ΝΩΤΙΑΙΑ ΜΥΪΚΗ ΑΤΡΟΦΙΑ: ΤΡΕΧΟΥΣΕΣ ΚΑΙ ΝΕΕΣ ΘΕΡΑΠΕΥΤΙΚΕΣ ΣΤΡΑΤΗΓΙΚΕΣ - ΑΝΑΣΚΟΠΗΣΗ.

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Περίληψη

Η νωτιαία μυϊκή ατροφία (SMA) είναι μια σπάνια γενετική διαταραχή που χαρακτηρίζεται από την προοδευτική εκφύλιση των κινητικών νευρώνων του νωτιαίου μυελού, οδηγώντας σε μυϊκή αδυναμία και ατροφία. Η πάθηση αυτή προκαλείται κυρίως από μεταλλάξεις στο γονίδιο του κινητικού νευρώνα επιβίωσης 1 (SMN1), το οποίο διαδραματίζει κρίσιμο ρόλο στη διατήρηση και τη λειτουργία των κινητικών νευρώνων. Η νόσος SMA εκδηλώνεται εντός ενός φάσματος κλινικών συμπτωμάτων και βαρύτητας, το οποίο σχετίζεται με την αντισταθμιστική λειτουργία της πρωτεΐνης SMN2, και ταξινομείται σε πέντε υποτύπους: τύπος 0 (συγγενής), τύπος I (νόσος Werdnig-Hoffmann), τύπος II (νόσος Dubowitz), τύπος III (νόσος Kugelberg-Welander) και τύπος IV (ενήλικη εμφάνιση). Μέχρι πρόσφατα, η θεραπεία ήταν μόνο συμπτωματική και περιλάμβανε αναπνευστική υποστήριξη, διατροφική υποστήριξη, φυσικοθεραπεία, ορθοπαιδική αντιμετώπιση των επιπλοκών. Ωστόσο, την τελευταία δεκαετία έχουν εγκριθεί και είναι πλέον διαθέσιμες αρκετές θεραπείες που τροποποιούν τη νόσο, όπως η ονασεμνογένη αμπεπαρβοβέκη, η νουσινερσένη και η ριζδιπλάμη. Σε αυτή την εποχή, κατά την οποία οι διαθέσιμες ειδικές για τη SMA θεραπευτικές επιλογές επεκτείνονται ενεργά, η αυξημένη κλινική υποψία και η άμεση και ακριβής διάγνωση της SMA (συμπεριλαμβανομένων των προγραμμάτων νεογνικού ελέγχου) είναι κρίσιμες για την έγκαιρη έναρξη εξατομικευμένης θεραπείας και την αλλαγή της πρόγνωσης των ασθενών με SMA.

Λέξεις Ευρετηρίου: Νωτιαία Μυϊκή Ατροφία, ονασεμνογένη αμπεπαρβοβέκη, γονιδιακή θεραπεία, αντινοηματικό ολιγονουκλεοτίδιο, νουσινερσένη, ριζδιπλάμη.

SPINAL MUSCULAR ATROPHY: CURRENT AND NOVEL THERAPEUTIC STRATEGIES – A NARRATIVE REVIEW.

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Abstract

Spinal Muscular Atrophy (SMA) is a rare genetic disorder characterized by the progressive degeneration of motor neurons in the spinal cord, leading to muscle weakness and atrophy. This condition is primarily caused by mutations in the survival motor neuron 1 (SMN1) gene, which plays a crucial role in the maintenance and function of motor neurons. SMA disease manifests itself within a spectrum of clinical severity, that is associated with the compensatory function of SMN2 protein, and is classified into five subtypes: type 0 (congenital), type I (Werdnig-Hoffmann disease), type II (Dubowitz disease), type III (Kugelberg-Welander disease), and type IV (adult-onset). Until recently, treatment was only symptomatic and included respiratory support, nutritional support, physiotherapy, orthopedic treatment of complications. However, during the

last decade, several disease modifying therapies have been approved and are now available, including onasemnogene abeparvovec, nusinersen, and risdiplam. In this era, when available SMA-specific treatment options are actively expanding, increased clinical suspicion and prompt and accurate diagnosis of SMA (including neonatal screening programs) are critical for the early initiation of individualized treatment and change in the prognosis of SMA patients.

Keywords: Spinal Muscular Atrophy, onasemnogene abeparvovec, gene therapy, antisense oligonucleotide, nusinersen, risdiplam.

Introduction

Spinal Muscular Atrophy (SMA) is a rare genetic disorder characterized by the progressive degeneration of motor neurons in the spinal cord, leading to muscle weakness and atrophy.[1] This condition is primarily caused by mutations in the survival motor neuron 1 (SMN1) gene, which plays a crucial role in the maintenance and function of motor neurons.[2] The loss of function or absence of SMN1 protein results in the impaired survival of motor neurons, leading to the characteristic symptoms of SMA. It is considered a rare disease (OMIMs: 253300, 253550, 253400, 271150) with an estimated incidence of approximately 1 in 10,000 to 20,000 live births, yet with a carrier frequency of 1/40 to 1/70 in the general population.[3] A recent nationwide study in Greece indicated an incidence of about 1/12,000, and a prevalence of at least 1.5/100,000.[4] SMA stands as one of the leading genetic causes of infant mortality (together with cystic fibrosis).[5]

