REVIEW ARTICLE

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Clinical outcomes of Onasemnogene Abeparvovec use in Spinal Muscular Atrophy – evaluating efficacy and therapeutic potential of gene theraphy

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Abstract

Introduction and Objective. Spinal muscular atrophy (SMA) is a degenerative neuromuscular disorder characterized by the progressive degeneration of α-motor neurons within the spinal cord and brainstem, leading to muscle weakness and atrophy. As the disease progresses, patients experience impaired ability to safely ingest food and maintain independent respiration, ultimately culminating in fatality. The aim of the review is to assess the efficacy and safety of using Onasemnogene Abeparvovec in the treatment of SMA.

Review Methods. The PubMed database was searched to identify studies assessing the effectiveness and safety of using Onasemnogene Abeparvovec. A total of twelve studies were identified using the search terms 'Onasemnogene', 'AVXS-101', 'gene-replacement therapy' and 'spinal muscle atrophy', with filters applied for 'Clinical Trial' and 'Randomized Controlled Trial'. Four of them did not focus on the efficacy of Onasemnogene in treating SMA1 and were therefore excluded from this analysis.

Brief description of the state of knowledge. Onasemnogene Abeparvovec (Zolgensma®) is an FDA-approved gene therapy for treating all types of SMA in patients under two years of age at the time of treatment. This therapy uses the adeno-associated virus 9 (AAV9) capsid to deliver complementary DNA (cDNA) encoding the SMN protein directly to motor neurons. A single intravenous dose of AAV9 crosses the blood-brain barrier, providing a functional copy of the SMN1 gene to the cells, which then produces the SMN protein.

Summary. Onasemnogene Abeparvovec has demonstrated substantial efficacy in treating SMA. The drug significantly enhances key clinical outcomes and is relatively safe to use, with only a few serious adverse effects attributed to the treatment.

Key words

Spinal Muscular Atrophy, Onasemnogene Abeparvovec, gene therapy

INTRODUCTION AND OBJECTIVE

Spinal Muscular Atrophy (SMA) belongs to progressive, degenerative neuromuscular diseases characterized by loss of α-motor neurons in the spinal cord and brainstem, causing weakness and atrophy of muscle [1]. The weakness initially manifests proximally but gradually extends to all skeletal muscles, ultimately resulting in the inability to eat safely or breathe without assistance, leading to eventual death [2].

The disease is attributed to a deficiency of the survival motor neuron protein, which is encoded by the SMN1 gene located on chromosome 5q [3]. This deficiency arises from mutations in the SMN1 gene, which lead to a reduced level of the ubiquitously expressed SMN protein. The dominant genetic cause, accounting for 95% of SMA cases, is a homozygous deletion of exon 7 in the SMN1 gene [4, 5]. This mutation occurs with a population frequency of approximately one in 50 individuals, leading to a prevalence of SMA of approximately one in 10,000 [6]. Other cases involved one copy of the common exon 7 deletion and a point mutation in the SMN1 gene [1]. The SMA is classified into five clinical subtypes on the basis of the age of onset of the condition and the highest achieved motor milestone. Type 1 SMAs, the most common form, account for nearly half of all cases. Most infants with type 1 SMA do not survive beyond the age of two years, making SMA one of the most prevalent genetic causes of infant mortality [1, 7].

Progress in understanding the molecular mechanisms underlying the pathogenesis of SMA has led to the development of potential therapeutic strategies. Current treatments focus on increasing SMN levels through SMN1 gene replacement via gene therapy, and enhancing the production of functional SMN protein by modulating SMN2 gene transcription or splicing, using antisense oligonucleotides (ASOs) or small molecules to promote the production of the protein[8].

Additional therapeutic options involve SMN-independent strategies targeting pathways downstream of SMN, neuroprotective approaches utilizing small molecules or stem cells, and interventions aimed at enhancing muscle strength and function [9]. The aim of this review study is to

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identify and analyze available studies regarding the clinical use of Onasemnogene Abeparvovec in the treatment of SMA, considering its safety profile.

