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CURRENT OPINION

Treatment Options in Spinal Muscular Atrophy: A Pragmatic Approach for Clinicians

Sithara Ramdas[1,2] · Maryam Oskoui[3,4] · Laurent Servais[1,5,6]

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Abstract

Spinal muscular atrophy (SMA) is a rare neurodegenerative neuromuscular disorder with a wide phenotypic spectrum of severity. SMA was previously life limiting for patients with the most severe phenotype and resulted in progressive disability for those with less severe phenotypes. This has changed dramatically in the past few years with the approvals of three disease-modifying treatments. We review the evidence supporting the use of currently approved SMA treatments (nusinersen, onasemnogene abeparvovec, and risdiplam), focusing on mechanisms of action, side effect profiles, published clinical trial data, health economics, and pending questions. Whilst there is robust data from clinical trials of efficacy and side effect profile for individual drugs in select SMA populations, there are no comparative head-to-head clinical trials. This presents a challenge for clinicians who need to make recommendations on the best treatment option for an individual patient and we hope to provide a pragmatic approach for clinicians across each SMA profile based on current evidence.

1 Introduction

Spinal muscular atrophy (SMA) is a rare, neurodegenerative disease characterized by progressive muscle weakness and atrophy due to alpha motor neuron loss. It is one of the most common inherited neuromuscular disorders with a carrier frequency of 1:50 [1, 2] and an incidence of 1:14,300 [3] based on recent data from several newborn screening (NBS) programs.

Key Points

There are currently three disease-modifying treatments approved for spinal muscular atrophy and several others are in clinical development.

Data available from clinical trials and from real-world evidence for the approved treatments demonstrate the benefits of these treatments in different populations, with the maximal benefits seen in patients treated before the onset of symptoms.

Several factors such as age at treatment initiation, disease severity, number of SMN2 copy, co-morbidity, and patient/family preference should be considered in treatment decisions.

SMA is an autosomal recessive disorder that results from deletion and/or mutation in the *SMN1* gene located on chromosome 5q13 [4]. The full-length mRNA normally produced from the *SMN1* gene encodes the essential SMN protein, which functions in RNA biogenesis. *SMN2* encodes an almost identical mRNA. There are five nucleotide differences between *SMN1* and *SMN2* mRNAs, of which a critical C-to-T nucleotide substitution at position 6 within exon 7 impacts alternative splicing of the pre-mRNA [5]. Although

✉ Laurent Servais
Laurent.servais@paediatrics.ox.ac.uk

1 Department of Paediatrics, MDUK Oxford Neuromuscular Centre and NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK

2 Department of Paediatric Neurology, John Radcliffe Hospital, Oxford, UK

3 Departments of Pediatrics and Neurology and Neurosurgery, McGill University, Montreal, Canada

4 Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, Canada

5 Division of Child Neurology, Department of Pediatrics, Centre de Référence des Maladies Neuromusculaires, University Hospital Liège and University of Liège, Liège, Belgium

6 Academic Paediatric Department, Level 2 Children Hospital–John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, UK

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low levels of functional SMN protein are produced from the *SMN2* mRNA, levels are not sufficient to fully compensate for the lack of protein production when the *SMN1* gene is mutated. However, production of SMN from the *SMN2* mRNA can modify disease severity with an inverse correlation between phenotype severity and *SMN2* copy numbers [6]. In addition to the numbers of copies of *SMN2*, several other positive and negative disease modifiers have been identified [7]. For instance, the variant c.859G > C in *SMN2* exon 7 creates a splice enhancer that facilitates exon 7 inclusion, leading to a mild SMA phenotype even in the presence of a single copy of *SMN2* [8]. These modifiers are not currently evaluated in clinical practice, although subjects are screened for *SMN2* copy number.

SMA encompasses a continuum spectrum of disease, classified into five subtypes, SMA0, SMA1, SMA2, SMA3, and SMA4, defined historically by the age at symptom onset and best motor milestone achieved (Table 1) [9]. Typically, subjects with SMA present with progressive muscle weakness, initially affecting proximal muscles and lower limbs, with areflexia and varying degree of bulbar and respiratory involvement, particularly in SMA types 0, 1, and 2. Cognition is usually preserved, although emerging data suggests that there is a spectrum of neurocognitive abilities in subjects with SMA1; these differences have only recently been recognized as patients with SMA1 who have been treated with disease-modifying therapies are now surviving well beyond the natural history (Table 1) [10–13].

2 Management of Spinal Muscular Atrophy (SMA)

In the current era of disease-modifying treatments for SMA, standards of care should be delivered by a multi-disciplinary team of professionals with expertise in management of neuromuscular disorders. Internationally agreed standards of care in SMA were published before the widespread approval of disease-modifying therapies [14–16]. Ongoing follow up according to standard of care remains an inclusion criterion across all clinical trials for SMA treatments. Adherence to these standards ensures that patients achieve the optimal benefits from novel treatments. Three disease-modifying therapies have been approved by the United States Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) (Table 2). The approved therapies increase levels of SMN protein either by gene replacement or by modification of *SMN2* splicing.

2.1 Costs of SMA Treatment

The cost of drug treatment of an SMA patient can be divided into the direct cost of the drug and the indirect costs involved in drug delivery and ongoing monitoring (Table 2). The indirect costs include the medical, pharmacy, nursing, hospital day case bed stay for nusinersen and onasemnogene abeparvovec administration, clinic reviews, and laboratory tests for pre- and post-treatment monitoring. This may also involve input from anesthesia and radiology services. The indirect

Table 1 SMA classification[a]

SMA type	Incidence	Age at symptom onset	Number of *SMN2* copies	Highest motor ability[b]	Life expectancy[c]
Type 0	< 1%	Antenatal	1	None achieved	Few days to weeks
Type 1	50%	< 6 months	1–7% 2–73% 3–20%	Non-sitters	Less than 2 years
Type 2	30%	7–18 months	2–16% 3–78% 4–5%	Independent sitting	Close to normal
Type 3a	10%	19 months–3 years	2–12% 3–50% 4–38%	Independent walking	Close to normal
Type 3b	9%	> 3 years	2–4% 3–31% 4–61% 5–4%		Normal
Type 4	< 1%	> 18 years	4–75% 5 or 6–25%	Independent walking	Normal