SMA was first described by the Austrian neurologist Guido Werdnig, who presented two young brothers presenting "muscular dystrophy of neurogenic cause", that was later attributed to SMA type II.[6] Since then, it became apparent that the disease manifests itself within a spectrum of clinical severity that is associated with the compensatory function of SMN2 protein. Presently, SMA is classified into five subtypes: type 0, type I (Werdnig-Hoffmann disease), type II (Dubowitz disease), type III (Kugelberg-Welander disease), and type IV (Table 1). It is important to note that 25% of SMA cases involve adult patients, underscoring the need of familiarization of adult neurologists for the diagnosis and management of this disease.[7] Moreover, an organized and smooth transition from the pediatrician to the neurologist should also be considered.[8]

Until recently, treatment was only symptomatic and included respiratory support, nutritional support, physiotherapy, orthopaedic treatment of complications. However, several specific therapies have now been approved and are available (Figure 1).[9] Reflecting on over a century of research, this narrative review outlines the evolution of SMA research and treatment advancements, showcasing significant progress despite the ongoing quest for a cure.

Pathophysiology

The pathophysiology of SMA involves a cascade of events triggered by reduced levels of functional SMN protein.[10] Normally, SMN protein functions in various cellular processes, including the assembly of small nuclear ribonucleoproteins (snRNPs), which are essential for pre-mRNA splicing in the nucleus. In SMA, decreased levels of SMN protein compromise snRNP assembly, leading to aberrant splicing of mRNA transcripts, including those encoding crucial proteins for motor neuron survival and function. SMA may also be considered among the disorders of programmed cell death, caused by the inadequate control of apoptosis.[11]

In 95% of the cases, the genetic variation involves the complete deletion of the survival motor neuron 1 (SMN1) gene, located on the telomeric segment of chromosome 5q13.[12] A virtually identical gene known as SMN2, produces a comparable yet less biologically potent protein product.[13] While the human genome typically contains no more than two copies of SMN1, the number of SMN2 copies can vary. The protein produced by SMN2 seems to partially ameliorate the symptoms of SMA, with a greater number of SMN2 copies generally correlating with a less severe manifestation and progression of the disease.

The loss of functional motor neurons in SMA results in denervation of skeletal muscles, particularly in proximal muscles.[1] In addition to motor neuron degeneration, SMA pathophysiology involves secondary changes in the neuromuscular system and surrounding tissues. Muscle fibers undergo atrophy due to denervation, leading to muscle weakness and decreased muscle mass. Skeletal deformities, such as scoliosis and joint contractures, may develop as a result of muscle imbalance and weakness. Furthermore, respiratory muscles may become affected, contributing to respiratory insufficiency and an increased risk of respiratory infections, which are significant sources of morbidity and mortality in individuals with SMA.

Clinical Characteristics.

SMA type 0 is used to describe neonates with the disease, presenting with severe weakness and profound hypotonia, likely originating before birth, often accompanied by reduced fetal movements during pregnancy.[14, 15] The majority of these infants do not

achieve any motor milestones. Additional features include absence of reflexes, bilateral facial weakness, atrial septal defects, and joint contractures. Respiratory failure is a significant cause of both morbidity and mortality, necessitating immediate noninvasive ventilation or endotracheal intubation upon birth. Life expectancy is notably shortened, with the majority failing to survive beyond 6 months of age.[16] Furthermore, arthrogryposis multiplex congenita, characterized by congenital joint contractures affecting at least two regions of the body, has been observed. SMA type 0 is very rare and has been characterized (together with SMA type IV) as the outlier of the phenotypic spectrum of SMA.

SMA type I typically manifests within the first months of life.[17, 18] Characteristically, affected infants are incapable of maintaining a seated posture without external support. Clinical indicators include pronounced hypotonia, weak cry, and respiratory distress. These infants display an inability to lift their heads when positioned prone and exhibit substantial lag in head movement when being transitioned from a supine to seated position. Notably, their resting posture often assumes a distinct "frog-leg" stance, reflecting a state of muscular laxity ("floppy" baby).[19] Limb weakness manifests severely and predominantly proximally. Bulbar muscle weakness complicates feeding, leading to arduous ingestion, persistent gurgling, and predisposition to aspiration pneumonia. Notably, facial muscle weakness is comparatively mild, imparting an alert countenance to these infants. Extraocular muscles are not involved. Typically, muscle stretch reflexes are absent, while sensory examination yields normal findings. Fine, subtle involuntary finger movements, termed minipolymyoclonus, attributable to dense fasciculations, may be discernible.[20] Around 50% of affected infants exhibit tongue fasciculations. While contractures are uncommon in initial stages, they may develop subsequent to prolonged immobility. Fatality typically results from respiratory insufficiency, pneumonia, or malnutrition before the age of two.[21]

The onset of symptoms associated with ***SMA type II*** typically occurs between 6 and 18 months of age.[17] Developmental delays in motor milestones often serve as the initial indicators of neurological involvement, with noticeable weakness in the legs preceding weakness in the arms. A subtle hand tremor, attributed to minipolymyoclonus, may raise suspicion for the condition. While the distribution, pattern, and progression of weakness mirror those observed in SMA type I, the severity of type II is considerably less, and the disease advances at a slower pace. Most children with SMA type II eventually achieve the ability to roll over and sit without external support, although independent walking is rare. Weakness in the trunk muscles contributes to the development of a characteristic rounded kyphosis when seated, and as shoulder strength diminishes, mobility decreases, ultimately leading to confinement to a wheelchair. Over time, contractures affecting the hips and knees, clubfoot deformities, severe scoliosis, and hip dislocation may emerge (Figure 2). The long-term outcomes for individuals with SMA type II vary significantly; while some succumb to respiratory failure during childhood, many others survive well into their third or fourth decade of life.

