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Emerging Therapeutic Strategies for Spinal Muscular Atrophy: A Comprehensive Review

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ABSTRACT

Spinal Muscular Atrophy (SMA) is a genetic disorder that results in progressive muscle weakness due to the degeneration of motor neurons in both the spinal cord and brainstem. While there is currently no existing cure for the disease, drugs, and gene therapies have emerged as treatments to manage the severity of symptoms and improve patients' outcomes. This literature review examines three major FDA-approved SMA treatments – Zolgensma®, risdiplam (Evrysdi®), and nusinersen (Spinraza®) – by analyzing results from key clinical trials. Zolgensma®, a gene replacement therapy, has resulted in increased event-free survival, acquisition of motor milestones, and maintenance of weight and respiratory function in patients. As the first oral SMA treatment, risdiplam approximately doubled SMN protein levels and improved motor function across various age groups. Nusinersen is another drug that allowed the achievement of WHO motor milestones and led to a reduced risk of mortality and permanent ventilation. Although there were adverse reactions and limitations with each treatment and its trials, the overall benefits such as increased motor function, respiratory status, and event-free survival were significant. This comprehensive review highlights the potential of these therapies to refine the treatment landscape for SMA. Further research monitoring long-term safety and exploring multiple approaches is warranted.

Introduction

Spinal Muscular Atrophy refers to a group of diseases that can damage and kill motor neurons in the brain and spinal cord that mainly affects children who are six to eighteen months old. It causes muscle weaknesses and can prevent a child from engaging in basic activities like walking and crawling. It is primarily regarded as a genetic disorder because mutations in the SMN1 gene result in its occurrence in most patients. As a result of this mutation, there is a deficiency in the SMN protein, which is crucial for motor neurons to function properly. Currently, an outward cure for this disease does not exist. However, various drugs and forms of gene therapy are being researched to lessen the effects of this disease.

Cure SMA has invested in various clinical trials regarding Spinal Muscular Atrophy for many years and has determined that four main stages are required for a trial to be successful. First, the drug is administered to 10 to 20 individuals in order to determine its effectiveness. Usually, these individuals are people who have the disease. Next, the drug is tested on a larger scale, usually 20 to 40 people. Then, the scale is increased even further with 100 to 200 people receiving the drug. The drug is generally compared to a placebo to determine its true efficiency. Lastly, the drug's outcomes continue to be monitored by researchers (Cure SMA).

Early diagnosis of Spinal Muscular Atrophy is significant as it allows professionals to recommend and begin a treatment plan sooner. According to *Zolgensma*®, newborn screening for SMA has been implemented widely throughout the United States and is able to detect 100% of SMA incidences at birth. There are multiple ways to diagnose SMA. Newborn screening and genetic testing are the primary means of identifying patients with the disease. A diagnosis is confirmed as soon as possible and depending on the results, the parents are

referred to a specialist. SMA can also be identified when a professional examines signs in the patient's movements and physical stability. These signs include muscle weakness, hypotonia, areflexia, impaired head control, paradoxical breathing, and reduced bulbar functions (Zolgensma®). After the diagnosis is confirmed, treatment is recommended immediately.

Due to the dangerous effects of Spinal Muscular Atrophy on the human body, gene therapies and drugs must be looked into in order to find the best treatment for patients with this disease. Medical professionals, patients, and the healthcare field as a whole will be extremely benefitted through the research on various treatments of SMA. However, while examining each of them, it is also significant to monitor the adverse reactions and side effects of these remedies on the patient.

Methodology

The primary goal of the research conducted was to examine the different treatments for Spinal Muscular Atrophy and how they may affect the patients to whom they are administered. The research done in this study is a secondary literature review. The information is based on various research articles and primary studies. Analyzing the results of clinical trials on gene therapies and treatments for Spinal Muscular Atrophy required the use of qualitative methods. To do this, data was collected from multiple primary studies, clinical trials, and research articles. Based on the results, conclusions were made regarding the effectiveness of different treatments on patients with SMA. Other factors such as adverse reactions and side effects were also examined while conducting research on these treatments. Two guiding professors in this research assisted in accumulating information about treatments for SMA as well as understanding them in the context of efficiency. Physical tools or materials were not used in this research besides online resources. Research biases were mitigated by analyzing various sources from various journals, authors, and trials from all over the world, ensuring a balanced perspective.