[a]Data from [14]

[b]From natural history studies

[c]Survival without invasive supportive care and without disease-modifying treatment

Table 2 Clinically approved spinal muscular atrophy treatments

	Patient population for which approval was granted	Direct cost (Euros)	Indirect costs (Euros)*
Nusinersen (intrathecal)	FDA—All 5qSMA patients EMA—All 5qSMA patients	1st year: €529,788 Subsequent years: €266,787/year	1st year: €9350 Subsequent years: €6600/year
Risdiplam (oral)	FDA—All 5qSMA patients EMA—5qSMA with a clinical diagnosis of SMA1, SMA2, or SMA3 or 5qSMA with 1–4 *SMN2* copies	For patients > 20 kg and aged ≥ 2 years: €322,766/year For patients < 20 kg and aged < 2 years: dose is dependent on weight	€150/year
Onasemnogene abeparvovec (intravenous)	FDA—5qSMA patients under 2 years of age EMA—5qSMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA1 or patients with 5qSMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene and weighing up to 21 kg	€2,061,700 (one-time cost)	€2700 for 1st year post-treatment

*Data from Dangouloff et al. [48]; the indirect costs include hospital bed and medical consultation costs directly related to drug administration without considering any treatment-related complications. Indirect costs do not include pharmacy and other hospital service costs, the medical and allied health professional cost to deliver standards of care, or non-medical costs

EMA European Medicines Agency, *FDA* US Food and Drug Administration, *5qSMA* spinal muscular atrophy

costs also need to factor loss of income due to time off work for parents/carers or an SMA adult for treatment-related visits. Any treatment-related complications that may arise will result in additional costs and may require inpatient stay and additional medical management-related costs.

2.2 Nusinersen (Spinraza®)

Nusinersen was the first SMA treatment to be approved by the US FDA (December 2016) and the EMA (May 2017). Nusinersen is an antisense oligonucleotide that increases the production of the SMN protein from the *SMN2* mRNA. It binds to a repressive splicing sequence in intron 7 of the *SMN2* pre-mRNA, leading to the inclusion of exon 7 in the mature mRNA and production of full-length SMN protein [17]. Due to its large size and poor blood–brain barrier permeability, nusinersen is administered via repeated intrathecal injections. This limits its availability beyond the intrathecal space. Steady therapeutic state levels of nusinersen in the cerebral spinal fluid (CSF) are reached between 28 and 64 days after the first dose [18, 19]. Patients are given four loading doses (days 0, 14, 28, and 63) and thereafter are treated every 4 months for life. The most common adverse effects are related to lumbar puncture (LP) and include vomiting, headache, and back pain [20].

Hydrocephalus has been reported and should be monitored for by measuring opening pressure during LP [21], but it must be noted that hydrocephalus is more common in SMA patients than the overall population so the association with nusinersen is uncertain [22]. One adult patient is reported to have developed symptomatic intracranial hypertension [23]. Slight elevation in protein levels in the CSF have been observed in some patients, but this abnormality spontaneously resolves and is not associated with clinical manifestations [24]. One adult patient suffered spinal adhesive arachnoiditis [25]. Other antisense oligonucleotides have been reported to cause renal toxicity, thrombocytopenia, and coagulation abnormalities, so analysis of full blood count, coagulation parameters, and quantitative spot urine protein testing are recommended before each intrathecal injection [26]. There are currently insufficient data regarding teratogenicity or safety during pregnancy and whilst breast feeding, so the current EMA label states that it is preferable to avoid nusinersen during pregnancy [27].

2.3 Risdiplam (Evrysdi®)

Risdiplam is a small molecule that acts as a modifier of splicing of the *SMN2* pre-mRNA. It promotes the inclusion of exon 7 in the mature mRNA and production of full-length SMN protein. Risdiplam was first approved by the FDA in August 2020 and by the EMA in March 2021. It is administered once daily by oral administration [28]. Risdiplam reaches a plasma steady state 7–14 days after the initial dose and is evenly distributed throughout the body including the central nervous system [29, 30]. The dose is age and weight dependent: in infants < 2 months, 0.15 mg/kg once a day, in subjects 2 months to 2 years, 0.2 mg/kg

once a day, in those > 2 years and up to 19 kg, 0.25 mg/kg once a day, and in those > 2 years and over 20 kg, 5 mg once a day. Commonly reported side effects are rash, diarrhea, aphthous ulcers, and nausea [31]. Effects of risdiplam on fertility of male cynomolgus monkeys and rats that result from FOXM1- and MADD-mediated changes within the germ cells in the testes have been reported [32]. Nevertheless, there was no evidence of damage to spermatogonia in non-human primates, and the observed changes in the testes were fully reversible in rats and non-human primates. The most recent EMA recommendation is to stop the drug 4 months before conception in males. Women treated with risdiplam should stop treatment 1 month before conception until the end of breastfeeding [29].