REVIEW METHODS

The PubMed database was searched to identify studies assessing the effectiveness and safety of using Onasemnogene Abeparvovec. A total of 12 studies were identified using the search terms 'Onasemnogene', 'AVXS-101', 'gene-replacement therapy' and 'spinal muscle atrophy', with filters applied for 'Clinical Trial' and 'Randomized Controlled Trial'. Four of them did not focus on the efficacy of Onasemnogene in treating SMA1 and were therefore excluded from this review.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Recently, three disease-modifying therapies have been approved for SMA patients, including nusinersen, an intrathecal antisense oligonucleotide that increases SMN protein synthesis from the *SMN2* gene; risdiplam, an orally administered drug that also targets the *SMN2* gene to boost SMN protein synthesis; and Onasemnogene Abeparvovec, a gene replacement therapy for the *SMN1* gene [7, 8]. Onasemnogene Abeparvovec (Zolgensma®) is an FDA-approved gene transfer therapy indicated for the treatment of all types of SMA in patients under two years of age at the time of administration [10].

The therapy utilizes the adeno-associated virus 9 (AAV9) capsid to deliver complementary DNA (cDNA) encoding the SMN protein directly to target motor neurons. A single intravenous administration of AAV9 is sufficient to cross the blood–brain barrier and deliver a functional copy of the SMN1 gene to patient cells, enabling the synthesis of the SMN protein [11, 12]. The SMN1 transgene, along with the synthetic promoter incorporated within the AAV9 vector, is critical for maintaining long-term SMN protein production [13].

RESULTS

On the basis of the above search algorithm, 12 papers were found on PubMed, with full access obtained for all. Four of them were not concerned with the efficacy of Osemnogene in treating SMA1 and were therefore excluded from the review. Among the eight selected studies, five described the initial results from four separate open-label, single-arm clinical trials (START, STR1VE-US, STR1VE-EU, and SPR1NT), and three were follow-up studies of the START trial [Tab. 1]. All the children had a genetically-confirmed diagnosis of SMA1 with a typical SMN1 disabling mutation, and two (in seven studies) or three (one study) SMN2 copies. The majority of them received the established therapeutic dose of 1.1×10^{14} vg/kg as a single infusion, except for patients from the START trial, who were treated with 6.7×10^{13} vg/kg or 2.0×10^{14} vg/kg, depending on the cohort. The clinical endpoints included ventilation-free survival, developmental motor milestone achievement and nutritional function. Apart from the first patient in the START trial, all the children were given prednisolone before and after the procedure to prevent aminotransferase elevation. Most of the studies used data from the historical Paediatric Neuromuscular Clinical Research (PNCR) cohort of patients with untreated SMA1 for statistical or descriptive comparisons. The identified articles provided a great deal of evidence confirming the clinical efficacy of oncogenes in the treatment of SMA1.

In the following sections, mostly the results that were classified as primary or secondary endpoints are presented.

Survival and ventilation. All the studies reported exceptional improvements in terms of ventilation-free survival in patients treated with Onasemnogene Abeparvovec, compared with patients with a natural history of disease, except for two follow-up articles that did not evaluate this effect. In the first study from 2017, all treated children (100%, n=15) survived without the need for permanent mechanical ventilation up to 20 months of age or more after a single infusion. In contrast, only 8% of the historical PNCR cohort reached this endpoint [14]. The results from three subsequent trials were consistent with the initial observations, reporting percentages of patients alive and ventilation-free as high as 91% [15], 97% [16], and 100% [17, 18] at the age of 14 months (vs 26% in the PNCR untreated cohort) and 82% [15] and 100% [17] at 18 months (vs 0% in the PNCR cohort). Furthermore, in the STR1VE-US trial, 15 (68%) patients did not require invasive ventilatory support at any time during the study [15]. The five-year follow-up of the START trial revealed the long-term persistence of ventilation-free survival in the treated population, except for one patient who received a lower, subtherapeutic dose of onasemnogene abeparvovec and who required permanent ventilation support at some point during the five-year observation period [19]. The additional analysis of the START cohort provided new information that treated patients experience, on average, 2.1 hospitalizations per year (1.4 due to respiratory reasons), whereas much higher hospitalization rates were observed in children not treated with SMA1 [20].