Drugs and Gene Therapy as Treatments for Spinal Muscular Atrophy

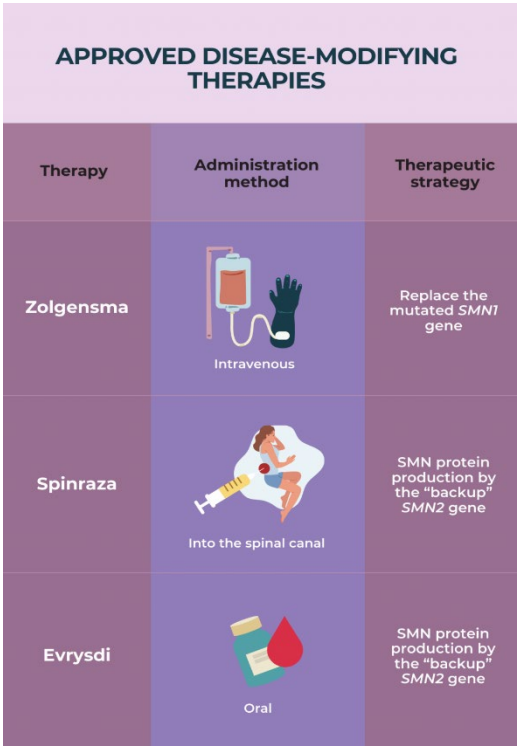

Figure 1. Three Main SMA Treatments and their Mode of Administration. Source: SMA News Today, 2023 Description: Zolgensma®, Risdiplam (Evrysdi®), and Nusinersen (Spinraza®) are three approved disease-modifying therapies aimed towards reducing symptoms of Spinal Muscular Atrophy in patients. They have different modes of administration and use various therapeutic strategies to achieve this goal.

Zolgensma®

As mentioned before, the survival motor neuron protein is produced by the SMN1 gene, which is crucial for maintaining the function of motor neurons. Zolgensma®, which was recently approved by the Food and Drug Administration, replaces this defective or missing SMN1 gene, enabling an increased production of the SMN proteins. This allows the loss of motor neurons to stop. As a result of the gene therapy, expression of the motor neurons was detected in cells of the brain, heart, liver, and skeletal muscles. The most common adverse reactions in clinical studies of patients who received Zolgensma® were elevated aminotransferases and vomiting, with an incidence of less than 5% (Zolgensma®). Aminotransferases are liver enzymes and when they exceed the normal amount, liver damage and inflammation can occur.

