qomi S, Asghari A, Salmaninejad A, Mojarrad M. Spinal Muscular Atrophy and Common Therapeutic Advances. Fetal Pediatr Pathol. 2019 Jun;38(3):226-238. doi: 10.1080/15513815.2018.1520374.
13. USFDA. https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease. [Accessed April 21, 2021].
14. Zolgensma. https://www.fda.gov/vaccines-blood-biologics/zolgensma. [Accessed April 22, 2021].

Cite this article:
Pathan A, Bairagi V. Onasemnogene Abeparvovec-xioi: Worlds' most expensive and approved therapy for spinal muscular atrophy. NeuroPharmac J. 2021; 6(1): 145-149. DOI: 10.37881/1.612