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REVIEW

What did we learn from new treatments in SMA? A narrative review

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Spinal Muscular Atrophy (SMA) is a progressive neuromuscular disorder caused by SMN1 gene mutations, leading to inevitable motoneuronal degeneration. The introduction of disease modifying therapies has dramatically altered its natural history, shifting management from palliative to proactive approach. The new phenotypes and differences in treatment response and efficacy, are all contributing to reshape our understanding of the disease itself. This paper aims to analyze the lessons derived from the recent therapeutic advances, focusing on key aspects such as therapeutic windows, impact of early treatment and both disease progression and treatment efficacy modifiers. Ultimately, we also aim to give insights on new models of data analysis being explored to optimize patient trajectories and individualize treatment strategies.

Our experience and the overall review of clinical trials and real-world data confirm that early treatment maximizes motor outcomes, especially when started in the pre-clinical phase of the disease. The significant clinical improvements in symptomatic type I infants treated at different ages has provided evidence of an expanded 'therapeutic window', previously reported as limited to the first few months after birth on the basis of neurophysiological findings. The available data also provide evidence that function at baseline, SMN2 copy number, and age at treatment all appear to represent critical determinants of response. The availability of long-term data is increasingly used to pilot new predictive models to support clinical decision-making and to adapt therapeutic goals based on patient-specific variables.

Key words: SMA, Disease modifying therapies, SMN2, Functional scales, Trajectories, machine learning

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Introduction

Spinal muscular atrophy (SMA), is an autosomal recessive disorder caused by mutations in the *survival motor neuron* (*SMN1*) gene[1], resulting in loss of motoneurons and subsequent muscular atrophy. Historically, SMA has been classified into three forms with pediatric onset (I, II, III) and a fourth form (type IV) with adult onset. In type I, the most severe form, the onset of clinical signs is at birth or in the first six months, and there is very severe weakness and reduced survival (less than 8% at 21 months)[2]. In type II SMA the onset of clinical signs is between 6 and 12 months with achievement of the ability to sit unsupported but not of independent walking. In type 3, the onset is generally after 18 months and, although independent ambulation is achieved, this but can be subsequently lost. In all the three forms with pediatric onset there was always progression of weakness and reduced functional abilities over time. The advent of disease modifying therapies has resulted in dramatic changes in the natural history of SMA[3]. Three disease modifying therapies are currently available with different mechanisms and route of administration. Two of the three therapies target the splicing of SMN2, resulting in increased SMN protein.

These include Nusinersen, an antisense oligonucleotide administered intrathecally every 4 months[4, 5], and Risdiplam, an orally bioavailable small molecule[6-8]. The other drug, onasemnogene abeparvovec, is a gene therapy targeting replacement of SMN1 by using a single intravenous delivery of a self-complementary AAV9–SMN1[9, 10]. The three therapies have resulted in increased survival and improvement or maintenance of key functional aspects and have also contributed to improve our knowledge on a number of aspects related to the mechanisms of the disease and, more generally, on the expectations related to the new therapies.

In this paper we will review the most relevant lessons learned from the new course of SMA. More specifically, we aim to focus on: i) what we have learned in terms of therapeutical windows and efficacy of the drugs at different ages; ii) impact of early treatment in presymptomatic patients;

iii) the identification of possible prognostic factors to define trajectories of progression in treated patients; iv) new models of analysis.

Therapeutic window

SMA is a progressive disorder associated with degeneration in motoneurons. In a pioneering study from 2005 Swoboda and her group used electrophysiological tests for the motor unit number estimation (MUNE) and maximum compound motor action potential amplitude (CMAP) in infants with type 1 SMA, reporting a rapid loss of motor units, with more than 95% of motor units lost within 6 months of age[11]. These findings have often been used as a paradigm to highlight that in type I SMA most of the degeneration in the motoneurons occurs in the first months after birth. The electrophysiological findings mirror what observed in clinical practice, with a rapid decline in motor function observed on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), a disease specific functional scales, specifically designed to follow changes in function in weak infants[12].

These findings, together with in-vivo studies in mice and large animals, have suggested a possibly tight temporal window for therapeutic intervention. Because of this, the first clinical trials in type I SMA were performed in infants younger than 6 months, confirming that early therapeutic intervention correlated with better motor performance and higher chances of longer survival[4, 7, 9].

Based on the success of the clinical trials, the three therapeutical options (nusinersen, onasemnogene abeparvovec and risdiplam) have received regulatory approval in several countries, with labels including wider age and severity ranges than those included in the clinical trials.