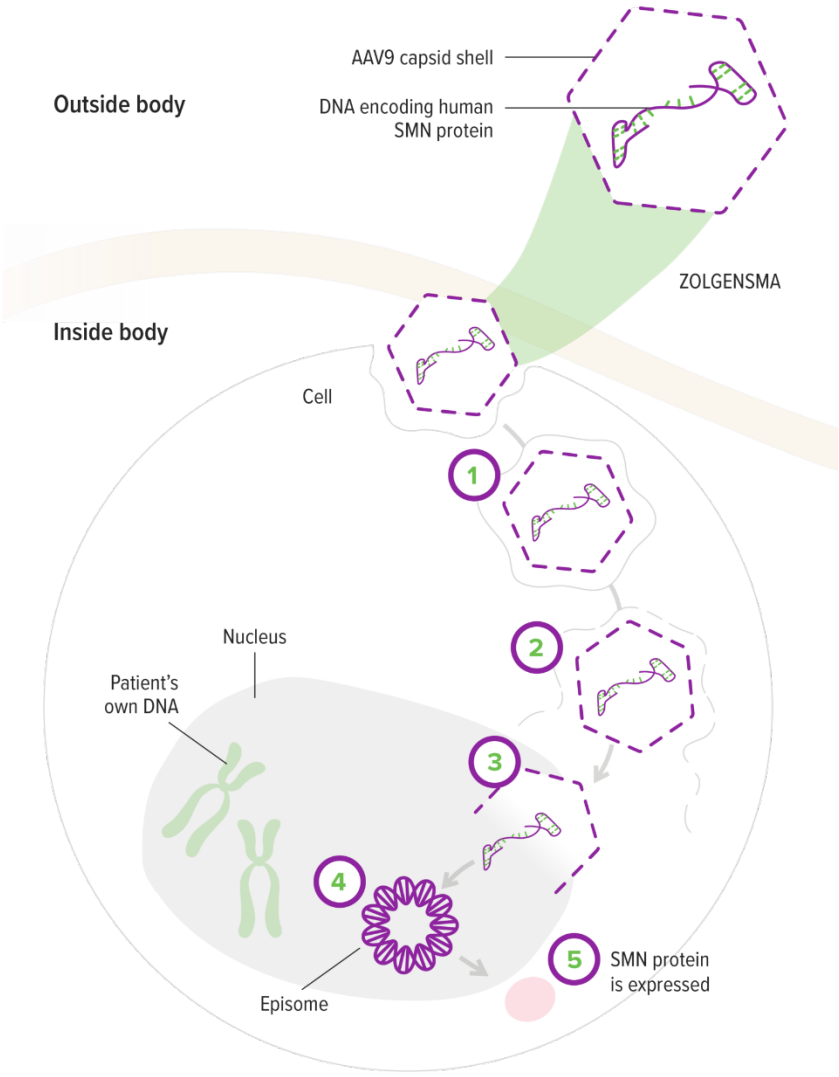

Figure 2. Zolgensma®'s Mechanism of Action. Source: Zolgensma®. Description: This gene therapy works by using an adeno-associated virus called AAV9 as a vector to deliver the human SMN gene to motor neuron cells. The vector enters the cells and brings the SMN gene to the nucleus. Then, the gene is introduced as recombinant, self-complementary DNA, forming a circular structure that stays in the nucleus of the motor neuron cells. The structure allows for continuous activation and expression of the SMN gene, addressing the genetic mutation that causes the disease.

When treating SMA with Zolgensma®, it is crucial to follow a specific, organized treatment plan in order for the patient to have the safest and most successful outcomes. First, appropriate patients for the administration of the therapy must be identified. Zolgensma® has been approved for children under the age of two who have a genetic defect in the SMN1 gene on both inherited copies (alleles) of the gene. Once the patient's caregiver has decided that Zolgensma® is the best option, various tests must be performed on the patient. First, a test must be done to provide genetic confirmation of a mutation in the SMN1 gene. Then, an AAV9 Antibody Test must be performed to ensure the presence of anti-AAV9 antibodies as it is a vector in the form of a virus. Next, some baseline tests will be done to evaluate liver function, platelet count, creatinine, and other proteins to confirm that the patient is clinically stable. If the patient has an infection or has a low baseline health status, administration of the treatment must be postponed until these symptoms are no longer present (Zolgensma®). Zolgensma® is a single intravenous infusion, meaning that it is administered directly to the patient's bloodstream through a vein. A programmable syringe pump is used to infuse the treatment and the dosage is dependent on the patient's body weight. After the Zolgensma® gene therapy has been administered, it is significant to monitor the patient's health status. Baseline tests must be conducted after the treatment as well. Liver function, platelet count, and troponin-I should be monitored according to a schedule based on the patient's stability. To manage the possible adverse reaction of an increase in liver aminotransferases, corticosteroids, which are anti-inflammatory drugs, should be given to patients before and after Zolgensma® infusion. In addition, patients may also need support for their respiratory, neuromuscular, and nutritional functions and it is recommended that a healthcare professional is appointed to coordinate this care (Zolgensma®).