Motor development. Independent sitting (for at least 5 s, 10 s or 30 s, as defined by the Bayley-III criteria or WHO criteria, depending on the study) was the most frequently assessed motor milestone. Up to 18 months of age, 14 (44%) patients were able to sit independently for at least 10 s in the STR1VE-EU trial and 14 (70%) in the START and STR1VE-US trials (in a *post hoc* analysis) [16], whereas 13 (59%) patients were able to sit independently for at least 30 s in the STR1VE-US trial [15]. Another study revealed that all 14 (100%) children achieved this milestone at 18 months, and 11 (79%) did so within the WHO normal developmental time window, probably because of earlier treatment at range 8–34 days than the several months in previous studies [17]. In comparison, none (0%) of the patients in the PNCR cohort were able to sit independently at that age. In 2022, two articles described other motor milestones resulting from early Onasemnogene-Abeparvovec treatment: 79–93% of patients could stand alone, whereas 34–73% were able to walk independently within the normal developmental time window (depending on the number of SMN2 copies and the use of BSID or WHO-MGRS criteria) [17, 18].

Rapid and sustained increases in CHOP INTEND or BSID gross and fine motor scores were reported in all the studies performed (exploratory endpoint), with a substantial percentage of patients attaining CHOP INTEND scores of

≥40 [14–21]. An additional *post hoc* analysis of patients from the START trial revealed that, with early dosing of CHOP, INTEND scores increase remarkably, even in patients with the lowest motor function at baseline, enabling them to achieve final scores similar to those of other treated groups [21]. Onasemnogene efficacy in terms of better motor function was paralleled by electrophysiologic evidence of improved motor nerve integrity reported in 2022 (exploratory endpoint) [17, 18].

Nutritional function. The ability to thrive was a composite endpoint defined by the swallowing function (for thin liquids), being fed exclusively by mouth and appropriate weight maintenance (>3rd percentile). In the 2021 trial, nine (41%) patients maintained the ability to thrive (14 (64%) maintained a proper weight, 19 (86%) were fed exclusively orally, and 12 (54%) tolerated thin liquids) at the age of 18 months vs 0 years in the PNCR historical cohort [15]. One year later, another study reported that 12 (86%) of the observed children were able to thrive (13 (93%) maintained a proper weight without the need for nonoral/mechanical feeding support, and that 13 (93%) tolerated thin liquids) at the same age [17]. The difference in percentages probably resulted from earlier treatment of the children from the latter trial. Three other articles also provided some evidence concerning improved nutritional function in the treated population [14, 16, 18].

Safety. In the first study, due to elevations in Aminotransferase levels in Patient 1, that patient and all the subsequent participants received approximately 1 mg/kg prednisolone per day, up to 30 or more days after the infusion [14]. Prednisolone treatment was used thereafter in all trials to mitigate hepatotoxicity and other adverse effects (SAEs), with possible prednisolone dose modifications as needed. In one study, two patients were switched to an equivalent dose of hydrocortisone on days 165 and 132 of prednisolone treatment [16].

The majority of patients in all trials experienced at least one serious SAE, although a few of them were judged to be associated with treatment. A total of two deaths occurred in the studied population after receiving the Onasemnogene Abeparvovec infusion, both of which resulted from respiratory illness and were deemed to be unrelated to the drug itself [15, 16]. The most commonly reported SAEs related to treatment (five cases in total) were elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, which were mostly asymptomatic and resolved with prednisolone treatment [14–16], and pyrexia (two cases) [16]. Other SAEs possibly resulting from Onasemnogene Abeparvovec infusions occurred only once, and included hydrocephalus [15], hypertransaminaemia, gastroenteritis, viral infections, hypernatraemia, feeding disorders, thrombocytopenia (TCP) and abnormal coagulation tests [16]. In the SPR1NT trial and the five-year follow-up of the START trial, no SAEs-related to treatment were observed [17–19]. The non-serious SAEs considered to be related to Onasemnogene infection included ALT and AST elevation (the most common effect), gastrointestinal symptoms, hypertransaminaemia, pyrexia, elevated cardiac enzymes (CK-MB and/or troponin I), TCP and hypertension, with the majority of them being mild, clinically asymptomatic, and resolving without prednisolone dose modification [14–18]. Other SAEs, serious or non-existent, were deemed unrelated to the drug, but rather unrelated to the disease itself and thus were not included in this review.

