Use of Onasemnogene Abeparvovec gene therapy for Spinal Muscular Atrophy

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Abstract

Spinal muscle atrophy (SMA) is an autosomal recessive and neurodegenerative disease caused by homozygous mutations in the survival motor neuron 1 (SMN 1) gene. SMA is distinguished by motor neuron degeneration, which is a result in weakness and increasing muscle atrophy. Children with a most severe form of SMA there were not able to sit independently. There was only 8% of children would survive beyond their 2 years of age without permanent ventilation support. One of these therapies, Onasemnogene abeparvovec, a gene replacement therapy based on the adeno-related virus, is a one-time intravenous infusion in which it delivers human function SMA. In addition to significantly improving survival, Onasemnogene Abeparvovec increases motor function and reduces the need for respiratory or nutritional support in many patients. Recommendations of Dosage and administration. Recommendations for Prophylaxis of prednisolone tapering and monitoring for potential adverse events, including hepatotoxicity, Elevated Troponin -I thrombotic microangiopathy, are described here.
Table 1.1 Demonstrates a sample for post-treatment monitoring. It also describes the Postmarketing experience, drug interactions and their use in a specific population, and even temporary vector shedding and waste handling.

**KEYWORDS**

Gene therapy, Onasemnogene abeparvovec, efficacy, safety, spinal muscular atrophy

**Introduction**

Onasemnogene abeparvovec is an adeno-associated virus vector-based (AAV-9) gene therapy it targets motor neuron cells, and it delivers a fully functional copy of the human SMN gene. It improves muscle movement and its function and survival in children with SMA through one-time intravenous administration that results in the expression of SMA protein in child Motor neurons.[1]

On May 24, 2019, the US Food and Drug Administration (FDA) approved Onasemnogene abeparvovec, a medicine for the treatment of spinal muscle wasting (SMA). Zolgensma is a trading name that has been marketed under Novartis which is a Swiss drugmaker and drug developer. This medication has been supported to be utilized in children under 2 years who are confirmed by genetic testing for SMA. [2] The expected treatment cost is $2.125 million (approximately 14 crore rupees) and the drug is administered as a one-time infusion over 1 hour. This makes it the most expensive drug to be marketed in the world.[3]

In 2019 in the United States Onasemnogene abeparvovec was firstly approved for medical use this medication has been supported to be utilized in children under 2 years old, who are affirmed by hereditary testing for SMA.[4] It was later approved by other authorities with similar scope [5]. The approval scope in some other jurisdictions, like Asia, the European Union, and Canada.[6]

At the time of June 2021, more than 1200 patients have been treated with Onasemnogene abeparvovec worldwide [7]. As more countries and regions approved IV Onasemnogene abeparvovec, questions have emerged respecting its execution by and by that was not shrouded in the endorsing data or a survey depicting the clinical preliminary experience [8]. This specialist’s assessment gives suggestions in key regions by a specialist board of neuromuscular experts who have treated SMA patients with Onasemnogene abeparvovec.[9]
ROLE OF ONASEMNOGENE ABEPARVOVEC

Onasemnogene abeparvovec is an in vivo virus linked to an adenovirus serotype 9 (AAV9) gene replacement therapy that delivers the SMN trans-gene under a ubiquitous promoter into target cells, through a one-time IV infusion.

With one dose, Zolgensma it can stop the progression of SMA. It is designed gene therapy that results to replace the function of missing or non-working SMN 1 gene that causes SMA.

Zolgensma can’t cure or reverse the damage that is already caused by SMA before treatment.[4]

In the stage, I START study, treatment of SMA patients less than 8 months of age. Without the requirements of permanent ventilation which is not seen in natural history, abeparvovec exhibited improvements in survival, which is not seen in natural history, abeparvovec exhibited. improving survival and achieving major milestones. The stage III STRIVE-US study exhibited the advantage-risk profile observed in the stage I study for a larger group. Long-term assessment for up to 5.6 years has demonstrated the maintaining motor milestones without a new safety signal in patients who have received the targeted therapeutic dose in START.[6]

Children with significant weakness, including those requiring invasive ventilator support, and the potential advantage of treatment in this subgroup of patients may be low because of irreversible loss of motor neurons as the disease progresses. Onasemnogene abeparvovec has not been studied [7]. Treatment of patients, involving those with the most severe form of SMA who required invasive mechanical ventilation and tracheostomy before getting Onasemnogene abeparvovec, has also been reported [8].