2.4 Onasemnogene Abeparvovec-Xioi (Zolgensma®)

Onasemnogene abeparvovec is a recombinant, self-complementary, non-replicating adeno-associated vector 9 (AAV9)-based gene therapy approved by the US FDA in May 2019 and by the EMA in May 2020. The vector delivers a fully functional copy of the *SMN* gene under control of a chicken-β-actin hybrid promoter with a cytomegalovirus enhancer [33]. It is administered as a one-time intravenous infusion and has systemic availability. The dose is 1.1×10^{14} vector genomes/kg. Patients need to have anti-AAV9 viral titers of < 1:50 prior to the infusion. Common side effects are pyrexia, nausea, vomiting, and liver toxicity [34–37]. In pooled analyses of clinical trials (including START, STR1VE-US, STR1VE-EU, and SPR1NT), a third of patients were reported to have hepatoxicity-related adverse events, with 90% of all patients developing post-infusion elevation in liver transaminases (aspartate aminotransferase, alanine aminotransferase, and bilirubin; all were < 2 × upper limit of normal [ULN]) [38]. To mitigate this hepatotoxicity, patients are given high-dose corticosteroids beginning 24 hours prior to infusion, and corticosteroid treatment is continued for several months with the total treatment duration depending on liver function. Moderate to severe hepatotoxicity requiring steroid dose escalation is more often observed in older and heavier patients than in younger subjects [39, 40]. Thrombocytopenia is common and can be transient and asymptomatic but can also be the first biological sign of more rare but serious occurrence of thrombotic microangiopathy. Thrombotic microangiopathy is a life-threatening event characterized by thrombocytopenia and microangiopathic hemolytic anemia that can progress to acute kidney failure [41]. Fatal outcomes have been reported in subjects treated with onasemnogene abeparvovec due to acute liver failure and to thrombotic microangiopathy [42]. One case of hydrocephalus was reported in the STR1VE-US study [43].

3 Literature Search

To provide a practical approach to treatment of SMA patients, we conducted a non-systematic review of PubMed from 2015 until January 1, 2024, using keywords spinal muscular atrophy AND (nusinersen/Spinraza OR onasemnogene abeparvovec/Zolgensma OR risdiplam/Evrysdi) to identify publications that describe clinical studies of the three clinically approved disease-modifying therapies for SMA. We compared our findings with recent systematic reviews and updated the research with additional recent papers. Data from the key pivotal trials leading to drug approval are summarized in Table S1 in the electronic supplementary material (ESM).

For analysis, we divided the SMA population into four clinical sub-groups: (1) patients treated pre-symptomatically or upon identification through NBS, (2) patients with SMA1, (3) non-ambulant patients with SMA2 or 3 and (4) ambulant patients with SMA3.

We decided to divide the later-onset forms according to function (non-ambulant and ambulant groups) as the two randomized controlled studies conducted in this population included non-ambulant SMA2 and 3 patients as well as ambulant patients [20, 44–47], and as the functional status rather than the SMA type is preferred in the latest version of standard of care [14, 15].

4 Patients Identified Pre-symptomatically or by Newborn Screening

Pre-symptomatic patients and patients identified by NBS are partially overlapping populations. About 40% of patients with two copies of *SMN2* who were identified by NBS have symptoms upon treatment initiation [3, 44, 48]. As trials conducted in pre-symptomatic patients included only patients with no symptoms, findings from these trials are not fully applicable in all patients identified by NBS as some may have symptoms at the time of treatment initiation and will thus have a less favorable prognosis.

Studies of truly pre-symptomatic patients demonstrated that patients with three copies of *SMN2* who are treated with nusinersen [49], onasemnogene abeparvovec [50–52] or risdiplam [52] before the age of 42 days have normal motor development. It must be noted that the follow-up times in these studies were short and heterogenous: 5 years, 2 years, and 1 year for nusinersen, gene therapy, and risdiplam, respectively. The outcomes in patients with two copies of *SMN2* treated before the age of 42 days and deemed non-symptomatic were more heterogenous. In the nusinersen 5-year-study NURTURE (ClinicalTrials.gov identifier: NCT02386553), 13 of the 15 patients (87%) walked

independently by the age of 5 years, and 7 of the 15 (47%) did so before the age of 18 months [49, 53]. Five patients (33%) needed a gastrostomy, and four patients needed respiratory intervention defined as invasive or noninvasive ventilation for ≥ 6 h/day continuously for ≥ 7 days or tracheostomy. It must be noted that none of the eight patients with a peroneal compound muscle action potential (CMAP) value > 2 mV and with elicitable deep tendon reflexes at baseline needed a gastrostomy tube or a respiratory intervention. In the onasemnogene abeparvovec trial SPR1NT (NCT03505099), all 14 patients with two copies of *SMN2* acquired sitting position by the age of 1 year [50]. Nine of the 14 patients were independent walkers at the age of 18 months, and no patient needed ventilation or nutritional support. In the RAINBOWFISH trial of risdiplam (NCT03779334), in eight patients with two copies of *SMN2*, five patients had a CMAP > 1.5 mV at 1 year [52]. All but one acquired a stable sitting position before the age of 1 year, and four were able to stand at the age of 1 year. No patient needed ventilation or nutritional support at the 1-year follow up. These data indicate that, regardless of treatment choice, patients with three copies of *SMN2* who have no symptoms of SMA and are treated before 42 days of life have normal or nearly normal motor development and do not need respiratory support at follow-up times ranging from 1 to 5 years [49, 51, 52].

Between 30 and 50% of patients with two copies of *SMN2* who were treated with nusinersen had motor impairment and bulbar or respiratory dysfunction [49]. This was not the case for this population treated with onasemnogene abeparvovec [48–50] or risdiplam [50]. It must be noted that the follow-up of patients treated with nusinersen is longer and that in the trials of onasemnogene abeparvovec and risdiplam, there were exclusion criteria based on CMAP; this was not the case for the nusinersen trial, which had broader inclusion criteria. Nevertheless, the schedule of four loading doses of nusinersen 12 mg over 2 months may not allow a sufficiently rapid attainment of therapeutic drug level—especially in rostral motor neurons. This provides the strong rationale for a more rapid dose escalation, as is currently performed in the DEVOTE protocol (NCT04089566) [54, 55].

Real-life data from across the world have confirmed the excellent prognosis of patients with three or four copies of *SMN2* who are treated early, and the overall good prognosis of patients with two copies who do not present with SMA symptoms at treatment initiation and who have higher CMAP values [3, 56–64].

