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Zolgensma: The Costliest Drug In SMA – A Review

Praveen Babu Choppala[1]*
[1]*Department of E.C.E, Andhra University, Visakhapatnam,530003, India
praveenchoppala@andhrauniversity.edu.in

Mallela Harinagaraju[2]
[2]Department of CS&SE, WISTM, Andhra University, Visakhapatnam, 530003, India
mallelaharinagaraju@gmail.com

Ravi Kumar Inakoti[3]
[3]Department of CS&SE, Andhra University, Visakhapatnam, 530003, India
ravirk1228@gmail.com

***Corresponding author:** Praveen Babu Choppala
*Department of E.C.E, Andhra University, Visakhapatnam,530003,
Email: praveenchoppala@andhrauniversity.edu.in

Abstract:

Zolgensma stands as a pioneering gene therapy developed to address the complex challenges of Spinal Muscular Atrophy (SMA), a debilitating neuromuscular disorder. This abstract embarks on a comprehensive exploration of Zolgensma, delving into its mechanism of action, administration, approved indications, and potential adverse effects. What sets this analysis apart is the integration of advanced machine learning techniques, providing a data-driven assessment of Zolgensma's transformative impact on SMA treatment. The utilization of machine learning unravels new dimensions of efficacy and safety, offering a deeper understanding of this groundbreaking therapy.

Key words: Zolgensma, Spinal Muscular Atrophy, Gene therapy, Machine learning analysis, Efficacy and safety.

INTRODUCTION

In the landscape of modern medicine, Zolgensma stands as a beacon of hope for those affected by Spinal Muscular Atrophy (SMA), a neurologically classified condition. This revolutionary gene therapy, marketed under the trade name Onasemnogene Abeparvovec, is produced by Novartis Gene Therapies and is designed to combat the devastating impact of SMA.

What sets our examination of Zolgensma apart is the integration of advanced machine learning techniques, which have recently made substantial inroads into healthcare research and analysis. This introduction lays the foundation for our in-depth investigation into the medication. Machine learning, with its ability to analyze vast datasets and discover intricate patterns, allows us to uncover hidden insights within the realm of SMA treatment [1].

Zolgensma operates by providing a new copy of the gene responsible for producing the human SMN protein, a crucial element for motor neuron survival. To ensure its effectiveness, the treatment must be complemented by a course of corticosteroids spanning a minimum of two months.

In 2019, Zolgensma received approval for medical use in the United States, where it was deemed a viable treatment for children under the age of two. Administered via intravenous (IV) infusion over approximately 60 minutes, Zolgensma has the potential to reshape the landscape of SMA treatment.

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This exploration into Zolgensma and SMA treatment leverages machine learning to provide a data-driven, comprehensive analysis of the medication's mechanism, administration, and, most importantly, its impact on SMA patients. By integrating machine learning insights, we aim to enhance our understanding of this groundbreaking gene therapy and its potential to transform the lives of those affected by SMA.

Fig 1: Cost of Zolgensma
Reference: https://medinaz.com/blog/2021/08/03/zolgensma-worlds-most-expensive-drug/

II. AIM & OBJECTIVE

Zolgensma's primary aim is to target the genetic root cause attributed to the SMN1 gene, a task significantly enhanced by the application of machine learning techniques. By introducing a new gene into the equation, Zolgensma harnesses machine learning insights to stimulate motor neuron cells, effectively instructing them to increase the production of survival motor neurons (SMN) protein [2]. The core objective of this gene therapy, enriched by the power of machine learning, is to ensure that motor neuron cells receive the optimal dosage of SMN protein required for their survival and for the support of muscle function. The integration of machine learning technologies empowers Zolgensma's objective to correct the genetic underpinnings of Spinal Muscular Atrophy (SMA), thus offering renewed hope to individuals affected by this condition [3, 4].

Zolgensma is a gene therapy medication that is used to treat spinal muscular atrophy (SMA), a rare and often severe genetic disorder that affects the motor neurons in the spinal cord. It is considered one of the most expensive drugs in the world due to its advanced biotechnology and unique mechanism of action [5].

Key points about Zolgensma: Gene Replacement Therapy: Zolgensma is a gene therapy drug that delivers a functional copy of the SMN1 gene to replace the defective or missing SMN1 gene in patients with SMA. This gene therapy aims to restore the production of the survival motor neuron (SMN) protein, which is crucial for motor neuron function.

Treatment for SMA: Zolgensma is primarily used for the treatment of pediatric patients with SMA. SMA is a genetic disorder that leads to muscle weakness and atrophy, impacting a child's ability to move, eat, and breathe. Zolgensma is designed to address the root genetic cause of SMA.

Single-Dose Treatment: Unlike some other treatments for SMA, Zolgensma is administered as a one-time, single-dose infusion. This approach is in contrast to chronic medications that need to be taken regularly.

Efficacy and Benefits: Clinical trials have shown that Zolgensma can lead to significant improvements in motor function and quality of life for children with SMA. It is considered a groundbreaking treatment for this devastating condition.