WHAT IS SPINAL MUSCULAR ATROPHY (SMA)?

Spinal Muscular Atrophy (SMA) is an autosomal recessive disorder. The genetic cause of SMA is SMN 1 gene that is not working properly or missing that gene [9]. That means the body cannot make enough SMN (survival motor neuron) protein, which is needed for motor neuron cell survival. Motor neuron cells are responsible for communicating with the legs, throat, arms, and many other areas of the body and let them work together properly. [10] So without enough SMN protein, the motor neuron cells lose their function and may die. As a result, patients with SMA experience difficulty in breathing, speaking, or muscle weakness. [11]

INDICATIONS AND USAGE

ZOLGENSMA is an adeno-associated virus vector-based gene therapy used for pediatrics treatment. [12] the patients below 2 years of old with spinal muscular atrophy (SMA). [13]
Limitations of Use

The repeated administration of Zolgensma for its safety and effectiveness has not been evaluated.[14]

In severe SMA (e.g., complete loss of motion of limbs, long-lasting Ventilation reliance) use of Zolgensma in this understanding has not been accounted for.[15]

**DOSAGE AND ADMINISTRATION**

Intravenous infusion of single-dose of Zolgensma is used.[16]

The dose for Zolgensma has been suggested to be $1.1 \times 10^{14}$ vector genomes per kilogram (vg/kg) of body weight. [17]

Table 1: Dosing

<table>
<thead>
<tr>
<th>Patient weight Range (kg)</th>
<th>Dose (ml)</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-3.0</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>3.1-3.5</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>3.6-4.0</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td>4.1-5.0</td>
<td>24.8</td>
<td></td>
</tr>
<tr>
<td>4.6-5.0</td>
<td>27.5</td>
<td></td>
</tr>
<tr>
<td>5.1-5.5</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>5.6-6.0</td>
<td>33.0</td>
<td></td>
</tr>
<tr>
<td>6.1-6.5</td>
<td>35.8</td>
<td></td>
</tr>
<tr>
<td>6.6-7.0</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td>7.1-7.5</td>
<td>41.3</td>
<td></td>
</tr>
<tr>
<td>7.6-8.0</td>
<td>44.0</td>
<td></td>
</tr>
<tr>
<td>8.1-8.5</td>
<td>46.8</td>
<td></td>
</tr>
<tr>
<td>8.6-9.0</td>
<td>49.5</td>
<td></td>
</tr>
<tr>
<td>9.1-9.5</td>
<td>52.3</td>
<td></td>
</tr>
<tr>
<td>9.6-10.0</td>
<td>55.0</td>
<td></td>
</tr>
<tr>
<td>10.1-10.5</td>
<td>57.8</td>
<td></td>
</tr>
<tr>
<td>10.6-11.0</td>
<td>60.5</td>
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</tr>
<tr>
<td>11.1-11.5</td>
<td>63.3</td>
<td></td>
</tr>
<tr>
<td>11.6-12.0</td>
<td>66.0</td>
<td></td>
</tr>
<tr>
<td>12.1-12.5</td>
<td>68.8</td>
<td></td>
</tr>
<tr>
<td>12.6-13.0</td>
<td>71.5</td>
<td></td>
</tr>
<tr>
<td>13.1-13.5(b)</td>
<td>74.3</td>
<td></td>
</tr>
</tbody>
</table>

Dose Volume is calculated:

The patient weight upper limit is a range for pediatric patients who are less than 2 years of age between 2.6 kg and 13.5 kg.[18]
Earlier to ZOLGENSMA infusion:

- Delay ZOLGENSMA in patients with concurrent infections until the infection has resolved due to the increased risk of the serious systemic immune response.[19] Clinical manifestations of infection shouldn’t be evident at the time of ZOLGENSMA administration.[20]
- Baseline testing should be performed for the presence of anti-AAV9 antibodies.[21]
- Screen liver function of patients.[22]
- Screen creatinine, complete blood count (hemoglobin and platelet count), and troponin-I level.[23]

One day earlier to ZOLGENSMA infusion, oral prednisolone at 1 mg per kg of body weight per day (mg/kg/day) for a total of 30 days [24] infusion which is equivalent to systemic corticosteroids.[25]

Through a venous catheter, a single dose of Zolgensma is administered intravenously.[26]

Follow the steps below for infusion:

- Recommendation of the backup catheter for insertion. A primary catheter is placed into a vein (generally a peripheral vein in the arm or leg) [28]
- For saline priming program syringe pump, or saline with prime tubing manually.[29]
- Administers slow infusion of Zolgensma over 60 minutes. Don’t infuse as an intravenously push or bolus [30]
- Saline with Flush line following completion of the infusion.[31]

Screening for liver function by clinical examination and by laboratory examination regularly.

- Check liver status clinically and by assessing ALT, AST, total bilirubin, and prothrombin time after the 30 days of systemic corticosteroids treatment.[32]
- Taper the systemic corticosteroids dose slowly for the next 28 days or longer if needed. Inpatients with unexceptional findings (normal clinical exam, total bilirubin, prothrombin time, ALT and AST levels below 2 × upper limit of normal [ULN]): Do not stop systemic corticosteroids all of sudden.[33]
- If liver function abnormalities longer, continue corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until AST and ALT values are both below 2 × ULN and all other evaluation return to normal range, and then taper the corticosteroid dose gradually over the next 28 days or longer if needed.[34] Do not stop systemic corticosteroids all of sudden.[35]
- If liver function abnormalities continue to preserve > 2 × ULN after the 30 days of systemic corticosteroids, consult a pediatric gastroenterologist or hepatologist [36]
- If oral therapy of corticosteroids is not tolerated, consider intravenous corticosteroids as clinically indicated.[37]
Table 1.1

Sample for post-treatment monitoring schedule

<table>
<thead>
<tr>
<th>Test</th>
<th>Wee k 1</th>
<th>Wee k 2</th>
<th>Wee k 3</th>
<th>Wee k 4</th>
<th>Wee k 5</th>
<th>Wee k 6</th>
<th>Wee k 7</th>
<th>Wee k 8</th>
<th>Wee k 9</th>
<th>Wee k 10</th>
<th>Wee k 11</th>
<th>Wee k 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver function</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Platelet’s count</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Troponin -I</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓ = monitoring Performed

Preparation

- Defrost Zolgensma before use. The ingredient of the Zolgensma kit will defrost in around 12 hours whenever set in a refrigerator, or around 4 hours if placed at room temperature. If defrost in a refrigerator, take it out from the refrigerator on the day of dosing.
- When defrost Zolgensma is a clear to slightly cloudy, colorless to unclear white liquid, free of particles. Visually examine vials for particulate matter and discoloration before infusion. Do not utilize vials if particulates or discoloration are present.

DO NOT SHAKE.

- Draw the proper dose volume from all vials into a syringe, eliminate air from the syringe, cap the syringe, and take the syringe at room temperature to the patient infusion location.
- Use Zolgensma within 8 hours of drawing into the syringe. Dispose of the vector-containing syringe if the drug is not infused within the 8-hour timeframe.
Laboratory Testing and Monitoring to Estimate Safety.