NBS programs have revealed that a large proportion (40–50%) of patients with two copies of *SMN2* have symptoms at the time of treatment initiation [3, 44, 64, 65]. Even if treated immediately, these patients are very likely to have impaired motor development or proximal weakness; none of these patients have been reported to be ambulant at the age of 18 months, but ambulation was acquired at a later date in several patients [3]. Nevertheless, it must be acknowledged that these patients would have represented the most severe SMA1 patients as they display symptoms during the first weeks of life. As several of these patients have been reported to acquire ambulation after treatment, patients identified by NBS have much better prognosis than patients identified by symptoms, as independent ambulation has very rarely been attained by treated SMA1 patients. Finally, there is currently lack of clarity on whether patients identified by NBS and then treated have normal cognitive development. One study reported cognitive delay in patients with two copies of *SMN2* [66] and another found better language development in patients with two copies of *SMN2* who were identified by NBS in comparison with patients treated after diagnosis due to symptom onset [67]. Hence, it is important that patients identified by NBS are also monitored for cognitive abilities as new phenotypes may emerge as more patients are treated.

At the severe end of the spectrum, there is very little data on SMA0 patients who present with severe contracture or respiratory insufficiency at birth [68, 69]. Prognosis in these patients—even when identified by NBS—appears to be poor, but more data are needed to determine whether these infants will benefit from disease-modifying therapy [68, 69]. The severity of motor, respiratory, and bulbar symptoms experienced by these patients will inform decisions on treatment of patients with SMA0 identified in the future. Cognitive development will need closer monitoring given the incidence of brain malformation in SMA0 [70] and the emerging central nervous system phenotype in patients with SMA1 who have been treated with a disease-modifying therapy [11, 13, 71].

5 Patients with SMA1

SMA1 patients are the largest cohort of newly diagnosed SMA, but, due to the severity of the disease, were not a prevalent population globally until the advent of disease-modifying therapies. Several clinical trials have assessed the safety and efficacy of the three approved treatments in this patient population. The first trial (NCT01839656) was a phase II, open-label, dose escalation study in SMA1 patients under 6 months of age with two or three copies of the *SMN2* gene [72]. The first cohort (4 patients) received 6 mg of nusinersen and the second cohort (16 patients) received 12 mg of nusinersen in multiple intrathecal loading doses over the course of several months followed by maintenance doses of 12 mg. The baseline mean score on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scale was 30, and 45% had feeding difficulties. At the last follow up (maximum 3.7 years), 15 of the 20 participants (75%) were alive. In the 13 patients who were evaluated, the mean CHOP-INTEND score increase

was 17.3 points from baseline, and 7 of the 13 (55%) did not require permanent ventilation. No data on bulbar function were reported for this cohort.

Only one randomized controlled trial that included only SMA1 patients has been conducted [73]. This study, ENDEAR (NCT02193074), compared nusinersen 12 mg and a sham procedure. It enrolled patients with two copies of *SMN2* who were younger than 7 months. The mean age at first dose was 163 days, and the mean baseline CHOP-INTEND score was 26.6. The treatment group of 80 patients were compared with 41 SMA1 patients who received a sham procedure [18, 19, 73]. At the interim analysis, there was a difference between the analyzed subjects in the treated cohort and the control group. Motor milestones were met by 21 of the 51 patients (41%) in the treatment group and none of the 27 patients (0%) in the control group ($p < 0.001$). This led to early termination of the study. In the final study analysis, 37 of 73 patients (51%) in the treatment group met motor milestones, and infants with disease duration < 12 weeks at treatment initiation had better response than those whose treatment was delayed. The likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use of permanent assisted ventilation, 0.53; $p = 0.005$). At study end, 31 of 80 patients (39%) in the nusinersen group and 28 of 41 patients (68%) in the control group had died or had received permanent assisted ventilation [73, 74].

The three clinical trials of SMA1 patients treated with onasemnogene abeparvovec included 70 patients and all three reported improvements in motor assessments [43, 75–77]. The first dose-finding study, START (NCT02122952), included 15 patients with SMA1 and two copies of *SMN2*. There were three patients in the low-dose cohort (mean age 6.3 months) and 12 in the high-dose cohort (mean age 3.4 months including with two prenatal diagnoses). At the end of the dose-finding study, in the high-dose group (the dose used in the subsequent treatments), mean CHOP-INTEND score increased by 24.6 points from a mean baseline score of 28 [75]. At the 5-year follow up, 53% of patients were on nusinersen dual therapy and achieved motor milestones were maintained. All 10 patients under follow up who were initially in the high-dose cohort and two of three patients (66%) originally in the low-dose cohort were alive and without permanent ventilation and no patient had to initiate new respiratory support or increase the baseline respiratory support [76]. Two patients in the high-dose cohort achieved standing with assistance (neither was on nusinersen), indicating that motor function gains were stable long-term with potential for ongoing gains. In the 12 patients treated with a high dose in the START study, at baseline, seven (58%) patients were able to feed orally and at 24-month follow up, six of those seven (86%) patients continued to be exclusively orally feeding. Eleven of the 12 (92%) were able to speak [78].

The START phase I–II study was followed by two phase III studies: STR1VE-US (NCT03306277; 22 patients) and STR1VE-EU (NCT03461289; 33 patients). Both included SMA1 patients with one or two copies of *SMN2*. All were treated before 6 months of age [43, 77]. Due to a wider inclusion criterion in STR1VE-EU (patients were allowed to have a nutritional support at baseline in STR1VE EU), patients were slightly stronger at baseline in STR1VE-US as exemplified by the difference of CHOP-INTEND scores at baseline (33.5 for STR1VE-US vs 28 for STR1VE-EU). In the STR1VE-US cohort, the CHOP-INTEND score at 6 months post-treatment increased by a mean of 14.6 points. At 14 months of age, 20 of 22 patients (91%) were alive without permanent ventilation. At 18 months of age, 18 of 22 patients (82%) were not on any respiratory support, and 17 of 19 patients (89%) were reported to be managing 75–100% of their daily nutritional requirements orally. In the STR1VE-EU cohort, CHOP-INTEND score at 6 months post-treatment increased by a mean of 13.5 points. At 18 months of age, 32 of 33 (97%) were alive, two of nine patients (22%) who had required non-invasive ventilatory support at baseline had been weaned off this support, and four of nine patients (44%) who required feeding support at baseline no longer required this support.