Various clinical trials have been conducted on patients with SMA to evaluate the effectiveness of Zolgensma® in relieving symptoms. A key study in examining the effects of Zolgensma® on SMA treatment is the STR1VE Trial. This phase 3 trial studied patients who were symptomatic and less than six months of age. It was a longitudinal study as the patients were examined until they turned eighteen months old and focused on the efficacy of the Zolgensma® treatment. The primary result of this study was that Zolgensma® led to a significant increase in event-free survival in patients with Type 1 SMA compared to their natural history. 20 out of the 22 patients studied were free of permanent ventilatory support at their 14-month physician's visits. These results continued until the end of the study as they turned eighteen months old. In addition to an increase in patient survival, new motor milestones were reached by many of the participants. 13 out of the 22 patients studied were able to sit without support for more than 30 seconds at their 18-month physician's visit. This is a significant achievement as many infants with Spinal Muscular Atrophy are not able to do this during their lifespan. Additionally, it allows scope for the development of various cognitive, motor, and sensory skills that will aid the patient in social development and functional independence (Novartis, 2020). Another endpoint reached by some participants in the study was the ability to thrive at 18 months of age. This consists of three main components: the ability to swallow thin liquids, go without non-oral feeding support, and maintain weight. 9 out of 22 patients met all three criteria, with a higher proportion achieving each component independently. In natural history, SMA patients were not able to meet these standards. Additionally, 15 out of 22 participants did not need non-invasive ventilatory support during the study, whereas most patients with Type 1 SMA would require this support at 12 months of age (Zolgensma®). Overall, the STR1VE Trial proved that Zolgensma® played a significant role in increasing patients' survival and quality of life.

The START trial also examined the effects of this therapy on patients. It included fifteen patients with SMA Type 1 and lasted for two years. In this group, the symptomatic patients who had symptoms before 6 months of age were divided into low-dose and high-dose cohorts. It was found that two years after infusion, all patients in the high-dose cohort were alive and did not require permanent ventilation. Most patients in this cohort were also able to achieve and maintain motor milestones such as sitting without support and head control. 11 out of 12 patients in this group received a score of 40 or more on the CHOP INTEND test, which evaluates motor function in SMA patients. Historically, patients with the disease do not receive these high scores. This trial also determined that Zolgensma® aided participants in improving their respiratory status, nutritional status, and bulbar functions. The START Long Term Follow-Up (LTFU) study was conducted 7.5 years after patients were infused with Zolgensma® to determine the durability of the effects of the therapy. 10 out of 12 of the high-dose cohort patients enrolled in this study and it was found that patients continued to demonstrate positive results, such as maintaining motor milestones (Zolgensma®). This trial is ongoing and it is expected that these outcomes will continue to improve in the future.

The SPR1NT clinical trial included presymptomatic SMA patients who were divided into two groups: those who had two copies of the SMN2 gene and those who had three copies of the SMN2 gene. According to Ryner Lai from *Rare Disease Advisor*, treating patients with SMA before they start showing symptoms has resulted in earlier achievement of developmental milestones (Lai, 2023). It was found that all presymptomatic patients with two copies of SMN2 were able to sit without support for over 30 seconds at their 18-month physician's visit. 71% of patients even achieved the milestone of walking alone. Most participants attained these goals at an appropriate age as well, exhibiting the efficiency of Zolgensma®. 93% of patients in this same group were able to go without nutritional support as they maintained their body weight. All presymptomatically treated patients did not need respiratory ventilation. All participants who had three copies of SMN2 were able to stand alone for over three seconds at their 2-year-old physician's visit, many of them achieving this milestone during the age-appropriate time period. All patients maintained nutritional and respiratory status without a need for any kind of support. LT-002 is an ongoing follow-up study that includes patients from the SPR1NT trial. It was observed that patients maintained all motor milestones achieved previously and a few of them improved their motor functions further (Zolgensma®).

Zolgensma® has produced beneficial and quick results, making it an effective gene therapy in the overall treatment of Spinal Muscular Atrophy. However, there are some limitations in these studies. Safety regarding a repeat administration of Zolgensma® was not addressed in the resources. In addition, the effects of Zolgensma® infusion in patients with advanced SMA who have symptoms such as full paralysis of limbs and permanent dependence on a ventilator have not been evaluated. As of March 2024, over 3,700 patients have been treated with Zolgensma® (Novartis, 2024).