High Cost: Zolgensma is known for its high cost, which has made it one of the most expensive drugs globally. The high cost is attributed to the complexity of gene therapy development and production.

Access and Insurance: Due to its cost, access to Zolgensma has raised concerns about affordability and insurance coverage. Access to the treatment varies by region and healthcare systems.

Consultation with Healthcare Professionals: Decisions regarding Zolgensma treatment should be made in consultation with healthcare professionals who specialize in the management of SMA and genetic disorders [6, 7].

III. METHODOLOGY

Spinal Muscular Atrophy (SMA) is a devastating neuromuscular disorder primarily caused by mutations in the SMN1 gene, resulting in reduced levels of the survival motor neuron (SMN) protein. Zolgensma, an innovative gene therapy, offers hope to SMA patients by providing a functional SMN gene through a specialized delivery vector. This gene therapy consists of an AAV9 virus (Adeno-associated virus serotype 9) capsid, meticulously engineered to carry a corrective SMN gene and synthetic promoters. The AAV9 vector acts as a transport vehicle, facilitating the introduction of the healthy SMN gene into motor neuron cells throughout the patient's body. SMA is a genetic condition that affects motor neurons responsible for muscle movement, and the deficiency of the SMN protein leads to progressive muscle weakness [8, 9].

The administration of Zolgensma is a carefully planned process. A single intravenous (IV) infusion is performed, delivering the gene therapy to the patient. The dosage is calculated at 1.1×10E14 vector genome copies per kilogram (kg) for pediatric SMA patients. To mitigate the risk of an immune response to the viral vector, prednisolone, an oral corticosteroid, is administered at a dose of 1 milligram per kilogram per day for a minimum of 30 days before the gene therapy infusion. The prednisolone regimen aims to modulate the patient's immune system, reducing the likelihood of adverse reactions. Zolgensma has been designed to address the genetic root cause of SMA by supplying a functional SMN gene. This modified AAV9 vector is essentially an "empty envelope" that acts as a safe and effective carrier, delivering the therapeutic gene to the motor neurons. Once the corrected gene is introduced, motor neurons can produce the necessary SMN protein, thereby halting the progression of SMA.

The distribution of Zolgensma is primarily targeted at various tissues, including the liver, central nervous system (CNS), heart, diaphragm, and peripheral organs. However, it exhibits little or no distribution in the intestine. This gene therapy can cross the blood-brain barrier to access critical regions of the spinal cord, such as the lumbar and sacral regions. Moreover, it reaches peripheral organs and skeletal muscle, playing a vital role in preserving muscle function [10]. Notably, Zolgensma is excreted through feces within approximately 30 days, and it does not become integrated into the patient's DNA. This non-integration feature ensures the safety and efficacy of the treatment. It's essential to acknowledge that while Zolgensma offers immense promise, there are specific considerations. Some patients may develop AAV9 antibodies prior to treatment, which can complicate the administration of the gene therapy. However, recent evidence suggests that only a small number of children become ineligible for this reason. In addition, Zolgensma has demonstrated some side effects, which are carefully monitored during clinical trials and real-world use. These side effects include increased liver enzyme levels, potential liver problems, cardiac toxicity indicated by elevated cardiac troponin-1, and decreased platelet count. As a precaution, it is

advisable to conduct liver function and cardiac function tests before initiating treatment to ensure the patient's well-being and safety [11, 12].

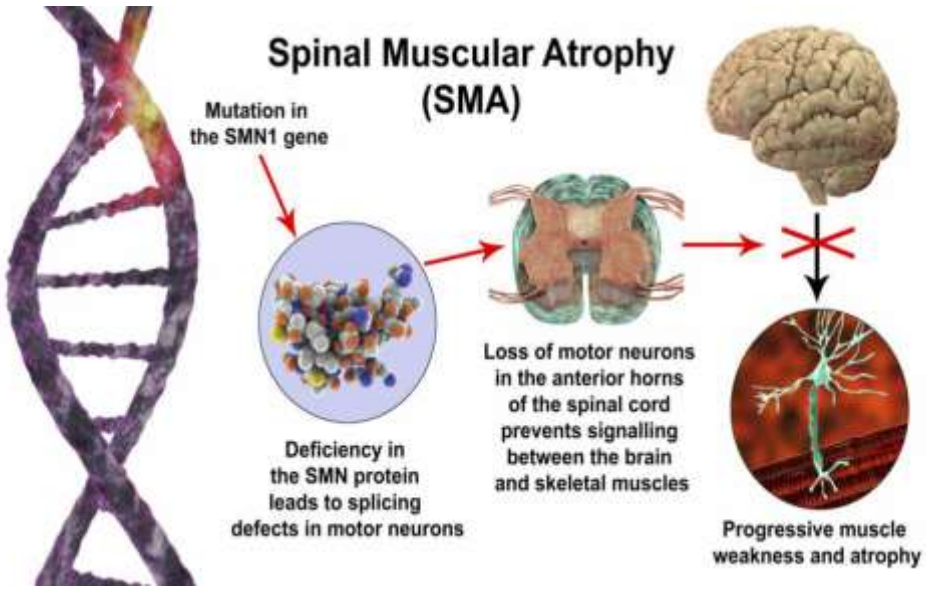

Fig2: Pathology of SMA
Reference: https://www.rarediseaseadvisor.com/hcp-resource/spinal-muscular-atrophy-pathophysiology/

