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REVIEW ARTICLE OPEN ACCESS

NEW TREATMENTS FOR SPINAL MUSCULAR ATROPHY IN BRAZIL: NUSINERSEN, ON AS EMNOGENEABEPARVOVEC AND RISDIPLAM, A REVIEW

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ABSTRACT

Introduction: Spinal muscular atrophy (SMA), characterized by the destruction of alpha motor neurons in the spinal cord, is an autosomal recessive genetic disease that causes impairment in the neuromuscular development of patients and is caused, in the vast majority of cases, by a homozygous deletion in the survival gene motor neuron 1 (SMN1). Considering the reduced quality of life resulting from the disease, its treatment is extremely important. Threenew ─ and the only ─ drugs available (nusinersen, onasemnogeneabeparvovec, and risdiplam) are capable of improving motor performance and life expectancy of patients. **Objective:** To review studies involving the use of nusinersen, onasemnogeneabeparvovec, and risdiplam for the treatment of patients with SMA, discussing the effects and examining the benefits of these drugs. **Methods:** Qualitative integrative literature review of articles from the Pubmed, Google Scholar and Cambridge Libraries databases, using the descriptors "Spinal Muscular Atrophy", "Atrofia Muscular Espinhal", "Zolgensma", "Onasemnogene Abeparvovec", "Nusinersen", "Spinal Muscular Atrophy Treatment", "Atrofia Muscular Espinhal Tratamento", "AVXS-101", "Spinraza", "Spinal Muscular Atrophy Gene Therapy", "Atrofia Muscular Espinhal Terapia Gênica", "Risdiplam" and "Evrysdi". **Results:** The studies show that the use of these new treatments for SMA promoted improvements in motor function, decreased fatigue, and reduced length of hospitalization, in addition to contributing to an increase in patients' life expectancy. To measure these benefits, the analyzed articles used scores such as Hammersmith Motor Functional Scale Expanded (HFMSE), Revised Upper Limb Module (RULM), Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), Children's Hospital of Philadelphia Adapted Test of Neuromuscular Disorders (CHOP ATEND), 6 Minutes Walk Test (6MWT) and Compound Motor Action Potential (CMAP). **Conclusion:** It is possible to conclude that nusinersen, onasemnogeneabeparvovec, and risdiplam are effective in the treatment of SMA, as they promote improvement in the motor and respiratory function of patients. In the search for the best therapy, it is necessary to take into account factors such astoxicity, route of administration, site of action, and cost of such drugs.

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INTRODUCTION

Spinal muscular atrophy (SMA) is a disease that impairs the neuromuscular development of patients due to the destruction of alpha motor neurons, whose cell bodies are found in the anterior horn of the spinal cord. SMA is an autosomal recessive genetic disease, caused, in 95% of cases[1], by a homozygous deletion in the survival motor neuron 1 (SMN1) gene, located on chromosome 5q13.2. In humans, each chromosome 5 allele has two forms of the SMN gene: telomeric and centromeric, SMN1 and SMN2, respectively[2,3,4].

The SMN1 form is responsible for the complete production of the SMN protein and the SMN2 form is related to the incomplete production of this protein. Both forms have 9 exons – 1, 2a, 2b, 3, 4, 5, 6, 7, 8 –, but only 8 of them are used to encode the protein in question[1]. The incomplete production of SMN by the SMN2 geneand consequent early degradation of this protein is related to the fact that most of the mRNA transcribed by this gene does not present exon 7, which is the stop codon of SMN. Only 10% of the protein produced by this last form is functional[1]. It is known that, even if the functional copies of the SMN protein translated by the SMN2 gene are few, they are determinants for the attenuation of the SMA phenotype. Regarding this protein, its mechanism of action is not exactly known,

but it is known that it influences RNA processing in all cells, including alpha motoneurons, favoring their development and survival. As a result, SMN deficiency results in the destruction of these motor neurons, which causes hypotonia, atrophy, and muscle weakness ─ which are generally more proximal than distal ─ as the main features of this disease[5,6]. There are five types of SMA, ranging from 0 to 4[7-9] (Table 1). The disease was classified based on the severity of symptoms, genotype (number of copies of the SMN2 gene), response to treatment, motor performance (sitting, not sitting, walking), and age of the disease onset[1,2,10,11]. Categorization is descending in severity and lethality.

TREATMENT

Nusinersen: Nusinersen, marketed as Spinraza®, is a synthetic antisense oligonucleotide. It was the first drug approved for thetreatment of SMA. Its function is to increase the production of SMN protein by acting on the SMN2 gene precursor. As mentioned before, most of the RNAs transcribed by this gene do not have exon 7. The function of nusinersen is precisely to inhibit the splicing of this exon ─ including it ─, thus increasing the formation of functional SMNs[12, 13]. Therefore, nusinersenincreases motor performance and decreases ─ or even prevents ─ the progression of the disease. Its administration is made chronically through the intrathecal route (around the spinal cord), starting as soon as possible in the patient's life. Taking the intrathecal route into account, its effect is limited to the central nervous system[12].