DISCUSSION

The meta-analysis performed by Yang D. et al. included a sample of 250 patients with SMA from 10 qualified clinical trials [22]. The primary outcome was the efficacy of Onasemnogene in SMA patients, which was based on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and motor-milestone achievements. The maintenance of CHOP INTEND scores ≥40 points (clinically meaningful) was detected in 86.9% of the patients during the long term and 76.7% during the short-term (less than six months) follow-up after initiating the same administration regimen. The improvement in the ICI-resistant effect of CHOP during follow-ups for both terms was not statistically significant. The collective incidence rates of at least one new motor milestone achievement were 85.5% and 79.9%, both at both of the follow-up, respectively. However, there were no significant difference in motor milestone improvement during both follow-up terms after added effect estimates, and between groups with a different number of SMN2 copy. The most common SAEs included fever, vomiting, TCP, and elevated ALT and AST. Thus, patients were divided into two subgroups: up to eight months old and more than eight months old. Among the younger group, TCP occurred in 5% and elevated ALT and AST occurred in 28.5%. In the older group, the combined incidence rates of TCP and elevated ALT and AST were 79.3% and 71.7%, respectively.

This meta-analysis had several limitations. First, there were no control groups in the included studies, which limited the value of the evidence. Second, the included studies were only cohort and case series studies, which are inferior to randomized controlled trials in terms of the value of the results. Moreover, no endpoints of general survival and event-free survival, which are crucial in treatment assessment, were included. Finally, the limitations of each study included in this meta-analysis, i.e., differences in SMA types, small numbers of available samples and heterogeneity of population cohorts.

In the meta-analysis conducted by Fernandes B. D. et al., three clinical trials encompassing 66 patients with SMA were included [23]. Achievement of motor milestones was assessed by the Bayley-III Scales of Infant and Toddler Development, CHOP INTEND, and the WHO Multicentre Growth Reference Study. During the 12-month follow-up, global survival was predicted at 97.56% and event-free survival was predicted at 96.5%. Analysis of the data extracted from the studies revealed that 87.28% of the patients reached a CHOP-INTEND score ≥ 40. The proportion of treatment-related adverse events was 52.64%. There was no analysis of other adverse effect-related data, except for a proportion of serious adverse effects of 61.11%.

For limitations, similar to the previously described meta-analysis, there was no active control group. The number of studies that included patients was very limited. No randomization was performed. Most of the analyzed data were deemed statistically insignificant. In contrast, the included studies had a high risk of bias. Patients' age during the administration of Onasemnogene Abeparvovec was very low.

Table 1. Studies included in the review (outcomes regarding exploratory endpoints and safety are provided in the Results section)