Risdiplam (Evrysdi®)

Risdiplam (brand name Evrysdi®) was approved by the US Food and Drug Administration in 2020 as the first non-invasive oral treatment for Spinal Muscular Atrophy. It helps the body produce more SMN protein, allowing for increased functioning of the motor neurons. Within four weeks of treatment, the amount of SMN protein in the body approximately doubled and was maintained throughout two years of studies (Evrysdi®). The most common side effects associated with this treatment for patients with later-onset SMA are fever, diarrhea, and rashes. Patients with early-onset SMA typically experienced the same symptoms in addition to upper respiratory infection, lung infection, constipation, cough, and vomiting. It is significant that patients and their caregivers consult with their healthcare providers and inform them of all medical conditions to ensure the safety of taking the treatment (Evrysdi®).

Clinical trials were conducted to test the drug and evaluate its effects. Over 490 people aged 16 days to 60 years participated in these trials, ensuring that both safety and efficacy were tested across all kinds of

patients. The SUNFISH trial was conducted on 231 children and adults with Type 2 or Type 3 Spinal Muscular Atrophy. This was a 2-part study, controlled by a placebo. Part 1 included 51 adults and children aged 2 to 24 years, including seven patients who could walk. This first part was meant to look into the safety and dosage of risdiplam. Part 2 consisted of 180 adults and children aged 2 to 25 years, all of whom were not able to walk. This portion measured both the safety and effectiveness of the drug in 120 people and compared these results to those of the placebo, which was given to the remaining 60 participants. The results of this study, specifically motor function, were measured using a scale called Motor Function Measure-32 Items (MFM-32). This measure assesses 32 different elements to evaluate motor function across the categories of standing/transfer movements, upper/lower body movements, and hand/foot movements. It was found that the average MFM-32 score in adults and children who took risdiplam increased by 1.36 points whereas the value decreased in those who took the placebo. This demonstrates that the drug led to improved motor functions across the span of just one year. However, as the MFM-32 score was observed over an additional year, there were some fluctuations in motor functions for those who took risdiplam as their scores tended to decline slightly before improving again at the 18-month point. The Revised Upper Limb Module (RULM) measures arm movements and the patient's ability to complete tasks. It produces a value dependent on various tests such as pushing buttons, lifting weights, and reaching to the side (Evrysdi®).