Genetic Therapy (onasemnogene abeparvovec) Onasemnogene abeparvovec (or AVXS-101), marketed as Zolgensma®, is an approved medicine that uses gene therapy to treat SMA. It inserts functional copies of the SMN1 gene into the motoneurons, replacing those mutated[14]. Thus, unlike nusinersen, onasemnogene directly treats the genetic cause of the disease[15]. For the insertion of functioning SMN1 genes in motor neurons, viral vector capsids AAV99 are used. The outcome is the increase of SMN protein expression in motor neurons, increasing the motor performance and life expectancy of patients. Onasemnogene is administered only once, through the intravenous route, in children under two years old who have biallelic mutations in the SMN1 gene[16,17].

Risdiplam: Risdiplam, the active substance in Evrysdi™, is the first oral medication approved for the treatment of SMA. Such as nusinersen, it takes action by modulating SMN2 gene splicing to produce complete SMN proteins[18]. However, unlike the antisense oligonucleotide, this drug fulfills its role by binding into two sites in the pre-mRNA: the exon splicing enhancer 2 (ESE2) in exon 7 and the 5' splicing site (5'ss) of intron 7 [18-24]. This interaction leads, respectively, to the displacement of the hnRNP splicing suppressor – which allowed the expression of the exon 7 deletion phenotype – and to the increase of the binding stability between U1 small nuclear ribonucleoparticle (U1 snRNP) and 5'ss[19,23,25]. This enables the inclusion of exon 7 in transcription, which results in the formation of functioning SMN proteins. Risdiplam should be administered daily, orally, after meals[26]. Due to its route of administration, Evrysdi is able to act both at the central nervous system level – since it can easily penetrate the blood-brain barrier – and at peripheral organs involved in the pathophysiology of SMA[21,27].

Objective: This article aims to review studies involving the use, for the treatment of patients with SMA, of nusinersen, onasemnogene abeparvovec and risdiplam, discussing effects and examining the benefits of these drugs.

METHODS

This article is a qualitative integrative literature review. For its elaboration, searches were made in the PubMed, Google Scholar and Cambridge Libraries databases, using the following descriptors: "Spinal Muscular Atrophy", "Atrofia Muscular Espinhal", "Zolgensma", "Onasemnogene Abeparvovec", "Nusinersen", "Spinal Muscular Atrophy Treatment", "Atrofia Muscular Espinhal Tratamento", "AVXS-101", "Spinraza", "Spinal Muscular Atrophy Gene Therapy", "Atrofia Muscular EspinhalTerapiaGênica", "Risdiplam" and "Evrysdi". Four articles produced from 2017 to 2022 were chosen on each medication ─ articles that exhibited studies on the effects of the three medicines in individuals with SMA. For the selection, there were the following exclusion criteria: review articles and paid articles. The data obtained was organized in a table (Table 2).

RESULTS

Nusinersen: The study by Darras et al. (2019)[28] was carried out with 28 children, of which 11 had SMA type 2 and 17 had SMA type 3. Treatment with nusinersen was able to increase 10.8 points on the Hammersmith Functional Motor Scale Expanded (HMFSE) test after 3 years of treatment in children with type 2 SMA and 1.8 points in children with type 3 SMA, demonstrating a great improvement in the patients' motor function. An increase of 4 points was identified in the Upper Limbs Module (ULM) score, which analyzes the function of the upper limbs, and in the 6 Minute Walk Test (6MWT), in which patients with type 3 SMA reached a distance of 92 meters larger after 3 years. In addition, one child in the group started to walk independently during the study. Regarding the CMAP and MUNE scores, children with SMA type 2 increased amplitude by 0.4mV, and children with SMA type 3 increased it by 0.3mV, thus, muscle innervation remained stable and without major changes at the end of 3 years of treatment. Furthermore, no important clinical improvements were found in laboratory values and neurological examinations related to the disease. Thus, the results indicate that patients with this neuromuscular condition acquire greater motor function in the long term, as well as a stabilization in the progression of the disease. The study by E. Mercuri et al. (2018)[29] was carried out with 126 children, divided into an experimental group (n=84) and a control group (n=42), but only 66 children of the first group completed the 15-month treatment with nusinersen. The study identified an improvement in the HFMSE from 6 months after starting treatment. At the end of 15 months, the nusinersen group had more children with improvements than the control group (57% and 26% respectively) in the HFMSE test. New World Health Organization (WHO) motor milestones were found in 20% of the experimental group vs 6% of the control group. An increase in the result of The Revised Upper Limb Module (RULM) was observed in both groups, with a difference of 3.7 points more in the experimental group. In addition, the study reveals that nusinersen is safe and that the adverse conditions that occurred in the experimental and control groups (17% and 29% participants) can be associated with SMA symptoms.