Study and year	Type of study	Characteristics of patients included in the ITT analysis	Inclusion criteria	Exclusion criteria	Type of intervention	Comparison	Primary and secondary endpoints	Additional interventions	Clinical efficacity
Mendell et al. 2017	Open-label, single-arm, dose-escalation, phase 1 clinical trial (START)	- 3 patients in low-dose cohort 1 (age 6.3 [5.9-7.2], F 2) - 12 patients in high-dose cohort 2 (age 3.4 [0.9-7.9], F 7)	- genetic diagnosis of SMA1 with homozygous SMN1 exon 7 deletion and two copies of SMN2	- c.859G>C SMN2 modifier mutation - persistently elevated anti-AAV9 antibody titer >1:50	- 6.7×10^{13} vector genomes [vg]/kg iv of AAV9-mediated gene therapy, for 60 min (low-dose cohort 1) - 2.0×10^{14} vg/kg iv of AAV9-mediated gene therapy, for 60 min (high-dose cohort 2),	- none (descriptive comparison with historical Paediatric Neuromuscular Clinical Research [PNCR] cohort of patients with untreated SMA1	Primary outcomes: - safety (treatment-related adverse events of grade ≥3) Secondary outcomes: - ventilation-free survival*	- patients 2-15 received 1 mg/kg of prednisolone per day, beginning 24 h before the infusion up to 30 days after (due to serum aminotransferase elevations in Patient 1)	- results concerning primary outcomes described in 'Safety' section - all the patients had reached an age of ≥20 months without the need for permanent mechanical ventilation (vs 8% in historical PNCR cohort at age 20 months)
Day et al. 2021	Open-label, single-arm, multicentre, phase 3 clinical trial (STR1VE-US)	- 22 patients (age 3.7 ±1.6 months, F 12), out of which 19 (86%) completed the study - all patients included in the study had 2 copies of SMN2 gene and were symptomatic (CHOP INTEND scores 18-54)	- age <6 months - diagnosis of SMA1 (symptomatic or presymptomatic) - typical genotype with a disabling mutation of SMN1 and one or two copies of SMN2 - up to date on childhood vaccinations	- failure in swallowing evaluation test before administration of treatment - bodyweight <3rd percentile	- single dose of $1{\cdot}1\times10^{14}$ vg/kg of onasemnogene abeparvovec iv for 30-60 min via a peripheral vein	- 23 untreated patients with SMA1 from PNCR natural history cohort	Co-primary endpoint (statistical hierarchical testing): - functional, independent sitting for ≥30 s at 18 months of age - survival (absence of death or permanent ventilation*) at 14 months Secondary endpoints (statistical hierarchical testing): - ability to thrive** at age 18 months - being independent of ventilatory support at age 18 months	- all patients received approx. 1 mg/kg of prednisolone per day, beginning 24 h before the infusion up to 30 or more days after (hepatotoxicity prevention)	- 13 (59%, 97.5% CI 36–100) patients achieved the endpoint of functional independent sitting (at mean age 12.6 months) vs 0 (p<0.0001) patients in PNCR cohort*** - 20 (91%, 95% CI 79–100) did not require permanent ventilation at age 14 months vs 6 (26%, p<0·0001) in PNCR - 9 (41%, 97·5% CI 21–100) patients maintained the ability to thrive vs 0 in PNCR - 18 (82%, 97·5% CI 59·7–100·0) patients did not use ventilatory support at age 18 months vs 0 in PNCR (p<0.0001)
Mercuri et al. 2021	Open-label, single-arm, multicentre, phase 3 clinical trial (STR1VE-EU)	- 33 patients received the treatment and were included in the safety population; 32 (age 4.1 ±1.3 days, F 19) were included in the ITT analysis (1 was excluded due to dosing at 181 days); all patients had 2 SMN2 copies and were symptomatic - additional *post hoc* analysis of 20 patients from START and STR1VE-US trials who met the inclusion criteria	- age <180 days - diagnosis of SMA1 with common biallelic pathogenic SMN1 point mutations or exon 7-8 deletion and 1 or 2 copies of SMN2	- previous, planned or expected scoliosis surgery before age 18 months - noninvasive ventilatory support for ≥12 h daily in 2 weeks before dosing - anti-AAV9 antibody titer >1:50	- single dose of $1{\cdot}1\times10^{14}$ vg/kg of onasemnogene abeparvovec iv for 60 min via a peripheral vein	- 23 patients from PNCR natural history cohort	Primary outcome: - independent sitting for ≥10 s at any visit up to the 18 months of age Secondary outcomes: - ventilation-free survival at age 14 months	- all patients received 2 mg/kg of prednisolone per day, at 24 h before the infusion and for 48 h after - then 1 mg/kg per day up to 30 days post-infusion	- 14 (44%, 97·5% CI 26–100) patients achieved the primary endpoint of functional independent sitting (at median age 15.9 months) vs 0 in PNCR cohort - in STR1VE-US and START post hoc analysis, 14 (70%) achieved the primary endpoint - 31 (97%, 95% CI 91–100) survived and were ventilator-free at 14 months vs 6 (26%, 8–44) in PNCR (p<0·0001)
Strauss et al. 2022	Single-arm, multicentre, phase 3 clinical trial (SPR1NT)	- 14 patients with two copies of SMN2 (age 20.6 ±7.9 days, F 10), out of which all completed the study	- genetic diagnosis of SMA - 2 or 3 copies of SMN2 gene - no clinical evidence of neuromuscular disease	- clinical signs of SMA at screening - baseline peroneal nerve to tibialis anterior compound muscle action potential (CMAP) <2 mV - elevated anti-AAV9 titers	- single dose of $1{\cdot}1\times10^{14}$ vg/kg of onasemnogene abeparvovec iv for 60 min	- 21 patients for two copies cohort and 81 for 3 copies cohort from PNCR natural history cohort	Primary endpoint and other motor milestones: - independent sitting for ≥30 s at any visit up to 18 months of age - motor milestones defined by the Bayley-III Scales of Infant and Toddler Development (BSID) and the WHO Multicentre Growth Reference Study (WHO-MGRS) Secondary endpoints: - ventilator-free survival at 14 months - weight ≥3rd percentile without the need for non-	- all patients received 1- 2 mg/kg of prednisolone per day, at 24 h before the infusion and for 48 h after - then 1 mg/kg per day for the minimum of 30 days post-infusion	- all 14 (100%, 97.5% CI: 77–100%) patients achieved the primary endpoint of independent sitting (at median age of 265 days) vs 0 in PNCR cohort (p<0.0001) - 11 (79%) stood alone within the normal developmental time window - 9 (64%) walked independently as defined by BSID criteria and 10 (71%) as by WHO-MGRS - all 14 (100%) patients were alive and free of permanent ventilation at 14 months vs 6 (26%) in PNCR (P<0.0001) - 12 (86%) children were thriving** at the end of the study