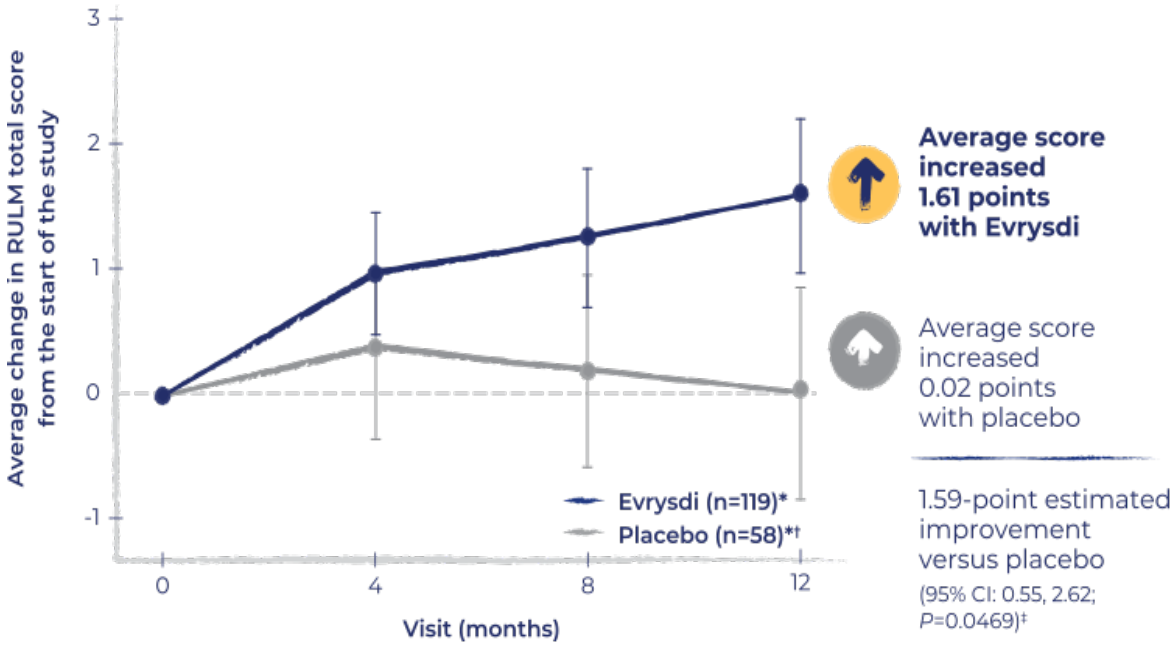

Figure 3. Change in RULM score over 1 year after taking Evrysdi® vs Placebo. Source: Evrysdi®. Description: The average RULM score for those who took the risdiplam medication increased by 1.61 points during the first year. In contrast, those who took the placebo only had an average score increase of 0.02 points.

Throughout the second year after administration, the average RULM score of patients increased steadily, with an average increase of 2.79 points. Therefore, risdiplam aided in improving both typical motor functions as well as upper limb movements (Evrysdi®).

The FIREFISH study was an open-label study that also contained two parts and included 62 infants who had Type 1 SMA. Part 1 focused on the recommended risdiplam dosage in 21 infants who were all 3 to 7 months of age. The second part measured the safety and effectiveness of the treatment on the remaining 41 infants who were aged 2 to 7 months. The Bayley Scales of Infant and Toddler Development-Third Edition

(BSID-III) was used to assess the physical abilities of participants, such as sitting and crawling. It was determined that one year after receiving risdiplam, 33% of participants from both parts of the study were able to sit without support for five seconds or more, as measured by BSID-III. This proportion increased to 60% after an additional year, meaning that motor functions were both maintained and improved. The Hammersmith Infant Neurological Examination-Module 2 (HINE-2) evaluates the eight primary developmental milestones for infants and it was also used to measure key achievements by participants in the study. It was found that two years after taking risdiplam, 28% of infants were able to stand, a milestone that patients with Spinal Muscular Atrophy would not have been able to achieve historically. Following their administration of risdiplam, over 80% of patients were alive and able to breathe without any permanent ventilatory support, such as a tracheostomy or intubation. Overall, the statistics from this trial are relevant as they prove that infants with SMA can improve both motor and respiratory functions through risdiplam. The treatment has produced unforeseen results as it truly reduces the severity of existing Type 1 SMA in infants. (Evrysdi®).

RAINBOWFISH is a third trial done by Evrysdi® and it is ongoing. It includes 26 presymptomatic newborns with genetically diagnosed Spinal Muscular Atrophy. The primary outcome of risdiplam on these participants was their ability to perform basic physical functions. Out of six infants who had two or three copies of the SMN2 genes, all of them were able to sit one year after receiving risdiplam. Four of them were able to stand and three could walk independently. Additionally, all six of the infants can breathe without permanent support. Although the infants did not exhibit symptoms of SMA, taking risdiplam was significantly advantageous as it increases development, lessening the severity of the disease (Evrysdi®).

A fourth clinical trial by risdiplam called JEWELFISH includes 174 patients of ages 1 to 60 years with Type 1, 2, or 3 SMA who previously received different SMA medications. This is an ongoing trial as of now and final results will be published once the trial is over (Spinal Muscular Atrophy UK, 2023).

Risdiplam has proven to be an effective and transformative treatment as it opened a new perspective for the treatment of Spinal Muscular Atrophy, being the first orally administered drug for this purpose. Various clinical trials support its positive effect on motor function, physical ability, and respiratory status. As of October 2023, over 11,000 patients worldwide have been treated with risdiplam, and this number is expected to continue increasing (Roche).