Risdiplam was assessed in the FIREFISH open-label study (NCT02913482) in SMA1 infants with two copies of *SMN2* up to 7 months of age, with a part 1 dose finding [30] and part 2 efficacy and safety [79]. Fifty-eight infants (17 in part 1 and 41 in part 2) were recruited, and the baseline median CHOP-INTEND score was 28 in part 1 and 22 in part 2. At baseline, 29 of 41 patients (71%) were not on any respiratory support and 33 of 41 (80%) were fully orally fed. At 24 months post-treatment initiation, CHOP-INTEND score > 40 was achieved by 31 of 41 (76%), 38 of 41 (93%) were alive, 37 of 41 (90%) did not require permanent respiratory support and 29 of 41 (71%) were fed fully orally.

There is an extensive literature on real-world data for nusinersen treatment. These patients are a very heterogeneous group with varying duration of disease and SMA-related co-morbidities. Outside clinical trials, the highest improvements in motor milestones in SMA1 patients were noted in young patients (< 2 years of age), those with shorter disease duration and higher baseline motor assessment scores, and those without need for invasive ventilation at baseline [80–83]. How *SMN2* copy number influences outcome when considering same age and same functional level is not well established, with conflicting reports indicating no influence and others suggesting a better outcome in patients with three copies of *SMN2*. Improvements in motor assessments in adolescents and adults with SMA1 after nusinersen treatment have been reported. In a study described by Łusakowska

et al. of 12 SMA1C patients with median age at treatment initiation of 28 years (range 12–45 years), seven of the eight patients assessed had a clinically meaningful increase in CHOP-INTEND score at month 26 [84]. Improvements in respiratory function were minimal [80, 81, 85], and progression to non-invasive or invasive ventilation during nusinersen treatment was not uncommon [83, 85–89]. Of note, no patient who was on tracheostomy ventilation was weaned off, and improvements in feeding support from pre-treatment baseline were not noted [81, 86, 90, 91].

There is an emerging body of real-life data for gene therapy in SMA1 patients. In a cohort of 177 SMA1 patients treated with onasemnogene abeparvovec, despite the limitations of a heterogenous follow up and many who had previous treatment with nusinersen, all reported improvements in motor assessments scores, with CHOP-INTEND score increases of 7–28 points over a follow-up period of 3–22 months [39, 40, 92–94]. Weiss et al. reported that improvement was most marked in infants aged < 8 months at the time of onasemnogene abeparvovec treatment with a mean CHOP-INTEND score increase of 13.8; but this cohort included six pre-symptomatic infants, which is likely to have influenced the responder rate [39]. Gowda et al. reported that in a cohort of 99 patients, patients who were aged < 6 months at the time of onasemnogene abeparvovec infusion had a 17.7-point gain (95% confidence interval [CI] 13.4–22.0) in CHOP-INTEND score, patients who were 6–12 months old had a 11.9-point gain (95% CI 8.4–15.4), patients who were 12–24 months old had a 4.4-point gain (95% CI − 2.8 to 11.6) and patients 24 months or older had a 3.8-point gain in score (95% CI − 3.6 to 11.2) [40]. Progressive respiratory decline is still noted after onasemnogene abeparvovec treatment, but some patients have been reported to achieve marginal improvements such as reduction in non-invasive ventilation duration. Patients also differ in terms of bulbar function after onasemnogene abeparvovec treatment. Worsening has been reported [94], as have maintenance at baseline level and/or improvements [39, 93, 95].

Two observational cohorts reported a total of 109 SMA1 patients treated with risdiplam. A large proportion of these patients were not treatment naïve. The safety and tolerability profile of risdiplam was similar to that observed in the clinical trials, but no efficacy data has been reported so far [96, 97].

Despite the impressive progress of SMA1 patients after treatment with disease-modifying therapies that has been reported not only in clinical trials but also in real-world observation, an emerging concern is the observation of neurodevelopmental and cognitive issues in the treated SMA1 population [11, 13, 71]. These findings have implications for clinicians, patients, and families. In the pre-disease modifying treatment era, most SMA1 patients did not survive long enough for cognitive function to be assessed, and those who did had significant physical disabilities, bulbar dysfunction, and respiratory support that limited routine assessment of cognition. Long-term survival in SMA1 patients beyond the natural history has also highlighted other potential issues including early onset scoliosis, which has been reported in many SMA1 patients who have been treated with disease-modifying therapies [84, 91].

6 Non Ambulant SMA2 and 3 and Ambulant SMA3 Patients

Children, adolescents, and adults with diagnosis of SMA2 or SMA3 after symptom onset currently represent the largest number of prevalent cases of individuals with SMA. These patients may be ambulant or non-ambulant. Two randomized controlled trials have been conducted in this population, both in children over 2 years of age [20, 46]. The first is CHERISH (NCT02292537), a randomized, double-blind, sham procedure-controlled study of nusinersen that included 126 children, 2–9 years of age with non-ambulant SMA without significant scoliosis, dysphagia, or respiratory compromise [20]. Most (74%) children had three copies of *SMN2*. A quarter (27%) were or have been able to walk with support, and none had acquired ambulation and lost it. Nusinersen was given in four loading doses in the first 2 months, and maintenance doses were given every 6 months. The study was terminated early after a pre-specified interim analysis demonstrated clinically important benefit in the treated group at 15 months (least-squares mean difference in change from baseline in the expanded Hammersmith functional motor scale (HFMSE) of 5.9 points (95% CI 3.7–8.1). The efficacy of nusinersen was also demonstrated in the final primary outcome, with a least-squares mean difference from baseline in HFMSE of 4.9 points (95% CI 3.1–6.7). The improvement over 15 months was driven by participants under 5 years of age, specifically those treated soon after symptom onset. The hierarchical secondary endpoints were focused on motor outcomes. Data have not been reported regarding respiratory and bulbar functions. Back pain and headache attributed to the lumbar puncture were reported in about one-third of treated children, with otherwise comparable rates of adverse events in the sham procedure and treated groups. Longer term follow-up of this cohort did not demonstrate the same rate of improvement on HFMSE in the children from the sham procedure group once they transitioned to nusinersen, supporting the strong effect of earlier treatment on response [98].