The onset of ***SMA type III*** occurs after 18 months of age, typically between 5 and 15 years, and is characterized by difficulties in walking.[17] Patients who experience onset before age 3 are categorized as SMA type IIIa, while those with onset after age 3 are classified as SMA type IIIb. This condition often resembles limb-girdle muscular dystrophy. As weakness in the muscles around the hips and pelvis progresses, affected individuals may exhibit a waddling (Trendelenburg) gait, accompanied by a protruding abdomen due to increased curvature of the lower spine, making climbing stairs challenging. To rise from a supine position on the floor, individuals may employ the Gowers maneuver. Subsequently, atrophy and weakness in the neck, shoulders, and arms develop, although lower extremity weakness typically surpasses that of the upper extremities. Fasciculations are more pronounced compared to SMA types I and II, and a fine tremor during movement is frequently observed. Tendon reflexes consistently diminish and eventually disappear, while sensory examination yields normal findings. The clinical course of SMA type III is characterized by a slow progression, often punctuated by prolonged periods of stability lasting several years. Predicting the eventual level of disability is challenging; however, if symptoms onset after age 2, it is probable that the individual will maintain ambulatory function well into their fifth decade of life and enjoy a lifespan comparable to that of the general population.

The majority of cases of the autosomal recessive, 5q-associated adult-onset, ***SMA type IV*** predominantly affect the proximal muscles.[22] Clinically, these cases present with a gradually progressive weakness in a limb-girdle fashion, resulting in challenges with walking, climbing stairs, and standing from a seated or prone position. Fasciculations are a notable finding, observed in approximately 75% of patients, with pronounced weakness often evident in the quadriceps muscles. While muscle cramps may occur, they are not a prominent feature, and bulbar signs, bony deformities such as scoliosis, and respiratory weakness are infrequent. The distribution of weakness in many cases resembles that seen in limb-girdle muscular dystrophies, hence the historical term "pseudomyopathic SMA".[23] Similarly to the recessive form, the majority of the cases of the autosomal dominant

adult-onset SMA, also known as Finkel-type SMA, typically commence in the third decade of life, predominantly affect proximal muscles, progress very slowly, and initially involve the legs before affecting the arms.[24] The majority of patients retain ambulatory function for decades following symptom onset.

Diagnosis.

SMA diagnosis involves a combination of clinical evaluation, genetic testing, electrophysiologic studies (electroneurography and electromyography) and, very rarely, muscle biopsy.

Clinical suspicion often arises from characteristic signs and symptoms observed during infancy or childhood, including progressive muscle weakness, hypotonia, decreased motor function, and respiratory difficulties.

Genetic testing is the cornerstone of SMA diagnosis, particularly identifying variations or deletions in the SMN1 gene on chromosome 5q13.[25] The absence or variation of SMN1 gene copies confirms the diagnosis, as nearly all SMA cases result from alterations in this gene. Additionally, the number of copies of the SMN2 gene, a closely related homolog of SMN1, may be evaluated. While SMN2 cannot fully compensate for the loss of SMN1, a higher number of copies may correlate with milder phenotypes due to increased production of functional SMN protein.

Electrophysiologic studies can provide supportive evidence for SMA diagnosis by assessing motor nerve function and detecting abnormal electrical activity in affected regions.[26] Compound muscle action potentials may exhibit diminished amplitudes, yet conduction velocities and sensory nerve conduction studies typically remain within normal ranges. During needle electrode examination, signs of acute denervation, such as fibrillation potentials and positive sharp waves, alongside fasciculation potentials, may be observed, indicating ongoing motor nerve damage. Additionally, evidence of chronic motor unit remodeling, stemming from a prolonged cycle of denervation and reinnervation, may manifest.

With the advent of genetic testing, muscle biopsy is less frequently utilized for SMA diagnosis.[27] It is typically reserved for situations where genetic testing results are inconclusive or unavailable. It may also be considered when there is a need to differentiate SMA from other neuromuscular disorders with similar clinical presentations. Muscle biopsy findings often reveal a distinct pattern known as grouped fascicular atrophy, particularly prominent in classic Werdnig-Hoffmann presentations. This pattern entails the atrophy of entire fascicles or groups of fascicles, juxtaposed with neighboring fascicles, often comprising hypertrophic fibers, predominantly of type I. However, it is crucial to note that myopathic alterations, such as variability in fiber size, fiber splitting, presence of internal nuclei, and fibrosis, may complicate the histological presentation, particularly in long-standing denervating disorders like childhood and juvenile SMA.

Management.

4a. Supportive Management

Current specific treatments for SMA do not provide a cure but instead aim to halt the disease progression. Therefore, supportive management remains the cornerstone of treatment. Supportive management of SMA aims to address the symptoms and complications associated with the condition, improve quality of life, and optimize functional abilities. A coordinated and multidisciplinary approach, typically involving neurologists, pulmonologists, physical therapists, occupational therapists, speech therapists, nutritionists, and social workers, is essential to offer SMA patients comprehensive care.