- Perform baseline anti-AAV9 antibody testing before ZOLGENSMA infusion. If anti-AAV9 antibody titers are reported as > 1:50 then retesting may be done. [43]
- Conduct the following tests at baseline and as given below. [44]
- Liver function (clinical exam, AST, ALT, total bilirubin, prothrombin time) weekly for the first month; on every other week for the 2nd and 3rd months, until results are average (normal clinical exam, complete bilirubin, and prothrombin results, and ALT and AST levels under 2 × ULN). [45] First-month platelet count done and then every other week for the 2nd and 3rd months until platelet counts return to baseline. [46]
- Troponin-I weekly for the 1st month, and then monthly for the 2nd and 3rd months, until troponin-I levels return to baseline. [47]

DOSAGE FORMS AND STRENGTHS

- ZOLGENSMA is a suspension for intravenous infusion. [48]
- ZOLGENSMA is given in a kit containing 2 to 9 vials. Vials are given in 2 fill volumes: 5.5 mL or 8.3 mL.
- ZOLGENSMA has a minute concentration of 2.0 × 10^{13} VG/mL, and each vial contains a volume of not less than either 5.5 mL or 8.3 mL. [49]
- The intravenous dosage is determined by patient body weight, with a recommended dose of 1.1 × 10^{14} mg/kg for pediatric patients. [50]

WARNINGS AND PRECAUTIONS

Acute Serious Liver Injury, Acute Liver Failure or Raised Aminotransferases

- Zolgensma can lead to Acute serious liver injury, acute liver failure, and raisedaminotransferases. The use of Zolgensma in hepatotoxicity (which may be immune-mediated), generally, signifies as raised ALT and/or AST levels and at times as acute liver failure or acute serious liver injury has been reported. [51] To reduce potential aminotransferase elevations, administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion. [52] Immune-mediated hepatotoxicity may necessitate an adjustment to the corticosteroid treatment regimen, including longer. [53]
- Patients with previously liver impairment or acute hepatic viral infection may be at higher risk of acute serious liver injury/acute liver failure. [54] Patients with ALT, AST, or total bilirubin levels (except due to neonatal jaundice) > 2 × ULN have not been studied in clinical trials with
Zolgensma.[55] The risks and benefits of Zolgensma infusion in patients with anterior hepatic insufficiency should be carefully weighed against the risks of not treating the patient. [56]

- Aminotransferase raised were very common in the clinical trials and postmarketing experience, asymptomatic reported in the managed admittance program and the postmarketing setting, cases of acute serious liver injury, and acute liver failure have been accounted.[57] Some patients have experienced raises in ALT and AST > 20 × ULN, prolonged prothrombin time and have been symptomatic (e.g., vomiting, jaundice), with the use of prednisolone, can relieve it. Occasionally requires extended duration and/or higher dose. Consult a pediatric gastroenterologist or hepatologist if acute serious liver injury or acute liver failure is suspected.[58]

- **Thrombocytopenia**: Before Zolgensma infusion, monitor platelets count weekly for the 1st month and then every other week for the 2nd and 3rd month until platelet counts return to baseline. [59]

- **Thrombotic Microangiopathy (TMA)**: If clinical manifestations and/or laboratory results occur, check with a pediatric hematologist and/or pediatric nephrologist immediately to manage as clinically indicated.[60]

- **Elevated Troponin-I**: Before Zolgensma infusion, monitor troponin-I weekly for the 1st month and then monthly for the 2nd and 3rd month until troponin-I levels return to baseline. [61]

### ADVERSE REACTIONS

Elevated aminotransferases and vomiting are the most common adverse reactions (incidence ≥ 5%) [62].

### Postmarketing Experience

During post-approval use of Zolgensma, the following adverse reactions have been identified. Because these reactions are reported spontaneously, it is not always possible to reliably estimate their frequency or determine a causal relationship to drug exposure.[63]

- **Blood and Lymphatic System Disorders**: thrombotic microangiopathy, thrombocytopenia

- **Hepatobiliary Disorders**: acute liver failure, acute liver injury.