							oral/mechanical feeding support at all visits up to 18 months of age - ability to tolerate thin liquids at 18 month		
Strauss et al. 2022		- 15 patients with 3 copies of SMN2 (age 28.7 ±11.68 days, F 9), out of which all completed the study					Primary endpoint: - independent standing for ≥3 s at any visit up to 24 months of age Secondary endpoints: - independent walking for ≥5 steps at any visit up to 24 months of age		- all 15 (100%) patients achieved the primary endpoint of independent standing (at median age of 377 days) vs 19 (24%) in PNCR (p<0.0001) - 14 (93%) patients achieved the secondary endpoint of independent walking (at median age of 422 days) vs 17 (21%) in PNCR (p<0.0001)
Mendell et al. 2021	Long-term follow-up of open-label, single-arm phase 1 clinical trial (START LTFU)	- 3 patients from low-dose cohort 1 (age 45.5 ±2.4 months, F 2, median time since dosing 5.9 years) and 10 patients from high-dose cohort 2 (age 33.7 ±7.7, F 5, median time since dosing 5.0 years) from START trial	- diagnosis of SMA1 with homozygous deletions of SMN1 and 2 copies of SMN2 (as in START trial)	- c.859G>C SMN2 modifier mutation (as in START trial)	- single high or low dose of AVXS-101 iv (details in START trial section)	- as in START trial	Primary outcomes: - long-term safety (treatment-related adverse events of grade ≥3); interim analysis 5 years after dosing Secondary outcomes: - long-term clinical efficacity (ventilation-free survival and developmental milestones achievement); interim analysis 5 years after dosing	- as in START trial - 3 patients in the low-dose cohort and 4 patients in the high-dose cohort were receiving nusinersen to maximize benefit	- results concerning primary outcomes described in "Safety" section - all 10 patients in high-dose cohort remained alive and ventilation-free; all 3 patients in low-dose cohort remained free and 2 were free of permanent ventilation
Al.-Zaidy et al. 2018	Follow-up analysis of open-label, single-arm phase 1 clinical trial (START)	- 12 patients from high-dose cohort 2 in START trial	- genetically confirmed diagnosis of SMA1 with homozygous deletions of SMN1 and 2 copies of SMN2 (as in START trial)	- as in START trial	- single high dose of AVXS-101 iv (details in START trial section)	- as in START trial	- primary and secondary endpoints as in START trial - additional reports on pulmonary support, nutritional support, swallow function, hospitalization rate and motor function during the 24-month follow-up period	- as in START trial	New findings (not reported in the original paper by Mendell et al.): - on average 1.4 hospitalizations due to respiratory reasons per year; mean proportion of study time spent in hospitalization =4.4%, and mean annualized rate of hospitalizations =2.1
Lowes et al. 2019	Follow-up analysis of open-label, single-arm phase 1 clinical trial (START)	- 12 patients from START trial grouped according to age at dosing (<3 months or ≥3 months) and baseline CHOP-INTEND scores (<20p or ≥20p) into 3 subsets: Early Dosing/ Low Motor (n=3, age 1.8 ±0.76 months, F 1), Late Dosing (n=6, age 5.1 ±1.56, F 2), Early Dosing/ High Motor (n=3, age 1.8 ±0.85, F 1)	- genetically confirmed diagnosis of SMA1 with homozygous deletions of SMN1 and 2 copies of SMN2 (as in START trial)	- c.859G>C SMN2 modifier mutation (as in START trial)	- single high dose of AVXS-101 iv (details in START trial section)	- as in START trial	- primary and secondary endpoints as in START trial - additional analysis of CHOP INTEND improvements and motor milestones in the subgroups at baseline, one-, two- and 24-months post dosing	- as in START trial	- rapid increases in CHOP INTEND scores in all subgroups, with the most marked changes in Early Dosing/Low Motor group (mean score change 35.0 ±6.24) - final CHOP INTEND scores in Early Dosing/Low Motor (50.7 ±5.77) similar to those of Early Dosing/High Motor (60.3 ±6.35)