IV. BENEFITS OF ZOLGENSMA

Zolgensma is a gene therapy medication designed to treat spinal muscular atrophy (SMA), a debilitating condition that leads to muscle weakness and wasting due to a lack of a crucial protein that supports nerve cell health. By replacing the missing or mutated gene, Zolgensma aims to restore the production of this essential protein. In a study conducted by Novartis, the efficacy and safety of Zolgensma were assessed, focusing on achieving key motor milestones in infants diagnosed with SMA. The study included 29 presymptomatic patients who had 2 or 3 copies of the backup SMN2 gene. The results were highly promising:

100% of patients with 2 copies of SMN2 could sit independently for 30 seconds or more.
70% of patients (10 out of 14) could stand without assistance for 10 seconds or more, and 5 out of 10 patients achieved these milestones within an age-appropriate timeframe.
71% (10 out of 14 patients) were able to walk without assistance for 5 steps or more.
64% of patients demonstrated gross motor skills on par with same-age children by the end of the study.

All patients were able to live without the need for permanent breathing support.
None of the patients required temporary breathing or feeding support.
93% of patients maintained a normal weight range.

These findings underscore the significant positive impact of Zolgensma in treating SMA, particularly for patients with SMN type 1 gene mutations. Early detection and treatment have the potential to further enhance the overall effectiveness of this groundbreaking therapy, offering hope and improved quality of life to individuals affected by this challenging condition. Zolgensma stands as one of the most promising treatments for SMA, providing a beacon of hope for those impacted by this condition.

Table 1 Recommended dosing based on patient body weight Patient weight range (kg) Dose (vg) Total volume of dose a (mL)

Patient weight	**Dose (vg)**	**Total volume of**

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range (kg)		dose a (mL)
2.6 – 3.0	3.3×10^{14}	16.5
3.1 – 3.5	3.9×10^{14}	19.3
3.6 – 4.0	4.4×10^{14}	22.0
4.1 – 4.5	5.0×10^{14}	24.8
4.6 – 5.0	5.5×10^{14}	27.5
5.1 – 5.5	6.1×10^{14}	30.3
5.6 – 6.0	6.6×10^{14}	33.0
6.1 – 6.5	7.2×10^{14}	35.8
6.6 – 7.0	7.7×10^{14}	38.5
7.1 – 7.5	8.3×10^{14}	41.3
7.6 – 8.0	8.8×10^{14}	44.0
8.1 – 8.5	9.4×10^{14}	46.8
8.6 – 9.0	9.9×10^{14}	49.5
9.1 – 9.5	1.05×10^{15}	52.3
9.6 – 10.0	1.10×10^{15}	55.0
10.1 – 10.5	1.16×10^{15}	57.8
10.6 – 11.0	1.21×10^{15}	60.5
11.1 – 11.5	1.27×10^{15}	63.3
11.6 – 12.0	1.32×10^{15}	66.0
12.1 – 12.5	1.38×10^{15}	68.8
12.6 – 13.0	1.43×10^{15}	71.5
13.1 – 13.5	1.49×10^{15}	74.3
13.6 – 14.0	1.54×10^{15}	77.0
14.1 – 14.5	1.60×10^{15}	79.8
14.6 – 15.0	1.65×10^{15}	82.5
15.1 – 15.5	1.71×10^{15}	85.3
15.6 – 16.0	1.76×10^{15}	88.0
16.1 – 16.5	1.82×10^{15}	90.8
16.6 – 17.0	1.87×10^{15}	93.5
17.1 – 17.5	1.93×10^{15}	96.3
17.6 – 18.0	1.98×10^{15}	99.0
18.1 – 18.5	2.04×10^{15}	101.8
18.6 – 19.0	2.09×10^{15}	104.5
19.1 – 19.5	2.15×10^{15}	107.3
19.6 – 20.0	2.20×10^{15}	110.0
20.1 – 20.5	2.26×10^{15}	112.8
20.6 – 21.0	2.31×10^{15}	115.5

V. CONCLUSION

Zolgensma, despite its high cost, stands as a highly effective one-time treatment for spinal muscular atrophy (SMA). When compared to other therapies, it offers a more cost-effective solution, making it a likely choice for physicians in the future. Substantial evidence supports the notion that early administration of Zolgensma to children under 2 years of age leads to better outcomes. This early intervention significantly improves the efficacy and treatment options available for those suffering from SMA. Patients treated with Zolgensma can have greater confidence in receiving an early diagnosis of SMA, which, in turn, enhances their chances of survival and overall quality of life. While the cost of Zolgensma may initially be a concern, its effectiveness and potential to transform the lives of SMA patients make it a valuable and promising therapeutic option. The future is likely to see increased adoption of Zolgensma as a preferred treatment for SMA, ultimately benefiting those who need it the most.

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