Given the respiratory complications associated with SMA, respiratory support is crucial.[28] This may involve interventions such as non-invasive ventilation, cough assistance devices, and airway clearance techniques to help maintain lung function, prevent respiratory infections, and manage respiratory distress. Orthopedic management plays a crucial role in the care of SMA patients, as contractures and scoliosis are notable comorbidities.[29] Orthopedic surgeons are involved in recommending interventions such as spinal fusion or the placement of spinal growing rods, particularly in cases of severe scoliosis that impairs respiratory function though restrictive lung disease. Additionally, physical therapy plays a vital role in maintaining range of motion, preventing contractures, and preserving functional mobility.[30] Therapeutic exercises tailored to the individual's needs can help strengthen muscles, improve posture, and enhance overall physical function. Furthermore, occupational therapy may facilitate activities of daily living, promote independence, and maximize participation in meaningful activities, including (but not limited to) the use of assistive devices, adaptive seating, and ergonomic modifications to optimize comfort and functionality. Importantly, speech therapists can address speech and swallowing difficulties commonly observed in individuals with SMA, providing interventions to improve oral motor function, swallowing safety, and communication skills. They may also assist with dietary modifications and feeding techniques to ensure adequate nutrition and hydration, together with the nutritionists that assess nutritional status, provide dietary counseling, and recommend nutritional supplements or feeding tubes as needed to address feeding difficulties and prevent malnutrition. Coping with a chronic condition like SMA can be emotionally challenging for both

individuals and their families. Psychosocial support services, including counseling, support groups, and access to community resources, can provide emotional support, education, and guidance to help navigate the psychosocial aspects of living with SMA.[31] Finally, palliative care focuses on improving quality of life and relieving symptoms associated with serious illnesses, including SMA.[32] Palliative care specialists can help manage pain, alleviate discomfort, and address end-of-life care preferences in a compassionate and holistic manner.

In addition to supportive care, significant advancements have been made in the treatment of SMA. Novel treatments such as gene therapy, antisense oligonucleotide therapy, and small molecule drugs have revolutionized the management of SMA by targeting the underlying genetic cause of the disease (Table 2).

4b. Gene Therapy

Onasemnogene abeparvovec, marketed as Zolgensma, was granted approval by the US Food and Drug Administration in May 2019 as a gene therapy for treating SMA in children under the age of two and by and the European Medicine Agency in June 2020 for all patients with a biallelic mutation in SMN1 and a clinical diagnosis of spinal muscular atrophy type 1 or up to three SMN2 copies. It comprises a single-dose, intravenous infusion of a non-replicating adeno-associated virus vector 9 (AAV9) capable of crossing the blood-brain barrier and carrying a functional copy of the SMN1 gene.[33] The AAV9 vector does not integrate into host DNA. Once inside the host cell, the AAV9 vector migrates to the nucleus, where the transgene functions as an episome – a distinct, stable chromosome apart from the host's native chromosome. Nevertheless, AAV vectors carrying single-stranded DNA exhibit limited gene expression efficiency since double-stranded DNA synthesis is necessary before gene expression can occur.

Initially, the phase 1 START trial evaluated the safety and efficacy of a single intravenous infusion of onasemnogene abeparvovec in symptomatic infants under 8 months of age diagnosed with SMA type 1 and possessing two copies of SMN2. Fifteen infants were enrolled, receiving either a low dose (6.7 ×10^13 viral genomes (vg)/kg; n = 3) or a high dose (1.1 ×10^14 vg/kg; n = 12) of intravenous onasemnogene abeparvovec.[33] At 20 months of age, all 15 infants were alive and did not require mechanical ventilation, marking a significant improvement compared to the 8% survival rate observed in historical control groups. Thirteen patients from the START trial participated in a long-term follow-up study, where all 10 children from the high-dose cohort remained alive without requiring permanent ventilation and maintained previously achieved motor milestones for up to 7.5 years post-treatment, underscoring the enduring efficacy of onasemnogene abeparvovec.[34]

The subsequent phase 3 trials, STR1VE-US and STR1VE-EU, administered the high dose utilized in the START trial to children under 6 months old diagnosed with SMA type I and possessing up to two copies of SMN2.[35, 36] Both trials revealed that over 90% of infants survived without requiring permanent ventilation at 14 months, compared to only 26% in the natural history cohort; moreover, approximately half achieved independent sitting by 18 months, a milestone not reached in the natural history cohort. Both STR1VE trials demonstrated a highly favorable benefit–risk profile for intravenous administration of onasemnogene abeparvovec in symptomatic infants with SMA under 6 months old, thereby bolstering the case for drug approval. This advantageous benefit–risk profile was further corroborated by the SPR1NT trial, which treated pre-symptomatic infants under 6 weeks old with 2 (n = 14) or 3 (n = 15) copies of SMN2.[37] While the START, STR1VE, and SPR1NT trials assessed the safety of onasemnogene abeparvovec in both symptomatic and pre-symptomatic infants with SMA, all participants weighed less than 8.5 kg. The industry behind onasemnogene abeparvovec initiated the Global Managed Access Program (GMAP) in January 2020, offering treatment to all SMA patients under 24 months old and weighing up to 21 kg. GMAP data indicated that safety outcomes for patients weighing 8.5 kg or more at the time of infusion were consistent with prior data from patients weighing less than 8.5 kg.[38]

Conclusively, during those clinical trials, onasemnogene abeparvovec demonstrated significant improvements in event-free survival, motor function, and attainment of motor milestones in SMA patients, with these benefits sustained over the long term (up to approximately 5 years).[34] Importantly, onasemnogene abeparvovec was also associated with an accelerated attainment of age-appropriate motor milestones and enhanced motor function in pre-symptomatic SMA children,[37] underscoring the advantages of early intervention and potentially the need for newborn screening programs. A recent systematic review and meta-analysis of all available studies confirmed that administration of onasemnogene abeparvovec was associated with better clinical outcomes, a finding that was more enhanced among the presymptomatic participants.[39] Importantly, this treatment exhibits favorable tolerability overall, notwithstanding the recognized risk of hepatotoxicity, which can typically be managed with prophylactic prednisolone. Recent real-world data derived from the RESTORE registry have also confirmed effectiveness of onasemnogene abeparvovec over a large patient population (168 patients), while demonstrated a safety profile consisted to that noted in the clinical trials.[40]