Nusinersen (Spinraza®)

Nusinersen (brand name Spinraza®) was the first drug approved by the US Food and Drug Administration to treat both adults and children with Spinal Muscular Atrophy. It is administered in the form of an intrathecal injection, or lumbar puncture, that is directed into the fluid surrounding the spinal cord (US FDA, 2016). As mentioned previously, SMA occurs due to a mutation in the SMN1 gene. However, this gene does have a copy called SMN2, which does not produce a sufficient amount of proteins for motor neurons to survive in people with the disease. Nusinersen aids SMN2 in producing more proteins, allowing motor neurons to survive and function. Before the nusinersen is administered, healthcare providers perform blood and urine tests to ensure that individuals are not at risk for bleeding and kidney damage. Common side effects associated with the drug are lower respiratory infection, constipation, fever, back pain, vomiting, and post-lumbar puncture syndrome. The dosage of nusinersen begins with four initial doses followed by maintenance doses administered three times a year.

Multiple clinical trials have been conducted to observe the effectiveness and safety of nusinersen on patients with SMA. An ongoing presymptomatic study called NURTURE includes 25 infants who have not exhibited any symptoms of SMA. It was observed that, 14 months after receiving nusinersen, all infants did not need permanent ventilatory support. Participants also achieved WHO milestones, motor milestones expected to be achieved by 2 years of age in healthy children by the World Health Organization. All infants sat without support. 88% could walk with assistance and 77% were walking on their own. Approximately five years later,

these proportions increased as 96% of participants could walk with assistance and 92% walked independently. Missing WHO milestones is one of the first, most common symptoms of Spinal Muscular Atrophy so for pre-symptomatic patients to achieve them was a major breakthrough. In addition, a majority of participants were able to suck and swallow properly, as well as go without tube feeds and suctions for excess saliva. However, there were limitations to this trial. There were not many participants and it was an open-label study, meaning that everyone knew who was receiving the drug. Also, there was no control group in this trial (Spinraza®).

ENDEAR was a pivotal trial including 121 children, all seven months or younger, with early-onset (Type 1) SMA. It was found that 51% of children who received nusinersen were motor milestone responders, meaning that their score on the HINE-2 test increased by at least two points in the ability to kick or at least one point in the categories of head control, rolling, independent sitting, and standing. None of the children in the control group experienced these responses. Overall, the risk of mortality or permanent ventilation was reduced by 47% in the group that was administered the treatment. However, the adverse reaction of collapsed lung was more common in the group treated with nusinersen. Although serious reactions did occur, there was an overall benefit for treated participants regarding motor function, survival, and respiratory support (Spinraza®).

CHERISH was another pivotal study on 126 children aged two to nine years with later-onset SMA. The Hammersmith Functional Motor Scale-Expanded (HFMSE) measures how well one can perform basic tasks such as lifting their head and climbing the stairs. An increase of three or more points on this scale reflects a clinically meaningful change. It was observed that 15 months after treatment, patients' scores increased by an average of 3.9 points, whereas control group participants' scores decreased by an average of 1 point. It was also found that treated patients' scores on the Revised Upper Limb Module increased by an average of 4.2 points. These improvements reflect overall development in motor function and upper limb function for treated patients compared to those in the control group. A limitation of this study, however, was that the dosing schedule used was different from the approved Spinraza® schedule, meaning that the study does not accurately reflect the outcomes of patients who go by the approved schedule. Supportive studies such as CS2 and CS12 demonstrate that those treated with nusinersen experienced an increase in their average walking distance, adding to their physical ability and health (Spinraza®).

Nusinersen is associated with alarming adverse reactions as demonstrated in various clinical trials. However, it is a solid approach to the treatment of Spinal Muscular Atrophy as it has resulted in countless positive outcomes, including expansion of motor function, physical health, and respiratory status.