* death or ≥16 h daily non-invasive ventilation support for ≥14 days in the absence of acute reversible illness or perioperative ventilation
** Ability to thrive is a composite endpoint defined by swallowing function (for thin liquids), feeding exclusively by mouth and appropriate weight maintenance (>3rd percentile)
*** One additional patient achieved an independent sitting milestone at the age of 16 months, but was uncooperative at the 18-month visit and thus was not judged to have achieved this endpoint during the evaluation.

Associations position. On 24 May 2019, Onasemnogene was approved by the FDA for the treatment of children less than two years of age with SMA with bi allelic mutations in the survival motor neuron 1 (SMN1) gene [24]. Other approved treatments were intrathecally administered nusinersen (Spinraza™) which, on 23 December 2016, was the first drug approved for SMA treatment in both paediatric and adult patients [25], and risdiplam (Evrysdi), which was approved on 7 July 2020 for patients aged two months or older [26]. To date, the EMA has approved only the first two drugs described above with the same indications as the FDA for Spinraza in later dates, i.e., the 30 May 2017 for Spinarza [27] and the 18 May 2020 for Zolgensma, but with different indications: the clinical diagnosis of SMA type 1 and patients with up to three copies of SMN2 [28].

Guidelines. The last Standards of Care prepared by the International Standard of Care Committee for SMA were published in 2017; therefore, only nusinersen was mentioned as the first potential treatment [5]. At that time, the focus of SMA treatment was on supportive care, age-related symptoms and associated clinical problems. To date, current information about the current state of knowledge about SMA treatment can be found either on official government websites, such as the USAs National Institute of Neurological Disorders and Stroke subdivision of National Institutes of Health or the UKs National Institute for Health and Care Excellence or community-founded SMA foundations. The same as drug-control agencies, institutions located in Europe, in contrast to those founded in the USA, do not recommend risdiplam in SMA treatment.

Other gene theraphies for neurological disorders. Gene delivery systems are being actively explored for therapeutic interventions in neurological diseases. Among them, the most promising in the current development of therapy are viral vectors, nanoparticles or CRISPR/Cas9 (clustered regulatory interspaced short palindromic repeats). These technologies offer novel approaches for genome modulation under various conditions [29, 30].