The second double-blind, placebo-controlled study, SUNFISH part 2 (NCT02908685), included 180 children, adolescents, and adults with non-ambulant SMA2 or SMA3 aged 2–25 years of age who were treated with risdiplam [46]. Most (87%) had three copies of *SMN2* and about one-third

(67%) had severe scoliosis. The intervention arm received risdiplam daily at an oral dose of 5 mg (for individuals weighing ≥ 20 kg) or 0.25 mg/kg (for individuals weighing < 20 kg). The primary endpoint of the study was met, with the least-squares mean change from baseline in the 32-item Motor Function Measure (MFM32) total score at month 12 showing a difference of 1.55 between the two groups (95% CI 0.30–2.81). Risdiplam was generally well tolerated with higher rates of diarrhea and rash in the treated group. Of note, no retinal toxicity was detected in the treated cohort. In open-label, long-term follow-up of up to 4 years, most patients had stable function without new adverse effects [99]. The data from the trials of nusinersen and risdiplam cannot be compared given the differences in inclusion criteria.

No randomized treatment trial of onasemnogene abeparvovec has been conducted in this population. Published treatment trials of the approved intravenous formulation of onasemnogene abeparvovec are being conducted in infants, with a study underway looking at safety in 48 older children who weighed ≥ 8.5 kg to ≤ 21 kg at treatment (SMART, NCT04851873). In this trial, serious treatment-related emergent adverse events were reported in one-third of participants. No cases of thrombotic microangiopathy or dorsal root ganglia inflammation were reported, with hepatotoxicity (20 of 24, 83%) and transient thrombocytopenia (17 of 24, 71%) reported in the majority.

A phase 1 study, STRONG (NCT03381729), included 32 children 6 months to 5 years of age with three copies of *SMN2* who were able to sit but not walk independently. These children were treated with three different doses of intrathecal onasemnogene abeparvovec (low, 6.0×10^{13} vg; medium, 1.2×10^{14} vg; and high, 2.4×10^{14} vg) [100]. The study enrollment was placed on hold by the US FDA because of dorsal root ganglia toxicity in animal studies; however, the hold was eventually lifted. In the high-dose cohort of 12 patients, the least-mean squares change in HFMSE from baseline to 12 months was 6.0 (95% CI 3.7–8.3). Serious treatment-emergent adverse events were reported in 7 of 32 patients (22%). There are currently two open-label trials of intrathecal delivery of onasemnogene abeparvovec in older children underway, STRENGTH (NCT05386680) and STEER (NCT05089656) [100].

7 Discussion

Use in clinical trials and the real world shows that disease-modifying treatments provide benefit to SMA-affected infants, children, and adults. Very few double-blinded randomized controlled trials have been conducted in the SMA population [20, 46, 73]. The great majority of trials have been open label, have used historical comparators, and have relied on objective outcomes such as sitting without support. A few randomized placebo-controlled studies have been conducted in infants with SMA, and studies in older populations with less well-established natural history should be conducted. There is, however, little incentive for the sponsors to conduct a high-cost multinational trial when the drug has already obtained regulatory approval with a broad label. Furthermore, there would be significant recruitment challenges in any treatment trial with a placebo arm when treatments are already available clinically. Non-inferiority trials are an acceptable alternative, enabling allocation concealment and randomization. Blinding may not always be feasible as it would necessitate co-administration of steroids to patients not receiving gene therapy or sedation for a sham intrathecal injection procedure for patients not receiving nusinersen. Use of an objective outcome or outcome assessor being a non-treating investigator could be used to maintain a lower risk of bias in these unblinded studies.

As no direct comparison trial between the different treatments is planned and given the high heterogenicity of patients in terms of age and function at baseline, it is very unlikely that strong evidence of superior efficacy of one treatment over another will ever become available. From the currently available evidence in patients with SMA2 and SMA3, the difference in effectiveness, if any, is predicted to be very small. Indirect comparisons must be conducted very cautiously, given the broad heterogeneity of the populations. The only difference that is supported by the currently available data is that the occurrence of bulbar dysfunction in patients with SMA1 or presymptomatic patients with two or three copies of *SMN2* appears to be more frequent in patients treated with nusinersen than with risdiplam or onasemnogene abeparvovec. Although bulbar dysfunction was not common in patients enrolled in pivotal studies of risdiplam and onasemnogene abeparvovec and is not reported as a common feature in real-world data of patients treated with onasemnogene abeparvovec, it is a growing concern in patients treated with nusinersen [87]. This difference may be due to several factors. The first one is the difference in the populations treated. Gene therapy is restricted in several countries to patients younger than one or two years, and the population of patients treated by nusinersen is broader. The second is related to the mode of administration of nusinersen that generates a lumbar-cranial gradient of nusinersen. The third is the progressive dose escalation of nusinersen that could generate a lower drug exposure during critical first weeks of treatment, especially at the bulbar level. Nevertheless, while the pharmacokinetics of the three disease-modifying treatments are obviously different, there are very few data on the pharmacodynamics—SMN protein level is reported only for risdiplam. Results from the DEVOTE study (NCT04089566), which employs a rapid nusinersen dose escalation, could confirm the latter hypothesis.