Although treated young patients have shown remarkable outcomes, the greater viral dosage required for older children and adults raises valid safety apprehensions. Indeed, there have been reports indicating that heavier children who received larger doses of onasemnogene abeparvovec presented more often elevated liver transaminase levels,[41, 42] although not consistently.[38] Exploring intrathecal administration of onasemnogene abeparvovec aims to address the challenge of requiring exceptionally high vector genome copies for intravenous treatment in older, and consequently heavier, patients. This approach seeks to achieve more effective transduction of the central nervous system.[43] A recent clinical trial explored the utilization of onasemnogene abeparvovec in older children via a fixed dosage and intrathecal administration, showing encouraging results.[44] A phase III trial, the STEER trial is currently recruiting, aiming to enroll 125 SMA patients aged ≥2 to <18 years old regardless of their weight, that will be treated with intrathecal administration of a fixed dose of onasemnogene abeparvovec. Study completion is expected in early 2025.

In addition to the constrained indications, primarily focused on young SMA patients, another obstacle of the gene therapy with onasemnogene abeparvovec is its limited accessibility and affordability, particularly in middle- and low-income countries.[45, 46] While a price of ≈ €1.7 million per dose sounds exorbitantly high in the public domain, the cost-effectiveness of onasemnogene abeparvovec, being a single-time treatment limited to new ("incident") cases, has been proven in various settings.[47-49]

Finally, regarding combined treatment, real-world data support the use of "add-on therapy" of nusinersen or risdiplam on top of onasemnogene abeparvovec (that has been previously administered) or the "bridging therapy", during which patients that were already treated with nusinersen or risdiplam receive onasemnogene abeparvovec.[40, 50-53] Currently, there is one ongoing, phase 4 trial, the RESPOND study evaluating the safety and efficacy of nusinersen in 60 patients (young children; aged 2 to 36 months) following treatment with onasemnogene abeparvovec. This trial is estimated to be completed at the end of 2025. Additionally, the JEWELFISH trial, testing risdiplam, enrolled patients that have previously received another disease modifying treatment, including onasemnogene abeparvovec (14 patients).[54] For the time being, there has been no there are no consensus guidelines on treatment choices, switching of treatments, or the indications of combination therapy.[55]

4c. Nusinersen

Nusinersen, classified as an antisense oligonucleotide, is administered intrathecally into the cerebrospinal fluid. It targets a specific region within intron 7 of the SMA gene, known as ISS-N1,[56] modulating the splicing of the SMN2 pre-mRNA, thus augmenting the expression of functional SMN protein.[57] Nusinersen is the first disease-modifying treatment that was approved in US in 2016 and in Europe in 2017.

Despite approval by the regulatory authorities for treating all SMA forms (including adults with SMA), initial clinical trials were confined to patients up to 14 years old, diagnosed with SMA types 1, 2, and 3, who were not reliant on mechanical ventilation. The first trial, known as the ENDEAR trial, was a phase 3 study focusing on the efficacy and safety of nusinersen in infants diagnosed with spinal muscular atrophy (SMA) types I and II.[58] This trial employed a randomized, double-blind, sham-controlled design and involved 122 infants. Among them, two-thirds received nusinersen treatment, while the remaining underwent sham treatment, with the final assessment conducted 394 days post-intervention. The sham arm was terminated prematurely during an interim analysis due to a significant disparity in survival rates between the two groups. In the final analysis, a considerably higher proportion of infants treated with nusinersen achieved a motor milestone response compared to those in the control group (51% versus 0%, respectively). Additionally, the event-free survival rate was significantly greater in the nusinersen group than in the control group (HR: 0.53, p=0.005), and overall survival was also notably higher among nusinersen-treated patients compared to the control group (HR: 0.37, p=0.004). Furthermore, patients with a shorter disease duration at screening were observed to be more likely to benefit from nusinersen treatment compared to those with a longer disease duration, highlighting the need for prompt diagnosis, potentially employing newborn screening programs.[59]

A similar study design was employed by the CHERISH trial, that included 126 children (2-12years old) with SMA types II and III.[60] This study was prematurely terminated due to favorable outcomes noted during the interim analysis in the interventional arm. In the nusinersen group, patients showed a notable increase of 4.0 points in the 15-month Hammersmith Functional Motor Scale Expanded (HFMSE) score compared to baseline, whereas those in the control group experienced a decrease of 1.9 points (p<0.001).