In the context of Duchenne muscular dystrophy (DMD), an X-linked recessive disorder, the most extensively studied therapeutic agent is ataluren. Although ataluren does not directly modify the genome, it inhibits the recognition of premature termination codons during translation, thereby facilitating the partial restoration of full-length dystrophin. Additionally, exon-skipping techniques utilizing antisense oligoribonucleotides (20–30 bp) have been developed to induce the translation of in-frame, Becker muscular dystrophy-like functional dystrophin. Owing to the large size of the DMD transcript (14 kb), smaller versions of dystrophin have been engineered to be compatible with adeno-associated virus (AAV) vectors, which have a limited capacity of 5 kb. AAV-mediated delivery has shown promise in restoring dystrophin expression and has a favourable safety profile. Furthermore, CRISPR/Cas9 genome-editing technology has shown substantial pre-clinical potential by reframing the mutated DMD gene, enabling dystrophin restoration in both *in vitro* and murine models [31].

In Parkinson's disease models, the use of adenoviral (Ad), AAV, and lentiviral (LV) vectors results in increased expression of glial cell line-derived neurotrophic factor (GDNF) in the striatum and substantia nigra. This approach inhibited toxin-induced degeneration of dopamine neurons and preserved functional striatal dopamine innervation. Current clinical trials are investigating AAV vectors to increase the synthesis of the human aromatic-L-amino acid decarboxylase (AAD) and LV vectors for the simultaneous delivery of tyrosine hydroxylase, AAD and GTP-cyclohydroxylase-1 [32].

In Alzheimer's disease, preclinical studies have reported promising outcomes using a chimeric AAV2/5 vector for the expression of nerve growth factor and secreted amyloid precursor protein. LV-GDNF administration has been shown to preserve cognitive functions, including learning and memory; however, it has not been effective in reducing amyloid and tau pathologies [33].

For Huntington's disease, AAV-based gene silencing using microRNAs targeting huntingtin (AAV5-miHTT) has been studied in murine models, where it nearly prevented mutant HTT aggregate formation and suppressed neuronal dysfunction. This approach is currently under a phase 1 and 2 clinical trial to assess its safety, tolerability, and proof-of-concept following a single bilateral injection [32].

In Charcot–Marie–Tooth (CMT) neuropathy, preclinical studies have demonstrated the efficacy of using neurotrophin-3 (NT-3) cDNA packaged in an AAV1 vector under the control of a muscle-specific promoter (triple tandem of muscle creatine kinase). Unfortunately, technical issues led to the suspension of a phase I/II trial (NCT03520751). CRISPR/Cas9 technology represents another potential therapeutic option for CMT, with ongoing studies in mice targeting the TATA-box of the P1 promoter of Pmp22, a gene involved in transcription initiation. Additionally, Pmp22 can be targeted via antisense oligonucleotide (ASO)-based silencing technologies [33].

Ongoing preclinical and clinical studies are also focused on other neurological diseases, including Frontotemporal Dementia, Rett Syndrome, and Amyotrophic Lateral Sclerosis. These therapies primarily utilize viral vectors, but research also includes polymer-based, lipid-based, and nanoparticle-based vectors [30].

SUMMARY

Onasemnogene Abeparvovec (Zolgensma®) is an FDA-approved treatment for children diagnosed with SMA, which exhibits substantial efficacy in the treatment of SMA compared with the natural progression of the disease. The drug significantly improves critical clinical outcomes, including survival rates, respiratory function, motor development, and nutritional status. While serious adverse events have been reported during onasemnogene therapy, only a subset of these events are directly attributed to the treatment. No double-blind, placebo-controlled, or active comparator trials have been conducted, which might be deemed unethical given the drug's high efficacy, as most patients with SMA1 do not survive beyond two years of age under natural disease progression. Other FDA-approved treatments for SMA include nusinersen (Spinraza™), which is administered intrathecally as the first drug approved for both pediatric and adult patients, and risdiplam (Evrysdi), which is an oral medication for patients aged two months and older. In contrast to US drug-control agencies, EMA do not endorse risdiplam for SMA treatment and differ in indications for Zolgensma usage. The most recent Standards of Care for

Spinal Muscular Atrophy only reference nusinersen as the initial treatment option.

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