SMN protein expression decreases with time in healthy individuals [101], and the degree of progress in SMA patients is limited by the numbers of surviving motoneurons at the time of the administration of the first disease-modifying treatment. High neurofilament levels are a well-established biomarker of neuronal destruction in SMA1 patients and in pre-symptomatic patients with two copies of *SMN2* [49]. Because of this, use of another different disease-modifying treatment after the administration of a first therapy may not generate a cumulative positive effect. Effects of combination treatments are being explored in the real world [102] and in more formalized clinical trials [103]. Several trials have explored or are exploring the safety of add-on risdiplam or nusinersen in patients previously treated with onasemnogene abeparvovec (JEWELFISH, NCT03032172; HINALEA 1, NCT05861986; and RESPOND, NCT04488133). In clinical practice, while the benefit of combination treatment remains debated, most clinicians agree with the use of a bridge therapy whereby patients identified through NBS who present a high level of maternal anti-AAV9 antibodies could be initially treated with nusinersen or risdiplam before delivery of onasemnogene abeparvovec once antibody titers subside. A treatment shift might be warranted to try to improve the trajectory of a patient. The question of combination efficacy cannot be addressed with current open-label trial designs where the continued effect of the gene therapy cannot be separated from the added benefit of the up-regulator of protein production from *SMN2* without parallel group randomization. Furthermore, in some jurisdictions, private insurers reimburse for add-on therapy inhibiting potential recruitment and influencing perception of effectiveness.

The 5-year follow-up data of 13 patients from the START cohort (NCT02122952) included 7 patients on concomitant nusinersen (3 in the low-dose cohort and 4 in the therapeutic-dose cohort) [76]. An analysis was not reported comparing those who were on monotherapy with onasemnogene abeparvovec and those on combination therapy, although the authors did report that the two patients who were able to stand without support were on monotherapy. The JEWELFISH study assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in pediatric and adult patients with SMA1, SMA2, or SMA3 previously treated with another disease-modifying therapy [103]. JEWELFISH included 15 SMA1 patients, 9 (60%) previously treated with nusinersen and 4(26%) previously treated with onasemnogene abeparvovec. The authors reported that treatment with risdiplam resulted in two-fold increase in SMN protein levels after 2 weeks of treatment and that this was sustained at 12 months of treatment; whether this increase will be reflected in any functional gains in this cohort remains to be seen as the efficacy data have not yet been reported.

The long-term toxicity of combination disease-modifying therapies will only be established over many years. Aligning observational data collection through international registries, mandating open access to trial data once published, and financially supporting this continued observational data collection in parallel to drug reimbursement are necessary to guide treatment decisions for future patients. Real-world data often fails to provide robust evidence to answer the question of potential benefits of shifting or adding therapies complexities of associated factors such as age and function at the different treatment initiation or shift points make the evaluation of efficacy extremely challenging [39, 104, 105]. As of January 2024, we were unable to find evidence in the literature that suggests a potential benefit of a switch or an addition of a disease-modifying treatment in previously treated patients. Further research is needed to evaluate the populations in which switching or adding medication may result in benefit.

SMA treatment initiated after symptom onset is not curative. Setting individualized treatment goals is needed to guide decisions on treatment continuation. Evaluation of treatment responses in clinical trials has been primarily based on improvement in motor function [106]. In the future, using clinical measures of response across different domains of value to the patient should be encouraged. Although SMN expression is highest during fetal and early development, low steady levels of expression are needed throughout life, supporting the rationale for continued disease-modifying therapies in adulthood. Nevertheless, the rate and adherence to treatment in adults is lower than in children. Setting realistic expectations and therapeutic objectives—including stability—may help to improve adult patients' adherence to treatment.

The three currently approved SMA drugs have different modes of delivery and side effect profiles, which do influence patient choices. Several studies have evaluated patient and family preferences and expectations. Most patients and families accept the burdens of treatment such as invasive intrathecal injections, but there is preference for oral and one-time intravenous treatments [107, 108]. The main goals of treatment for patients and families are improvement in motor function and breathing, although stability in disease was also mentioned as an important goal. There remains concern about risks of therapy, and some patients and families were open to trading gains in efficacy for a less invasive route of administration. Many patients and families advocate for combination therapies, although evidence of additional benefit remains to be demonstrated [107].

Onasemnogene abeparvovec has the advantage of being a one-time treatment and administration by the intravenous route is acceptable to patients and families. It's use is currently limited to patients younger than 2 years of age, however given its potential side effects, benefits versus risks

must be thoroughly discussed with families. Acute risk of thrombotic microangiopathy or acute liver toxicity constitute the main concerns in the short term. Given the risk of intercurrent illness-related severe immune activation after gene therapy, families need be committed to strict infection prevention strategies in the weeks preceding the treatments and for several months afterwards. This is hugely burdensome and the significant impact on the child, parents and siblings needs to be considered in the pre-treatment discussion. The medium-term and long-term risks of the gene therapy on liver toxicity, illustrated by several cases of chronic liver enzyme elevation, remain unclear, and there is uncertainty about its long-term efficacy. Nusinersen is administered as regular intrathecal injections. This is a painful procedure and most children must be sedated or given general anesthetic in order that the lumbar puncture used to deliver the drug can be safely performed. Given that the procedure must be performed every 4 months in the maintenance phase, many children develop procedure-related anxiety that can be a barrier to administration. In addition, scoliosis can create technical challenges in performing lumbar puncture, requiring X-ray- or CT-based guidance and the associated radiation risk. Risdiplam is given orally, but compliance can be an issue in both younger and older patients as it is a daily medication. No drugs have so far been demonstrated to be safe before conception or during pregnancy, and adult patients should be carefully advised on how to manage drug interruption before conception.

Finally, beyond safety, efficacy, and patient and family preferences, economic considerations play a major role in treatment accessibility. Medical and non-medical costs related to untreated SMA are high, with higher yearly costs of up to €70,392 per year for patients with severe forms of SMA [48, 109]. The cost of treatments are also very high (Table 2). The list price of nusinersen in Belgium is €88,298 per vial, which results in a cost of €529,788 in the first year and €266,787 per year thereafter. The yearly cost of risdiplam is comparable at €322,776, with lower indirect costs of administrating the drug. The one-time cost for injection of onasemnogene abeparvovec is €2,061,700, and there are high indirect costs associated with close monitoring for the first few months post-injection. Because of these very high costs, the price of disease-modifying therapy per quality-adjusted life-year is far above the usual thresholds of reimbursement approval in all countries. The value of therapy is better in patients identified by NBS than by symptoms. Given the dramatic decrease of additional medical and non-medical costs in this population, the cost per quality-adjusted life-year for NBS has been calculated as negative in several studies [110, 111]. In summary, initiating NBS programs generates cost savings and improvement of quality of life and life expectancy compared with post-symptomatic treatments.