- **General Disorders and Administration Site Conditions**: pyrexia

- **Investigations**: troponin increased.[64]
DRUG INTERACTIONS

Where beneficial, adjust a patient’s vaccination schedule to accommodate concomitant corticosteroid administration before and following Zolgensma infusion. Some vaccines, such as measles, mumps and rubella (MMR), and chickenpox, are contraindicated in patients receiving the vaccine on a significantly immunosuppressive steroid dose (i.e., ≥ 2 weeks of daily intake of 20 mg or 2 mg/kg body weight of prednisone or equivalent). Prophylaxis is not precluded for Seasonal RSV.[65]

USE OF ZOLGENSMA IN SPECIFIC POPULATIONS

1. Pregnancy

There are no reported data regarding Zolgensma use in pregnant women. [66]

2. Lactation

There is no information report on the presence of human milk, the effects on the breast-fed infant, or the effects on milk production. The formative and health benefits of breastfeeding must be considered, as well as the clinical need for Zolgensma from the mother and any possible adverse effects.[67]

3. Pediatric Use

Administration of Zolgensma to premature neonates is not recommended, before reaching full-term because concurrent treatment with corticosteroids can be detrimental to neurological development. Postpone Zolgensma infusion until the corresponding full-term gestational age is reached.[68]

Patients who received ZOLGENSMA infusion at age 0.5 to 7.9 months (weight range 3.6 kg to 8.4 kg). The safety of Zolgensma was studied in pediatrics.

Patients who received ZOLGENSMA infusion at age 0.3 to 7.9 months (weight range 3.0 kg to 8.4 kg). The efficacy of ZOLGENSMA was studied in pediatrics.

4. Hepatic Impairment

Patients with liver impairment Zolgensma therapy should be considered carefully. Patients with preexisting liver abnormalities cases of acute serious liver injury and acute liver failure have been reported with Zolgensma. In clinical trials, raised of aminotransferases was observed in patients following ZOLGENSMA infusion.[69]
TEMPORARY VECTOR SHEDDING AND WASTE HANDLING

Impermanent vector shedding of Zolgensma happens basically through body waste. Inform caregivers on the proper handling of patient feces; suggest procedures include sealing disposable diapers in disposable trash bags and then disposing into the regular trash. Give guidelines to caregivers and family members regarding proper hand hygiene when coming into direct contact with patient body waste. These precautions should be followed for not less than 1 month after Zolgensma infusion.[70]

CONCLUSIONS

Onasemnogene abeparvovec provides a quick and supportive improvement in motor function for young children less than 2 years of age with type 1 SMA and extends their lives. Zolgensma provides a novel, successful treatment that has assisted infants to achieved for example inhaling without a ventilator, sitting up on all alone crawling, and walking after a single dose infusion treatment. This deal is a life-changer for young people with this severe illness and their families. More patients seek this inventive therapy, treatment centers should prepare to deal with and manage the drug. Given the dynamic idea of SMA and the need to start treatment before irreversible motor neuron loss, doctors should be able to distinguish those patients eligible to receive. Concerns include world costlier medicine and potential liver toxicity. Long-term advantages and risks have not been determined.

DECLARATIONS

Ethics approval and consent to participate
Not Applicable

Consent for publication
Not Applicable

Availability of data and material
The review work has been carried out by us and we assure you that it can be provided to you whenever required.

Conflict of Interest
Declared None.

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Not applicable

Competing interests

Not applicable

Authors’ contributions

We have assured that “all authors have read and approved the manuscript”. All the authors have equal contribution and participation in this research work.

REFERENCE


4. The Hindu. FDA Okays $2M Medicine, Most Expensive Ever. [Last accessed on 2019 Jun 03].


46. RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: pulmonary and acute care; medications, supplements, and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018; 28:197-207.


64. Dyer O. Health ministers condemn Novartis lottery for Zolgensma, the world’s most expensive drug. BMJ. 2020 Feb 12;368:m580. Doi: 10.1136/BMJ.m580. PMID: 32051111.


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