Conclusion

Spinal Muscular Atrophy has historically been a devastating genetic disease with incredibly limited treatment options. However, emerging novel gene therapies and drug treatments such as Zolgensma®, risdiplam (Evrysdi®), and nusinersen (Spinraza®) have transformed the therapeutic landscape. The various clinical trials evaluated in this review have demonstrated the profound impacts these therapies can have on survival, motor function, milestone achievement, respiratory status, nutritional status, and the enhancement of overall quality of life for SMA patients across all types and ages. While each therapy has different administration methods and potential adverse effects that require monitoring, all of their benefits are very significant. Further research is still needed to examine the long-term safety and durability of the effects of these treatments. Additionally, it is important to investigate optimal treatment sequencing and approaches. Nonetheless, the arrival of these three therapies has ushered in a new era of hope for SMA patients and their families. With increased investment in research and appropriate access to treatment, the outlook for those affected by this disease has become tremendously brighter.

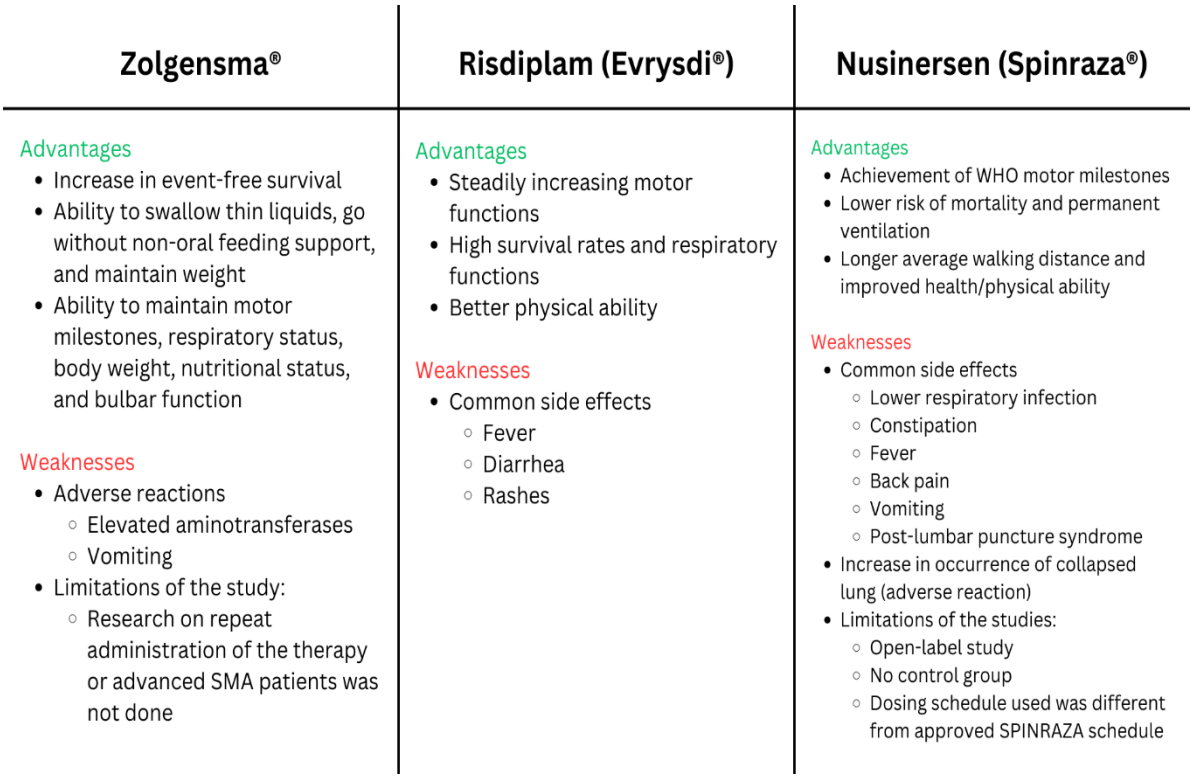

Figure 4. Advantages and Weaknesses of SMA Treatments. Source: Jayalasya Nagaraju (created with Canva.com) Description: All three treatments led to an increase in survival, motor function, and physical health. However, there were adverse reactions and side effects to all three, with some being more severe than the others. Limitations existed in all three studies.

Acknowledgments

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