The EMBRACE study also used a similar design (phase 2, randomized, double-blind, sham-procedure controlled study) and included 21 patients that would have been considered ineligible by the two previous trials.[61] The part 1 of this study was terminated prematurely, following the observed motor function improvements associated with nusinersen in the ENDEAR trial, allowing the enrolled patients to roll over to an open label extension study of nusinersen,

the SHINE trial. Despite its early termination and the limited sample size, the EMBRACE study managed to demonstrate a favorable long-term benefit-risk profile in this broader population of SMA patients.[61]

Since then, the inclusion of a sham comparator in nusinersen clinical trials was considered rather unethical. Thus, the NURTURE trial was designed as an open-label, single-arm study aimed at administering nusinersen to 25 presymptomatic infants possessing two or three copies of SMN2 gene within the first six weeks of life.[62] During the three-year follow-up, no instances of death or the necessity for continuous assisted ventilation were reported. Concerning motor milestones, all patients achieved the milestone of sitting without support, with 92% of them walking with assistance, and 88% walking independently. An additional two-year follow-up was also available, confirming the durability of treatment effect.[63] These findings underscore the critical importance of promptly initiating proactive nusinersen treatment following a genetic diagnosis of SMA in presymptomatic infants.

Not only the efficacy, but also the effectiveness of nusinersen has been largely confirmed by a rising number of real-world studies, concerning adult patients as well.[64-67] One of the largest observational studies was conducted in Germany and showed clinically meaningful improvements in motor function among a total of 139 adult SMA patients (aged 16-65 years).[68] Feasibility was also proven by a number of them, especially concerning the lumbar puncture, which can be challenging among patients with severe scoliosis or corrective spondylodesis.[69, 70] To address potential difficulties in managing the intrathecal administration of nusinersen, several approaches have been proposed: fluoroscopy-guided, CT-guided,[69, 71, 72] ultrasound-guided,[73] lumbar laminotomy,[74] transforaminal approach versus the conventional interlaminar approach,[75, 76] cervical versus lumbar approach.[77] A recent systematic review and meta-analysis collected all available 12 cohort studies and case-series and summarized the cumulative data of 384 adult SMA patients treated with nusinersen.[78] According to the data analysis, a statistically significant improvement on motor function, as assessed by the Hammersmith Functional Motor Scale Expanded and the Revised Upper Limb Module scores, was shown, while adverse events were limited to the administration procedure (namely, post lumber puncture headache and back pain).[78] More rare adverse events have been also reported, such as coagulation abnormalities and thrombocytopenia (including acute severe thrombocytopenia)[79] and renal toxicities (including fatal glomerulonephritis),[80] while the development of antidrug antibodies is infrequent with unknown clinical significance.[80]

A significant aspect to contemplate when it comes to nusinersen treatment is its substantial expense and the procedures involved in reimbursement:[81] a single dose of nusinersen is estimated to cost €72,000, resulting in a total expenditure of €430,000 for the initial year of treatment, followed by €220,000 annually thereafter. Yet, the significant financial strain associated with the symptomatic treatment and the disease course SMA patients underscores the high cost-effectiveness ratio of nusinersen treatment at the present price.[82] Another important consideration is that the clinical trials had a restricted duration of follow-up, offering limited understanding regarding the long-term consequences of nusinersen therapy.[83] A potential challenge that could complicate clinical practice is determining when the potential risks of continuing therapy for a specific patient outweigh the ongoing benefits, raising the issue of treatment discontinuation.[84, 85] Despite the consistent demonstration of efficacy in both clinical trials and real-world settings, there remains a need for further investigation into the long-term effects of nusinersen.

4d. Risdiplam.

Risdiplam is another option that has recently been added in the therapeutic arsenal for SMA. Its notable advantage lies in the sufficient distribution through oral administration, both in the central nervous system and in the periphery. Risdiplam is a small-molecule compound that targets two regions (TSL2 and ESE2) on exon 7 of the SMN2 gene and modulates SMN2 pre-mRNA splicing within the nucleus,[86] leading to increased levels of functional SMN protein. Risdiplam was granted approval in the US in 2020 and in Europe in 2021, initially for patients with SMA older than 2 months, subsequently expanding to all age groups. It is administered once daily, with the dosage adjusted based on the patient's age and body weight. For adults and children over 2 years old weighing 20 kg or more, the recommended dose is 5 mg per day. For children older than 2 years old but weighing less than 20 kg, the recommended dose is 0.25 mg/kg per day. For younger infants, the recommended dose ranges between 0.15-0.2 mg/kg once daily.

The efficacy of Risdiplam has been assessed in four pivotal trials. The FIREFISH trial (Part 1) constituted a phase 2-3, open-label study that enrolled 21 infants with SMA type I, aged 1-7 months old, and randomized them into two groups: the "low-dose" group receiving a dosage of 0.08 mg/kg per day and the "high-dose" group receiving 0.2 mg/kg per day.[87] Both groups showed an increase in the median concentration of SMN protein. Notably, seven infants in the high-dose group achieved the milestone of sitting without support for at least 5 seconds, while none in the low-dose group reached this milestone. Consequently, the higher dosage of

risdiplam (0.2 mg/kg per day) was selected for the subsequent phase of the study: the FIREFISH trial (Part 2). In this trial, 41 infants were included and treated with risdiplam 0.2mg/kg daily, and 29% of them achieved the milestone of sitting without support for at least 5 seconds at the 12-month follow-up, additionally showing significant improvements in motor function compared to historical controls.[88] After 24 months of treatment, 44% of infants were able to sit without support for at least 30 seconds, though they were still unable to stand unassisted.[89]

The SUNFISH trial enrolled patients with SMA type II and type III, aged between 2-25 years. The Part 1 of the study was a placebo-controlled, dose-finding study, aiming to identify the most appropriate dose, based on safety, tolerability, pharmacokinetic, and pharmacodynamic data among the 51 included patients.[90] According to the findings of Part 1, the selected dose for Part 2 was 5 mg for patients weighing ≥20 kg or 0.25 mg/kg for those weighing <20 kg. Part 2 was a phase 3, double-blind, placebo-controlled study with international recruitment, including 180 SMA patients that were randomized to receive either risdiplam or placebo for 12 months.[91] This study showed significant improvement in motor function among patients treated with risdiplam compared to placebo, while serious adverse events were similar between the two groups. Following the 12-month follow-up, all included patients were offered risdiplam administration for an additional year.[92] This extension of SUNFISH Part 2 trial confirmed the favorable efficacy and safety profile of risdiplam at this longer follow-up.