The study by T. Duong et al. (2021)[30], was carried out with 42 adult participants, with an average age of 33 years, that had SMA type 2 or 3 and who received doses of 12mg of nusinersen every 4 months. Improvements were found in the Children's Hospital of Philadelphia Adult Test of Neuromuscular Diseases (CHOP-ATEND) of 3.59 points per year, and in the SMA Functional Scale an improvement of 1.44 points per year. Regarding the TUG test, there was a decrease of 0.10 points in the scale, indicating a shorter time demand to complete the tasks. It was possible to analyze an improvement in ventilatory function, which suffered an increase in maximum expiration pressure (MEP) of 6.38 cm H2O per year and a decrease of 5.50 cm H2O in maximum inspiratory pressure (MIP) per year of treatment. Furthermore, adverse events were rarely recorded, the most common being local pain and headache caused by lumbar puncture and only 2 cases of thrombocytopenia that were cured spontaneously. Finally, the study by J. Montes et al. (2019)[31] was carried out with 14 participants aged 2-15 years with SMA types 2 and 3. These participants were divided into 4 groups, each of which received a different dosage of nusinersen (3mg; 6mg; 9mg; 12mg), in which the 9mg and 12mg groups reached the therapeutic window more quickly. The study was based on the 6MWT score to analyze the distance achieved by patients, observing an average increase of 17 meters on day 253 of treatment, and, on day 1050, a significant increase of 98

Table 1. Characteristics of the types of SMA

Type	Frequency	Symptoms Onset	Symptoms	Motor performance	Life Expectancy	Copies of the smn2 gene
0	Less than 1%[1].	Prenatal period or at birth[1].	Generalized weakness, hypotonia, respiratory failure, and feeding difficulties[1].	Patients are not able to sit nor walk, not having head control[1,2].	Less than 6 months of age[2].	1 copy[1].
1	45%[1].	6 monthsafter birth[12].	Muscle weakness (predominantly proximal), respiratory failure, feeding difficulties, and tongue fasciculation[1,2].	Patients are not able to sit unassisted – only with support – nor to walk independently[1,2].	Less than 2 years of age[12].	1 or 2 copies[1].
2	20%[1].	6 to 18 months[1].	Predominantly proximal muscle weakness, tongue fasciculations and atrophy, involuntary movements (minipolymyoclonus) and scoliosis[1].	Patients are able to sit by themselves but are unable to walk independently[12].	25 years[1].	3 copies[1].
3	30%[1,2].	Subtype A: from 18 months to 3 years. Subtype B: from 3-30 years[1].	Predominantly proximal muscle weakness, more on legs than arms, and abnormal gait[1,2].	Patients are able to walk[1,12].	Normal lifeexpectancy[1,2].	3 or 4 copies[1,9].
4	Less than 5%[2].	30 years[1].	Same as subtype 3.	Patients are able to walk, presenting normal gait.	Normal lifeexpectancy[1].	4 or more copies[1].

Table 2. Data from the analyzed theoretical frameworks

AUTHORS	TITLE	OBJECTIVES	RESULTS
B.T. Darraset al. (2019)[28].	Nusinersen in later- onset spinal muscular atrophy	To report results of long-term treatment with nusinersen of children with spinal muscular atrophy.	Long-term nusinersen treatment led to improvement in motor function and stabilized the disease in participants. In children with SMA type 2, an improvement in the HFMSE was observed. Improvement in the upper limbs was also evidenced. In the group of children with SMA type 3, there was improvement in the 6MWT and also in the HFMSE. It is concluded that the treatment with nusinersen is effective in improving symptoms in SMA types 2 and 3.
E. Mercuriet al. (2018)[29].	Nusinersen versus Sham Control in later-Onset Spinal Muscular Atrophy	To evaluate the efficacy and safety of nusinersen in children with late-onset spinal muscular atrophy.	Nusinersen was effective for children with late-onset SMA and was associated with a clinically significant improvement in motor function compared to the control group. New motor milestones were reached in patients who took the drug. In addition, an improvement in the HFMSE and RULM scores was observed.
T. Duongetal. (2021)[30].	Nusinersen Treatment in Adults with Spinal Muscular Atrophy	To evaluate the changes in motor function in patients with SMA after treatment with nusinersen, therefore show respiratory and neuromuscular functions in these patients.	Patients with SMA types 2 and 3 showed positive changes in motor and ventilatory functions, especially in the CHOP-ATEND and SMA Functional Scale. Nusinersen was tolerated by all participants, without significant adverse events.
Montes et al. (2019)[31].	Nusinersen improves walking distance and reduces fatigue in later-onset spinal muscular atrophy	To evaluate the efficacy of nusinersen in reducing fatigue on the 6MWT, besides its efficacy in improving motor function in individuals with SMA.	Results demonstrate clinically significant effects of nusinersenon motor function in children and adolescents with late-onset SMA. The treatment was able to reduce fatigue and improve the patients' performance in the 6MWT.
L.P. Lowes et al.(2019)[32].	Impact of Age and Motor Function in a Phase 1/2A Study of Infants With SMA Type 1 Receiving Single- Dose Gene Replacement Therapy	To characterize the motor function in infants with severe SMA type 1 after an initial dose of AVXS-101.	After 24 months of the application of AVXS-101, group 1 had an increase of 35 points in the CHOP-INTEND scale, reaching 50.7 points. Group 2 progressed 23.3 points, reaching 49.8 points, and group 3 progressed16.3 points, reaching the mark of 60.3 points.
S.Al-Zaidy et al. (2018)[33].	Health outcomes in spinal muscular atrophy type 1 following AVXS- 101 gene replacement therapy	To evaluate the health outcomes of AVXS-101 in babies with SMA type 1.	At the end of the study, 86% of the patients continued to eat orally, exclusively. With the AVXS-101 treatment, 11 children achieved full head control and were able to sit alone without support; 11 children sat for at least 30 seconds after 2 years; 9 children were able to roll over; and 2 were able to crawl, stand and walk on their own.
S.A. Al-Zaidy et al. (2019)[15].	AVXS-101 (OnasemnogeneAbeparvovec) for SMA1: Comparative Study with a Prospective Natural History Cohort	To compare the effects of AVXS-101 in babies with SMA type 1 from babies in ahistorical prospective cohort.	At 0 months of age, the mean CHOP-INTEND score was 37.0 points. At 24 months of administration of the drug, there was an increase in this score, reaching 56.5, with 92% of the children reaching the 40-point mark. The study also demonstrated a rapid rise in the CMAP score, going from 1.1 points at 6 months to 3.2 points at 24 months. 275 adverse events, mainly related to secondary diseases, including 53 serious events, with two cases associated with an asymptomatic increase in serum levels of aminotransferases.