Real world data are therefore also including type I patients older than 6 months, and this has allowed to establish the possible efficacy of the drugs in different age groups. The results of real-world data show that although, as previously reported, early treatment is always related to better outcome, a significantly improved motor function can also be observed in infants treated between 6 and 12 months, and to a lesser extent, in those treated in the second year.[13] Children treated after the age of two years show a less marked improvement, but some changes associated with improvement in activities of daily living can also be found in older children.

These findings are apparently discordant with the neurophysiological evidence of profound loss of motoneurons observed in the first few months after birth[11]. The apparent discrepancy may be partly explained by the presence of multiple populations of motoneurons, including a population that already shows irreversible damage, but also other populations in which the damage may be reversible[14]. The latter may contribute to the low response observed on electrophysiology, but because of the possible reversibility of the damage, can still benefit from SMN protein restoration with the available drugs, therefore widening the therapeutic window.

Impact of early treatment on disease course

While the studies in symptomatic patients had already suggested the dramatic impact on disease progression, even better results have been observed when the same drugs have been administered before the onset of symptoms[15-18]. The availability of the DMTs, together with the need for early treatment have prompted the increasing availability of neonatal screenings for SMA worldwide, which allowed to identify infants with mutations in SMN1 at birth, irrespective of whether they already show clinical signs or not[19, 20].

All three clinical trials in pre-symptomatic SMA patients have demonstrated that earlier treatments translate into greater potential for physiological timing for motor milestone's achievement. The first study in pre-symptomatic infants, the NURTURE (NCT02386553) study, included pre-symptomatic infants treated with nusinersen, showing that a significant proportion of them not only achieved all the relevant motor milestones, including independent ambulation, but that these were also often reached at the same age of their peers[16]. The 5-year follow up extension of this study confirmed the durability of these achievements, underlining the importance of early and continuous intervention[15].

These results were confirmed by subsequent trials using the other two available drugs. In the SPR1NT trial (NCT03505099), pre-symptomatic infants were treated with onasemnogene abeparvovec. The study had two arms, including infants with 2 or 3 SMN2 copies respectively, and expanded what observed in the NURTURE study. Namely, it showed that most infants reached the designated end point (sitting for 2 SMN2 copies and walking for 3 SMN2 copies), with infants with 3 copies often exhibiting normal motor development [17, 18]. Similar results have been recently reported for the RAINBOWFISH (NCT03779334) study using risdiplam.

The number of SMN2 copies however is not the only determinant of outcome as there is increasing evidence that even minor clinical signs, when present, may affect the progression of the disease[21]. These findings have highlighted the crucial role of early intervention in maximizing functional outcomes and have also challenged the state of our understanding of infants identified through the neonatal screening. Moreover, this evidence has further highlighted the need for a more precise nomenclature of the pre-clinical stage of this disease. To this end, particular attention has been devoted to the identification of a prodromic phase, when the infants may show minimal clinical and/or neurophysiological signs before the onset of overt clinical signs[22]. Based on this proposed nosology, there has been suggestion to stratify the cohort of pre-symptomatic infants into two

different categories: truly asymptomatic and paucisymptomatic. This classification is only possible if based on early neurological assessments, such as using standardized tools such as the Hammersmith Neonatal Neurological Examination (HNNE) [23]and the recently developed Floppy Infant Module[24] that have proved to be able of detecting subtle motor signs in infants who might have been assumed to be asymptomatic[25].
The application of this approach to real world data cohorts confirms the clinical and therapeutical relevance of this stratification. In a recent paper, analyzing treatment outcomes for infants identified through newborn screening, functional outcomes reflected pre-clinical stage. In particular, those classified as fully asymptomatic (normal HNNE) all acquired independent ambulation within 18 months of age. On the other hand, only 1/3 of the paucisymptomatic patients achieved this, with worse outcomes in the symptomatic cohort, despite receiving equal treatment[26].
Overall, these insights have reshaped genetic counseling, newborn screening policies and long term therapeutic strategies, positioning SMA as a disease which could be proactively rather than reactively managed[27].

Factors that influence progression/ efficacy trajectories

The increasing availability of long term follow ups data from real world evidence is highlighting a wider variability of progression trajectories, making it also possible to identify possible prognostic factors in terms of response to treatment. We and others have reported that baseline values, age and SMN2 copies appear to play a relevant role[13, 28-30].