The JEWELFISH trial, which is a multicenter, exploratory, non-comparative, open-label study, enrolled 174 patients with SMA type I, II and III, aged between 6 months and 60 years, that had previously received another disease modifying treatment (RG7800, olesoxime, nusinersen, or onasemnogene abeparvovec). In the interim analysis of this study, that was conducted after 1 year of treatment with risdiplam, it was shown that safety and pharmacodynamics (including the increase of SMN protein) were consistent in patients who had received any previous treatment compared to those that were treatment naïve.[54] The results of the primary analysis at 24-month follow-up have been announced at the Muscular Dystrophy Association Clinical and Scientific Conference 2023, showing a sustained >2-fold increase in median SMN protein levels versus baseline, irrespective of previous treatment and stabilization of the overall motor function,[93] while the peer-reviewed publication is awaited.

Finally, the single-arm RAINBOWFISH trial is currently ongoing and enrolling presymptomatic infants (aged from birth to 6 weeks old) with SMA and two or three SMN2 copies. Preliminary data of this trial have recently been released, showing that the motor scores of the 5 patients receiving risdiplam for at least 12 months were similar to those of young children without spinal muscular atrophy.[94]

Growing evidence from real-world data supports the safety and effectiveness of risdiplam.[95-98] This data highlights its positive impact on both measurable motor function outcomes and patient-reported reported outcomes.[99, 100] Furthermore, it indicates risdiplam as a viable option for individuals ineligible for gene therapy or those unable to tolerate or who have failed nusinersen treatment.[101] Switching from nusinersen to risdiplam has recently been demonstrated as feasible and safe, while motor improvements remained among the 17 adults included in this observational study.[102]

4e. Further considerations.

Despite the huge advancements in the treatment of SMA, several clinical unanswered questions remain. Exploring the optimal dosages of onasemnogene abeparvovec, nusinersen, and risdiplam beyond the parameters investigated in current clinical trials is crucial. Additionally, determining the ideal therapeutic window and evaluating the potential for switching or combining survival motor neuron protein-enhancing therapies, along with adjunct therapies independent of survival motor neuron protein, is essential.

Consideration should be given to prenatal intervention in fetuses with one or even two SMN2 copies, weighing the safety and efficacy of in utero treatment versus early delivery followed by prematurity treatment. Similarly, assessing the benefits of treating presymptomatic infants with four or more SMN2 copies is vital. Pediatric neurologists should familiarize themselves with newborn screening protocols to enable early detection and prompt intervention for infants diagnosed with spinal muscular atrophy. Additionally, they should remain vigilant regarding potential delayed systemic adverse events, as well as monitor for drug-related toxicities.

Understanding the unique adverse events associated with these emerging therapies over extended treatment periods is necessary for informed decision-making. Furthermore, anticipating changes in disease characteristics with aging and implementing appropriate surveillance measures is important. Neurologists are expected to encounter adults with severe spinal muscular atrophy who, with treatment, are increasingly likely to survive into adulthood. They also need to be prepared to manage adults for whom the benefits of treatment may be subject to debate, as some argue that the modest benefits do not justify the significant costs to both the individual and society. Identifying the most effective clinical biomarkers or patient-reported outcome measures for monitoring disease progression and treatment response,

particularly in adults, is critical.

Finally, establishing centralized international real-world longitudinal databases is imperative for monitoring the long-term efficacy, durability, and potential toxicities of available treatments, as well as for identifying treatment responders and non-responders, and documenting treatment-induced changes in disease presentation. Expert consensus is essential for determining surveillance protocols aimed at detecting organ involvement that may not manifest clinically but could render individuals more susceptible to environmental or other stressors.

Conclusions.

Recent advancements in treating SMA represent a significant transition from merely addressing symptoms to targeted therapies, showcasing notable progress in research. The gene therapy onasemnogene abeparvovec, recently approved for SMA treatment, has demonstrated substantial improvement in both survival rates and motor function during clinical trials. Nonetheless, challenges such as limited accessibility, affordability, and safety concerns among older patients persist, prompting ongoing investigations into combination therapies with nusinersen or risdiplam. Nusinersen, the pioneer disease-modifying treatment for SMA, has been approved for use across diverse age groups, based on both clinical-trial and real-world data. Risdiplam, a newly sanctioned SMA treatment, boasts oral administration convenience and has exhibited efficacy across various age groups, making it a feasible alternative for individuals ineligible for gene therapy or intolerant to nusinersen. Exploring optimal dosages, therapeutic windows, and the benefits of prenatal intervention and presymptomatic treatment, along with incorporating newborn screening protocols, are pivotal endeavors. Establishing centralized databases and formulating consensus guidelines are vital for ensuring long-term treatment monitoring and enhancing patient care in SMA.

Disclosures

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Figure 1. Launch dates of targeted therapies for Spinal Muscular Atrophy in Europe and in the United States of America (USA).