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J.R. Mendell et al. (2017)[34].	Single-Dose GeneReplacement Therapy for Spinal Muscular Atrophy.	To study the replacement of the mutated SMN1 gene for a functional one after the administration ofonasemnogeneabeparvovec.	The High-Dose group had an increase of 24.6 points at the end of the study, reaching 52.8 points in the CHOP-INTEND score, while the Low-Dose group achieved 7.7 points, reaching 24 points. 4 patients had an asymptomatic increase in serum levels of aminotransferases, which was attenuated with treatment withprednisolone.
B.T. Darras et al. (2021)[35].	Risdiplam-Treated Infants with Type 1 Spinal Muscular Atrophy versus Historical Controls	To evaluate the efficacy and safety of risdiplam in children with SMA type 1.	The risdiplam treatment in children with SMA type 1 for 12 months resulted in an improvement of at least 4 points in the CHOP-INTEND score in 37 of 41 patients, indicating better motor function. In the HINE-2 parameter, which evaluates motor skills, 78% of the children had an increase of at least 2 points. Additionally, 35 out of 41 were classified as event-free Survival. 254 adverse events were reported.
M. Eugenio et al (2022)[36].	Risdiplam in types 2 and 3 spinal muscular atrophy: A randomised, placebo-controlled, dose-finding Trial followed by 24 months of treatment	To assess the safety, tolerability, PK, and PD of risdiplam in patients with SMA types 2 and 3, therefore to determine the pivotal dose for SUNFISH Part 2.	The study showed an improvement or stabilization in the MFM32, RULM, and HFMSE scores at month 24 of the risdiplam treatment. At the end of 24 months, there were no significant improvements in respiratory function. 737 adverse events were reported in 49 (96%) patients. The pivotal dose for Part 2 is 5 mg for patients weighing 20 kg or more and 0.25 mg/kg for patients weighing less than 20 kg.
Baronello et al (2021)[37].	Risdiplam in Type 1 Spinal Muscular Atrophy	To show the results from the dose-finding part 1 of a study of risdiplam in babies who have SMA type 1 aged 1-7 months; to present the selection of the dose for part 2 of this study.	A total of 21 infants were enrolled. At baseline, the median CHOP-INTEND was 24 points and, at month 12, a total of 11 infants (52%) had a score of 40 or more points. Nevertheless, as of the clinical data-cutoff date, a total of 202 adverse events were reported, of which 24 were serious adverse events. Besides, 3 infants had died at the time of the data cutoff.
Hahn et al (2022)[38].	Short-term safety results from compassionate use of risdiplam in patients with spinal muscular atrophy in Germany	To expose the first real-world data on the characteristics of german patients; to report the short-term safety of risdiplam in clinical practice in Germany.	134 people were chosen to participate ─ 36 patients with SMA type 1 and 98 patients with SMA type 2. During the safety report period, a total of 130 adverse events were observed in 44 case reports. The most common non-serious adverse events in SMA type 1 were gastrointestinal disorders. In SMA type 2, it was diarrhea, followed by headache, aphthous ulcer, constipation, and nausea.

meters, as well as a 3.8% reduction in muscle fatigue. Participants aged ≤11 years walked more and experienced less fatigue than those aged > 11 years.