Baseline values

The increasing availability of long term follow ups data from real world evidence is highlighting a wider variability of progression trajectories, making it also possible to identify possible prognostic factors in terms of response to treatment. The severity of functional impairment at baseline can help to predict the magnitude of changes over time and the overall progression in treated patients[13, 28-30]. The experience with the STR1VE EU trial (NCT03461289), that also allowed infants who required nutritional or respiratory support at baseline acquired milestones, who had not been included in previous trials, showed that these infants were still able to achieve important milestones such as rolling head control or sitting but these were achieved at a later age than those with no requirement for nutritional and respiratory support infants[10]. These achievement were observed outside the time frame of the study and could only be observed on the longer follow. These data have been confirmed by real world data also showing that patients with the most severe phenotypes such as tracheostomy, PEG and very low scores on the CHOP INTEND or HINE had very limited functional responses[13,31]. All together these findings strongly suggest that baseline data should be taken into consideration when discussing treatments with families in order to raise the appropriate expectations. This data also confirms that long-term follow-up of all treated children is needed to have a better understanding of the possible efficacy of the drugs that may have different timing in different individuals.

Age at treatment

With the advent of DMTs there has been an attempt to define more precise "trajectories of drug's efficacy" according to age and type of SMA. Both clinical and preclinical data indicate that early treatment will be critical to modulate the rapid and progressive degeneration seen in SMA, especially in type I as demonstrated both in clinical trials and in real world data[4, 13, 31].
The interpretation of treatment efficacy becomes even more difficult in type II and III patients who have more variable trajectories even in untreated patients. Natural history studies consistently show that there is an overall progression in both type II and type III and that this progression is not linear. In type II there was an overall stability or even a trend to improve until the age of 5 years, followed by a steep deterioration until puberty and a relative stabilization after that[32-34]. After the age of 14 years some difficulties are related to the fact that all patients had a scoliosis > 50° and had more severe contractures. In type III the stable phase with a. trend to improvement is up to 7.5 years followed by a decline that is more obvious for the children who have onset of clinical signs before the age of 3 years (type III a). These patients have a higher risk of losing ambulation[32].
Because of this variability in progression in different age groups in untreated patients, the response to treatment can only be appreciated by comparing the results of the treated patients to age appropriate controls[35]. In younger children in whom there is already stability or minimal improvement the expected therapeutical response should exceed the improvements observed in natural history. In the patients who are in the in the steep decline phase, who, in the absence of treatment consistently lose points on a yearly basis, a minimal improvement or even stability would be clinically meaningful.

SMN2 copy number: the role of 4 copies

The updated recommendations on standards of care have reported consensus on the need to routinely assess SMN2 copies at the time of diagnosis as the number of SMN2 copies is currently the main SMA phenotype modifier[1]. Lower SMN2 copy number correlates with increased disease severity, rapid disease onset, and poor prognosis, even if this, however, does not always hold true for individual cases[36]. As expected, individuals with higher copy number have more often milder phenotypes but the magnitude of responses does not always correlate with the copy number.
Over the last few years there has been more attention to individuals with 4 SMN2 copies, especially when these are detected during neonatal screening. There is no consensus on the immediate treatment of patients with four or more SMN2 copies, as these patients do not typically present as early or severe forms of SMA[37]. So far none of the clinical trials in presymptomatic patients has included infants with 4 SMN2 copies. Because of this, even in countries where treatment is available for all the infants identified by NBS, irrespective of the copy number, not all clinicians or families opt for early treatment. The difficulties in predicting the severity of the phenotype in patients with 4 copies is further complicated by the lack of validation and reproducibility data on SMN2 copy number determination among different laboratories[38]. This issue is even more relevant for patients with higher number of SMN2 copies, with increasing evidence of discordances between different laboratories in cases of retesting. Recently our

group, with a nationwide approach, has contributed to expand the existing literature on 4 SMN2 copies, confirming that even if none of the individuals in our cohort had the most severe SMA types, there was a variability of phenotypes in the untreated populations with a frequent risk of progression and in some cases, loss of ambulation[38]. The availability of detailed information from a large cohort, including the risk of developing more severe phenotypes, will help families and clinicians to make a more informed decision on early therapeutic intervention.

New models of analysis

The availability of multiple sources on real world data has prompted the suggestion to use new models of analysis for a better interpretation of the results. In a pilot study we have explored the possibility to develop a predictive model based on machine learning to explore and quantify the influence of clinical variables on functional scales[39]. The results of our pilot study, even though limited by the single centre cohort, clearly demonstrates the feasibility to use artificial intelligence and trained models for the prediction of individualized trajectories of disease progression using individual variables.

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Conflicts of interest statement

EM is PI and has participated to advisory boards for Biogen, Roche, Novartis and Scholar Rock.
MCP declares personal fees for speaker activities from Biogen, Roche and Avexis
GC and MV have nothing to disclose

Authors' contributions

All four authors contributed to designing the content of the paper, in writing and reviewing the manuscript.

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