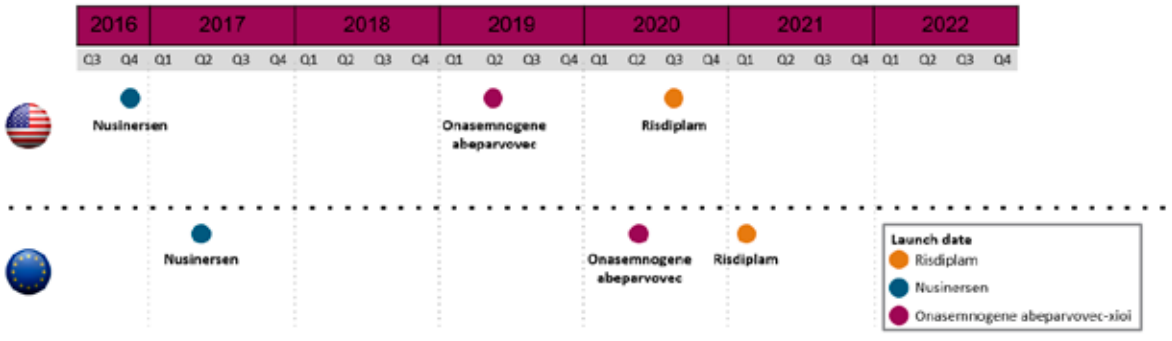

Figure 2. Severe scoliosis in an adult patient with Spinal Muscular Atrophy type II (A). The patient has been treated with computed-tomography-guided transforaminal intrathecal nusinersen injections (B) without any complications and excellent adherence for the past 4 years.

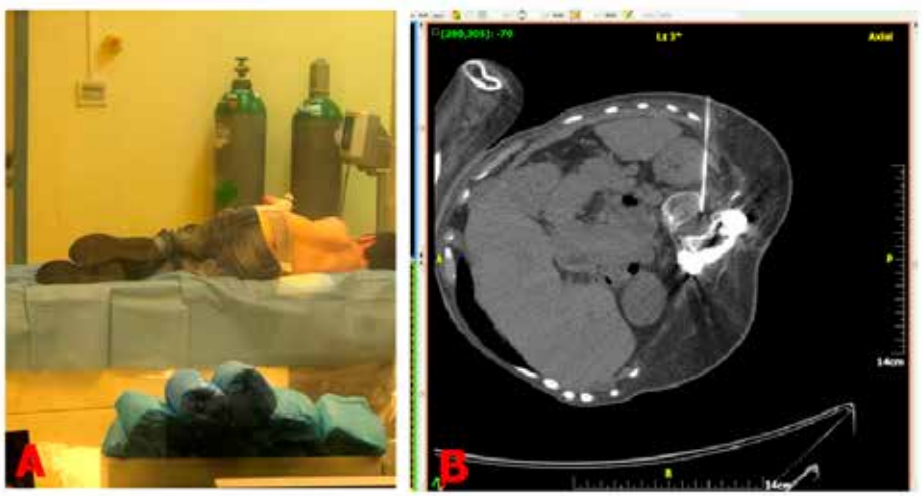

Table 1. Classification of Spinal Muscular Atrophy.

Type	Age of symptoms occurrence	Clinical Manifestations
0 (congenital)	In utero	Hypotonia Early respiratory failure Generalised muscle weakness Death in the first month of life*
I (Werdnig-Hoffman disease)	0-6 months	Weakness of head support Inability to sit up Hypotonia Reduction of reflexes Respiratory failure Swallowing disorders Death in the first two years of life*
II (Dubowitz disease)	6-18 months	Progressive proximal muscle weakness Hypotonia Reduction of reflexes Restrictive respiratory failure Difficulty walking Death in the third decade of life*
III (Kugelberg-Welander disease)	>18 months	Able to walk Progressive proximal muscle weakness Normal life expectancy
IV (adult-onset)	>21 months	Mild progressive proximal muscle weakness of lower limbs Normal life expectancy

*** If** untreated.

Table 2: Disease-modifying treatments for Spinal Muscular Atrophy.

Treatment	**Onasemnogene abeparvovec**	**Nusinersen**	**Risdiplam**
Trade Name	Zolgensma	Spinraza	Evrysdi
FDA approval	May 2019	December 2016	August 2020
EMA approval	June 2020	April 2017	February 2021
Mechanism of Action	Gene therapy with self-complementary AAV9 with human coding SMN1, leading to the production of SMN protein from SMN1 transgene.	Antisense oligonucleotide specific to ISSN1 in intron 7 of SMN2, modulating the splicing of the SMN2 pre-mRNA, thus augmenting the expression of functional SMN protein.	Small-molecule compound that targets two regions (TSL2 and ESE2) on exon 7 of the SMN2 gene and modulates SMN2 pre-mRNA splicing within the nucleus, leading to increased levels of functional SMN protein.
Indication (per EMA)	SMA patients with a biallelic mutation in SMN1 and a clinical diagnosis of spinal muscular atrophy type I or up to three SMN2 copies	SMA patients	SMA patients with a clinical diagnosis of SMA Type I, Type II or Type III or with one to four SMN2 copies
Route of Administration	single-dose, intravenous infusion; intrathecal administration under investigation	Intrathecal administration	Oral
Dose	1.1 x 10^{14} vg/kg	12mg per administration (4 loading doses on days 0, 14, 28 and 63, and then once every 4 months)	Stratified by age and body weight
Cost	≈ €1.7 million per dose	≈ €72,000 per dose	≈ €20,000 per month (adult SMA patient)

FDA: Food and Drug Administration; EMA: European Medicine Agency.