ONASEMNOGENE ABEPARVOVEC

In Lowes et al. (2019)[32], 12 patients were grouped by a combination of age at dosing, between older than three months (Late Dosing) and younger (Early Dosing). In addition, they were also classified according to the baseline CHOP-INTEND scores, over 20 points (High Motor) and under 20 points (Low Motor). Therefore, to the first group, “Early Dosing/Low Motor”, the administration occurred within less than three months. This group presented an initial score of 15.7 points in the CHOP-INTEND, while the second group, “Late Dosing/High Motor” achieved an initial score of 26.5 points, with an average age of 5.1 months. To the third group, “Early Dosing/High Motor” the administration occurred early. This group presented 44 points initially. After the administration of AVXS-101, there was a comparison between 1, 3, and 24 months, and all patients showed a fast increase in scores. Patients in group 1, after 24 months, had an increase of 35 points, reaching 50.7 points. The second group progressed 23.3 points, reaching 49.8, and the third group progressed 16.3 points, reaching the mark of 60.3, almost achieving the maximum value of the scale, which is 64 points. Furthermore, contrary to the natural progression of the disease, almost all patients (11) were able to sit alone for 5 seconds or more after 24 months of treatment, and 9 of 12 patients were able to sit alone for more than 30 seconds. In Al-Zaidy et al. (2018)[33], at the beginning of the study, the 12 participants had a mean age of 3.4 months and, by the end of the two years of follow-up, 10 participants did not need non-invasive ventilation (NIV), and 0 patients required tracheostomy, and, in the final study visit, 7 of these 10 patients didn’t need any ventilatory support. In addition, 58% of all patients (7 of 12) were able to eat orally without nutritional support and, at the end of the study, 6 of 7 patients (86%) continued to eat exclusively orally. With the AVXS-101 treatment, 11 of the 12 children achieved full head control and were able to sit on their own without support. Of all 12 children, 11 sat for at least 5 seconds, 10 for at least 10 seconds, and 9 for at least 30 seconds during the 2 years of follow-up. Also, during the study, 9 patients were able to roll over and 2 were able to crawl, stand and walk on their own. After continuous observation, which lasted 2 years, 2 other children were able to reach the mark of sitting alone for at least 30 seconds, which was then reached by 92% of the children. In Al-Zaidy et al. (2019)[15], 12 children took the dosage of onasemnogeneabeparvovec, at 0 months of age. The average of CHOP-INTEND was 37.0 points and, after that, with 12 months of the administration, there was an increase of 13 points, reaching the mark of 50 and, in addition, at 24 months of age, an increase of 6.5 points, presenting, then, 56.5 points. Furthermore, 11 (92%) children reached the mark of 40 points. 11 children treated with AVXS-101 achieved and maintained the milestone of sitting without support for ≥5 seconds, 10 achieved sitting without support for ≥10 seconds, and 9 were able to sit without support for ≥30 seconds by 24 months of follow-up. In addition, 2 children could stand and walk without support. Besides, the infants demonstrated a substantial increase in CMAP peak area values, from a mean of 1.1 mV/s at 6

months of age to a mean of 2.8 mV/s at 12 months, and 3.2 mV/s at 24 months. Nevertheless, in this study there were a total of 275 adverse events, mostly related to the underlying diseases, of which 53 were serious adverse events, with two cases treatment-related and related to the asymptomatic increase of aminotransferases levels in the blood. In the study by Mendell et al. (2017)[34], 3 of the 15 patients who were included in the study were part of the "Low-Dose" group, in which low doses of the drug were taken with an average age of 6.3 months, while in the second group, the remaining 12 patients took a high dose of the medication, with a mean age of 3.4 months. As of August 7, 2017, at the end of the study, all the patients had reached an age of at least 20 months and did not require permanent mechanical ventilation. All patients, in both groups, had increased scores from baseline on the CHOP-INTEND scale, with High-Dose increasing by 9.8 points at one month of the study to 15.4 points at the end of 3 months and 24.6 at the end of the study, with a baseline of 28.2 points, counting 52.8 in total. The Low-Dose cohort, with 7.7 points from the baseline score of 16.3, reached a total of 24 points. 11 of the 12 patients in group 2 were able to sit without support for 5 seconds, 10 for at least 10 seconds, and 9 for at least 30 seconds. In addition, 11 achieved the ability to speak, 11 achieved head control, 9 managed to roll over and 2 were able to crawl, stand and walk on their own. Nevertheless, 10 of the 12 patients in this group did not require NIV. Furthermore, 4 patients had an asymptomatic increase in serum levels of aminotransferases (ALT and AST), which were attenuated with prednisolone.

Risdiplam: The study of B.T. Darras et al. (2021)[35] was carried out with 41 children with SMA type 1. Patients over 5 months of age took a dose of 0.2mg per kilogram of body weight of Risdiplam, administered orally per day, while patients younger than 5 months initially received 0.04 or 0.08 mg per kilo daily, and between 1 to 3 months later, there was a readjustment to 0.2mg per kilo. After 12 months, 56% of the patients achieved a score greater than or equal to 40 on the CHOP-INTEND, and 90% achieved improvements of 4 points from baseline. Event-free Survival, defined as being alive without the use of permanent ventilation, showed that 35 of the 41 children did not need to use ventilation, with 11 of 12 children using it prophylactically. Another parameter used was the HINE-2, and 78% of the children achieved an improvement of at least 2 points in the ability to kick, or at least 1 point in head control, rolling over, sitting, crawling, standing, or walking. The treatment with Risdiplam was able to improve motor milestones and respiratory function, although adverse events such as pneumonia (in 13 children), hypotonia and respiratory failure were recorded, with 3 children dying during the study, the cause being linked to the respiratory complications of SMA. In M. Eugenio et al (2022)[36], the SUNFISH part 1 study was performed, with 51 patients ─ of which 73% had SMA type 2 and 27% had SMA type ─ aged between 2-25 years, to analyze the effective dose, safe and tolerable, to perform SUNFISH part 2 with Risdiplam. Patients underwent 5 different cohorts, with oral doses of Risdiplam of 0.02, 0.05, 0.15, and 0.25mg/kg, randomly assigned to the placebo and control group for 12 weeks. During part 2, doses of 5mg were administered to patients weighing more than 20kg, and 0.25mg/kg to patients weighing less than 20kg, for at least 24 months of treatment (mean rate of 31.9 months). 737 adverse events were reported during the study period, with 49 (96%) patients experiencing at least one, and 15 (29%) experiencing severe adverse events. The most common adverse events were pyrexia (55%), cough (35%), upper respiratory tract infection (31%), and the most severe adverse events were pneumonia and femur fracture. There was an increase in SMN protein in the blood during the study period. At the end of the 24 months of treatment, patients aged 2-11 years increased by 3.7 points on the MFM32 (n=44), and patients aged 12-25 years, 1.5 points. In the RULM score (n=51), patients aged 2-11 years increased by 2.9 points, and patients aged 12-25 years, increased by 1.7 points. In the HFMSE (n=51), patients aged 2-11 years had an increase of 1.4 points, and patients aged 12-25 years had a decrease of 0.7 points. A higher percentage of patients treated with Risdiplam achieved stability or an increase in motor function by the MFM32 test compared to the comparative group (81.3% vs 44.4%). No clinically significant changes in respiratory function were found.