Both pharmacological and non-pharmacological strategies are currently being tested in late-stage clinical trials in SMA patients. An example of a non-pharmacological intervention is spinal electrical stimulation (NCT05430113). Add-on pharmacological treatments are also being tested [112]. The most advanced strategy is anti-myostatin therapy (NCT05115110, NCT05337553, and NCT05156320). Although levels of circulating myostatin are low in untreated patients with SMA [113], inhibition of myostatin could improve muscle growth in SMA patients treated with a disease-modifying treatment. Pyridostigmine has recently demonstrated its efficacy in a double-blind, cross-over study (NCT02941328) and given its low price may warrant use as an add-on treatment [114].

7.1 Treatment Approach for Pre-symptomatic Patients and Those Identified by NBS

The benefits of disease-modifying treatments in patients who present with symptoms are clear but treatment of patients pre-symptomatically, usually made possible by identification through NBS, is truly transformative. Indeed all pre-clinical and clinical evidence indicate that efficacy of disease-modifying treatments is most optimal when administered early [115]. Given this, NBS for SMA, which is highly reliable [3], is cost effective [48, 111, 116, 117]. NBS should be implemented in all countries where disease-modifying treatments are available to the entire population, and the NBS process should be accelerated to allow treatment initiation as soon as possible.

The treatment chosen should be the one that reaches motor neurons at therapeutic concentrations as rapidly as possible. The clinical team must take into consideration the availability of drugs, temporary contra-indications like maternal AAV-9 antibodies, and specific drug pharmacokinetics. Treatment of patients who have two or three copies of *SMN2* should not be a matter of debate; these patients should be treated as soon after diagnosis as possible with a disease-modifying therapy. Our shared opinion is that patients with four copies of *SMN2* should also be offered early treatment given the risk of symptom development in early infancy and the irreversible loss of motor neurons that occurs in SMA patients. Palliative treatment should be discussed for families of infants with the very severe and early-onset form of SMA that is often associated with a single copy of *SMN2*.

Given the high percentage of patients with two copies of *SMN2* who have symptoms at the time of diagnosis following NBS and the less favorable prognosis in this population, families with risk factors should consider testing in utero and elective delivery preterm as there is a risk of motor neuron loss if pregnancy continues full term. In pre-term infants, the corticosteroids given with onasemnogene abeparvovec may adversely affect neurodevelopment and severe hepatoxicity

could be encountered. For these reasons, our opinion is that risdiplam, if available, should be the preferred treatment at late prematurity. Gene therapy could then be administered once the baby reaches 38 weeks' gestation.

7.2 Treatment Approach for Infantile-Onset SMA

Efficacies of the three SMA disease-modifying treatments have been demonstrated in clinical trials, and there is now a large body of real-world data supporting effectiveness. In infants treated after onset of symptoms, none of these treatments are curative, however, and it is important to set realistic expectations with families from the outset. There are a few important points to consider when choosing the most appropriate treatment for an infant newly diagnosed with SMA1. The first is the difference in pharmacodynamics and pharmacokinetics among the three disease-modifying treatments; it requires a much longer time for nusinersen to reach therapeutic levels (28–64 days) compared with risdiplam and onasemnogene abeparvovec (7–14 days). This delay is particularly relevant early in the disease process when there is a precipitous drop in the numbers of motor neurons and when it is critical to halt this loss as promptly as possible. Second, there is more evidence of preservation or improvement in bulbar function with risdiplam and onasemnogene abeparvovec compared with nusinersen [38, 49–52]. Third, a high anti-AAV9 antibody titer, liver dysfunction, or infection may preclude the use of onasemnogene abeparvovec. The risk of side effects due to onasemnogene abeparvovec is high in older and heavier SMA1 patients. In newly diagnosed infants with SMA1, our opinion is that onasemnogene abeparvovec (if it can be safely administered) or risdiplam (if rapidly available) should be recommended. Nusinersen is an efficacious and safe option that should be considered if onasemnogene abeparvovec or risdiplam are not available or safe to administer, and nusinersen can be used as a bridge if access to the other therapies is expected to be delayed by a few weeks. The results of the DEVOTE trial, which is evaluating the safety and efficacy of a higher dose of nusinersen, may alter these recommendations.

7.3 Treatment Approach for Late-Onset SMA

Currently, for children 2–5 years of age with late-onset SMA who are non-ambulant and who have three copies of *SMN2*, the best available evidence for motor function improvement is treatment with nusinersen or risdiplam. Efficacy in randomized trials has also been demonstrated in children up to 9 years of age with nusinersen and in older children to adults 25 years of age with risdiplam, albeit at a lower treatment effect. For all other age groups, the best available evidence comes from observational studies using historic comparator groups, which have a risk of bias. Consideration of patient preferences for mode of administration and side effect profiles should guide choice of the disease-modifying therapy for patients who have late-onset SMA [118, 119]. Although there is some evidence of effectiveness of onasemnogene abeparvovec in older children, the significant short- and long-term risks associated with the gene therapy often outweigh potential benefits.

8 Conclusions

SMA is now considered a treatable condition, although cure remains unfortunately out of reach for patients who present with symptoms at treatment initiation. Whilst those treated before symptoms appear and most of those identified by NBS show normal or near normal developmental profiles so far, long-term data is needed on the treatment effectiveness. Setting realistic and patient-oriented expectations in discussions with patients and families is key to treatment compliance and satisfaction. Evidence from clinical trials and real-world data clearly demonstrate that screening of newborns for SMA is an ethical, medical, and economical imperative.

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Authors' contributions LS had the original idea for the review, conducted the literature search and drafted the paper. MO conducted the literature search and drafted the paper. SR conducted the literature search and drafted the paper. All authors have read and approved the final submitted manuscript, and agree to be accountable for the work.

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