In Baronello et al. (2021)[37], a total of 21 infants participated in the study. The final doses that were established by the dose-escalation method were 0.08 mg per kilogram once daily in the low-dose cohort, and 0.2 mg per kilogram once daily in the high-dose cohort. The low-dose cohort included 4 infants, and the fourth infant and all the subsequently enrolled infants composed the high-dose cohort (17 infants). At baseline, the mean score achieved in CHOP-INTEND was 24 points, and none of the infants were able to sit without support. 5 of the 21 infants received respiratory support, ─ of which 4 received this support prophylactically. In the high-dose cohort, a total of 7 infants were able to sit without support for at least 5 seconds, 9 were able to maintain upright head control at all times, and 1 was able to bear weight in standing. No infants in the low-dose cohort were able to perform these functions. At month 12, a total of 11 infants (52%) had a CHOP-INTEND score of 40 or higher, and over the 12-month period, no infant lost the ability to swallow, and a total of 18 infants (3 in the low-dose cohort and 15 in the high-dose cohort) were able to feed orally, either exclusively or in combination with a feeding tube. There were no findings suggestive of risdiplam-induced retinal toxic effects. Nevertheless, as of the clinical data-cutoff date, a total of 202 adverse events were reported, of which a total of 24 were considered serious adverse events. Three infants died at the time of the data cutoff. In Hahn et al. (2022)[38], a total of 134 people participated of the study ─ of which 36 patients had SMA type 1 and 98 patients had SMA type 2. The treatment with ridisplam lasted 5.0±2.7 months in the SMA type 1 cohort and 3.4±1.9 months in the SMA type 2 cohort. During the safety report period, a total of 130 adverse events were observed in 44 case reports. For SMA type 1, 30 adverse events were reported in 13 cases with 2 serious adverse events in 1 patient. For SMA type 2, 100 adverse events were reported in 31 cases, including 8 adverse events in 2 patients. The most common non-serious adverse events in SMA type 1 were gastrointestinal disorders: diarrhea was observed 3 times, and abdominal pain and salivary hypersecretion occurred 2 times. In SMA type 2, diarrhea was the most common non-serious adverse event, followed by headache, aphthous ulcer, constipation, and nausea.

DISCUSSION

Nusinersen: Nusinersen was the first drug in the world to be used in the treatment of SMA, being approved in Brazil in 2017. The efficacy of this drug is proven throughout all four studies. In the first one[28], 28 children who took nusinersen showed significant improvements in motor function, which is evidenced by the increase in the HFMSE score – a scale used to assess motor function in individuals with SMA types 2 and 3. However, this improvement was greater in children with SMA type 2, which can be explained by some items on this scale ─ such as climbing stairs, crouching, and jumping ─ which are more difficult to achieve, regardless of the type of atrophy. In the second study[29], 126 children were divided into 2 groups – in which 84 were part of the group who took nursinesen and 42 of the one who took a placebo. However, only 66 of the experimental group reached the end of the research, thus completing the 15-month treatment. This group showed more improvement in motor function and acquisition of new motor milestones than the control group. In the experimental group, there was an improvement in the HFMSE score by month 6; however, after this period, the difference between this group and the control one became more apparent. The short-lived improvement in the control group during the first few months of the treatment period likely resulted from a placebo effect. Furthermore, the greatest improvements in HFMSE scores over the 15-month period were seen in younger children and in those who received treatment soon after the onset of the symptoms. The third study[30] was conducted with 42 adult patients with SMA types 2 and 3, and improvements were reported, including a greater range of active movement of the fingers and hands, a louder voice, and an improved jaw movement and speech. For motor measures, the most punctual improvement was observed by using CHOP-ATEND – average slope = 3.59 points/year – and the Spinal Muscular Atrophy Functional Rating Scale, SMAFRS, (average slope = 1.44 points/year). Furthermore, improvements in this scale were more noticeable in those with more

severe phenotypes (non-sitter patients with SMA type 2 and those with 3 SMN2 copies). Thus, respiratory measurements also exhibited a mean rate of change, indicating improvement after treatment with nusinersen. The fourth study[31] was carried out with 14 patients aged 2-15 years and with SMA types 2 and 3. It was based on the 6-minute walk test to analyze the distance covered and fatigue. This study showed that the use of nusinersen demonstrated improvements in ambulatory function, with clinically significant increases in walking distance and modest decreases or stabilization in fatigue. Furthermore, in individuals with SMA, fatigue was associated with a decrease in low-rate repetitive nerve stimulation, possibly due to developmental abnormalities or functional changes at the neuromuscular junction. Thus, the study points out that the use of the drug, when started early, has more positive effects, given that patients aged ≤11 years had less fatigue and walked more. Analyzing the results of all 4 studies, it is possible to say that nusinersen is effective in the treatment of SMA by improving motor performance, increasing life expectancy, and decreasing ─ or even inhibiting ─ the need for permanent ventilation and the progression of the disease. In addition, by being an oligonucleotide, it has high specificity for its target ─ previously inaccessible ─, acting on it with reduced toxicity and systemic exposure, besides a longer half-life[14,39]. However, although this drug has many advantages, its administration ─ intrathecal ─ is invasive and can cause discomfort (headache, back pain, and vomiting)[13,40].

Onasemnogene Abeparvovec: Onasemnogeneabeparvovec is the first drug to use gene therapy. It was approved more recently than nursinersen ─ in Brazil, in 2020. Its effectiveness has been proven throughout all 4 studies. The first[32], carried out with 12 patients, analyzes the effect of onasemnogene in babies with SMA – who were divided into three groups according to age. All subjects who took the proposed therapeutic dose of Zolgensma® improved their CHOP-INTEND score after the first dosage. The first group, the early dosing/low motility group, demonstrated a mean gain of 35.0 points from a baseline of 15.7, while the late dosing one had a mean gain of 23.3 from a baseline of 26. 5. Furthermore, the early dosing/high motility group quickly reached an average score of 60.3, close to the scale's maximum (64), from a baseline of 44.0. This demonstrates that the dosage at the onset of the disease's symptoms, regardless of its severity, can allow significant gains in motor function and achievement of motor milestones. Thus, these results demonstrate the efficacy of using AVXS-101, besides the importance of neonatal screening for the identification of affected babies to maximize the therapeutic benefit of early treatment. The second study[33], carried out with 12 patients, used gene replacement therapy with AVXS-101. According to the results presented, the average proportion of hospitalization time was 4.4% and, in comparison to the previous studies, this one demonstrated a lower average number of annual hospitalizations (2. 1 versus 4.2) and a shorter average length of stay (6.7 versus 13 days). In addition, 7 patients did not require ventilation, and 11 had stable or improved swallowing function, as demonstrated by the ability to take oral food. Thus, it's possible to conclude that the treatment was able to reduce the number of hospitalizations and preserve the function of the respiratory system since the treatment made it possible to reduce the need for pulmonary and nutritional support. Thus, the reduction in the use of ventilation and nutritional support can decrease the general use of health care related to those affected and increase their functional independence.

The third study[15], conducted with 12 babies with SMA type 1, showed that the mean baseline CHOP-INTEND score for babies treated with former AVXS-101 was 28.2, improving to 56.5 at 24 months of age. This demonstrates that the use of onasemnogene brings benefits, given that these babies achieved new motor milestones, such as sitting without support and walking. Additionally, the mean baseline CHOP-INTEND score for babies with SMA type 1 who did not use the medication was 20.3, worsening to 5.3 at 24 months of age. Thus, the use of the drug has positive effects, as Zolgensma® increased the probability of survival, rapidly improved motor function, and allowed the achievement of motor milestones in sick babies. The fourth research[34] was conducted with 15 patients ─ all of them, after using Zolgensma®, were alive and free of adversities at 20 months of age. In addition, this study was combined with another one carried out with 12 patients who received a high dose of the drug – of these, 11 sat down without support, 9 rolled over, 11 ate orally and spoke and 2 walked independently. In both studies, patients had increases in the CHOP INTEND score from baseline. This shows that the motor function achieved was clinically significant, as reflected in eating (raising the hand to the mouth), sitting, and talking. Thus, onasemnogene therapy resulted in extended survival, improved motor function, and increased CHOP INTEND scores to levels not previously seen in SMA. Thus, these improvements resulted in a lower percentage of patients requiring support than those in historical studies. Considering all 4 studies, it is possible to say that onasemnogene is effective in the treatment of SMA, as it improves motor performance; preserves respiratory function and thus decreases the need for permanent ventilation; allows patients – in this case, with types 1 and 2 – to have motor ranges such as the ability to sit down; and increases life expectancy. However, like nusinersen, Zolgensma® has bad adverse effects, such as vomiting and hepatotoxicity[41,42]. As hepatotoxicity leads to liver damage, the monitoring of the liver for 3 months is necessary[16]. If the intoxication of this organ doesn't cure spontaneously, it isimportant to use high doses of corticoids to repress the hepatic immune response[43].

Risdiplam: Risdiplam is a small molecule distributed systemically and administered orally that modifies SMN2's pre-messenger RNA (pre-mRNA)'s splicing. This drug was approved in October 2020 in Brazil. By using this medication, improvement in the motor functions of nurslings is expected. Besides, risdiplam is an alternative for kids and adults that are not eligible for the treatment with nusinersen or onasemnogene. The first study[35] was carried out with 41 babies with SMA type 1 and, after 12 months of treatment using oral risdiplam, an increase of at least 4 points on the CHOP-INTEND score was observed in all babies who were alive. 56% of the babies achieved 40 points or more on the CHOP-INTEND score, which is a different finding when compared to historical cohorts of untreated babies, in which this score decreased. Some adverse events were observed in this group, such as pneumonia, hypotonia, and respiratory failure, however, oral treatment with the drug resulted in higher percentages of babies who reached motor milestones, survived without the need for ventilation, and showed improvements in motor function. This shows that the use of this drug is promising, as it has advantages for patients, but longer studies are needed to determine the long-term effects of risdiplam in the treatment of SMA type 1. The second study[36] was carried out to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam. It was conducted with 51 patients with SMA aged 2 to 25 years. Efficacy tests included the 32-item Motor Function Measure (MFM32), HFMSE, and RULM. The total MFM score was compared to an external weighted study and there was a statistically significant difference of 3.99 points between Risdiplam and the comparator, which marks significant improvement and represents the gain of a new function or the improvement in several motor functions after 24 months of treatment. However, as the aim of part 1 of this study was to select the dose of risdiplam and evaluate the pharmacological and safety properties, it was not possible to make a concrete assessment of efficacy. This assessment is being evaluated in part 2 of the study. Part 1 demonstrated a positive safety profile in patients with SMA types 2 and 3 and revealed that the treatment resulted in an increase in SMN protein levels in the blood.

The third study[37] was conducted with 21 babies divided into 2 groups: 4 babies were part of the low-dose cohort and 17 of the high-dose cohort. At the beginning of the research, none of the nurslings could sit without support, but in the 12th month, 90% of the patients were alive without the need for permanent ventilation, which means they didn't have to go through a tracheostomy or positive pressure ventilation. Besides, 7 of 21 patients were able to sit without support, which is not expected in patients with SMA type 1, according to studies. In this study, risdiplam increased functional SMN protein levels in the blood, however, it wasn't certain this medication resulted in clinical benefits, because clinical outcomes can only be compared

qualitatively with historical cohorts. Part 2 of this research is in progress to evaluate the long-term effects and security of risdiplam in SMA type 1. In the fourth study[38], 134 people were chosen – of which 36 patients had SMA type 1 and 98 had SMA type 2. Thus, the research's goal was to analyze whether the safety and efficacy data of risdiplam were under the profile of other ongoing studies. The chosen patients were selected according to non-responsiveness or inability to tolerate the other approved treatment options. Overall, headache, fever, and upper respiratory tract infections were shown to be the most common adverse effects. Diarrhea, nausea, rash, and headache were the most frequently observed risdiplam-related adverse effects, and pneumonia was the most common serious adverse effect in SMA types 1 and 2. Most reported adverse effects were associated with an underlying disease or the SMA's progression, and the overall rate of these effects decreased over time with continued treatment with risdiplam. Therefore, this study presents the first real data of patients with SMA types 1 and 2 in Germany who are not eligible for treatment with onasemnogene or nusinersen, besides showing that the newly approved drug may be an option to reduce the gap in the treatment of SMA.

Cost: Since November 2019, the Brazilian Unified Health System (SUS) has offered treatment with Spinraza for approximately 370 children with SMA type 1[44]. In 2021, the cost of this therapy was expanded for patients with type 2 of this disease[45]. For those who are not included in the group treated by SUS, the cost of this drug is close to 1 million reais per year[46,47], and it must be administered chronically and periodically, every 4 months. Zolgensma and Evrysdi – incorporated into the public healthcare system, respectively, in December and March 2022 – are offered exclusively to people with the most severe type of SMA[47,48]. However, if the individual does not meet the requirements established by the Ministry of Health for the application of the first drug (i.e., children over six months old and/or who are using invasive mechanical ventilation for more than 16 hours a day), its single dose would cost approximately R$6.4 millions[48,49]. Finally, Evrysdi has the advantage of having the lowest cost per dose, costing 25,370 reais[50]; however, it is important to emphasize that this medication is for chronic daily use and its dosage is related to the patient's weight – which means that the price of the treatment is influenced by the child's anthropometric measurements, increasing its value as the child grows[47].

CONCLUSION

Nusinersen, onasemnogeneabeparvovec and risdiplam are effective in the treatment of SMA, as they promote improvement in the motor and respiratory functions of patients. In the search for the best therapy, it is necessary to consider factors such as toxicity, route of administration, site of action and cost of such drugs. Bearing this last factor in mind, all medicines have high and not very affordable prices. It is concluded, therefore, that, to reverse this situation, it is extremely important to have greaterdissemination, in the scientific community, of the new technologies used in the creation of these drugs.

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