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Review

Spinal muscular atrophy: A changing phenotype beyond the clinical trials

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Abstract

Spinal muscular atrophy is a monogenic, progressive motor neuron disorder caused by deletion or mutation in the *SMN1* gene. A broad range of phenotypic severity, from very weak infants (Type 1) to ambulant children (type 3), is modified mainly by the number of copies of the "backup" *SMN2* gene. Since the discovery of the role of both genes, basic research into the pathobiology of SMA, with in vitro and animal model studies, has identified therapeutic targets. Development of clinical outcome measures, natural history studies and standard of care guidelines have contributed to the development of protocols for therapeutic drugs now under clinical investigation. Following regulatory approval of the first drug treatment for SMA in the US (December, 2016) and marketing authorization in Europe (June, 2017), the prospects for care of these patients have changed. The evolution of the phenotype of SMA now needs to be considered beyond the clinical trials. This perspective review discusses potential new trajectories in the phenotype of SMA and the need for multidisciplinary teams to prepare for this changing landscape.

Keywords: Spinal muscular atrophy; *SMN1* and *SMN2* genes; Therapeutic approaches; Evolving phenotypes; Standard of care; Combinatorial therapies; Changing epidemiology

1. Introduction

The range of phenotypes observed within classic spinal muscular atrophy (SMA) represents a continuum of one genetically defined disease, from very weak infants to ambulant children and adults. Various eponyms, terminology and classification schemes evolved in the century following Werdnig's and Hoffmann's early reports in the late nineteenth century, as the full expression of the disorder was identified [1]. There has been an evolving process over the past three decades to classify and divide SMA into the three most common types 1, 2 and 3 based on age of symptom onset and maximal motor function achieved [2]. This classification has been useful, to a degree, for predicting survival and motor function, but has its limitations as the predictive value is only to a moderate degree [3]. In some aspects this schema has been rather rigid, creating some chaos among clinicians studying SMA [4]. Following the discovery of the causative gene for SMA [5], *SMN1*, and the rescue gene, *SMN2*, there has been substantial investigation in genotype–phenotype relationships and pathology of the disease. *SMN1*, absent or mutated in all patients [6,7], is considered the determinant of the disease, whereas its highly homologous counterpart, *SMN2*, present in all patients, is viewed as a modifier of the phenotype [8,9]. Indeed, the number of copies of the "backup" *SMN2* gene is inversely related, in a general sense, to the severity of the phenotype. This correlation, however, is not absolute and prediction about the course in individual SMA patients should account for clinical features in the patient, to include the age of onset and achieved milestones. The generation of laboratory animal models in 2000 and onwards (reviewed in [10]), has allowed remarkable progress in the knowledge of the genetic basis and relevant aspects of the pathobiology of the disease. As naturally occurring animal models for SMA do not exist, these transgenic mice and knockdown porcine models likely have limitations in their ability to reflect all aspects of the human condition. Besides the current pathology described in humans [11] what is needed is a model for humans with SMA, covering the full spectrum of phenotypes that incorporates the various clinical features and predictive and prognostic biomarkers [12]. The SMN protein is ubiquitously expressed and theoretically required for the normal function of all cells

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by impacting various aspects of RNA metabolism through its recognized function in the assembly of the spliceosomal complex of proteins. SMN also plays an important role in other processes (reviewed in [13]). The precise function of SMN in motor neurons and the possible consequences of its reduction in other types of neurons and glia and in other organs still need definition. What is clear is that there is a differential sensitivity to a deficiency of SMN protein, with motor neurons being the most vulnerable. Treatments that partially restore the levels of SMN protein only in motor neurons may, over time, unmask the effects of chronic SMN deficiency in other tissues. Thus, intrathecal delivery of drug may limit systemic exposure and make these non-CNS tissues vulnerable to chronic SMN deficiency. Despite these unsolved issues, a substantial body of successful research has led to the development of preclinical advanced therapies and the discovery of targeted treatments. Following regulatory approval of the first drug treatment for SMA in the United States in December 2016 and marketing authorization in Europe in June 2017, there is now an even more urgent need to consider how the clinical features of SMA will be altered and to prepare for future evolution of this disorder. This perspective review presents an overview of this anticipated changing scenario of SMA as the phenotype changes/modifies/transforms (Fig. 1).

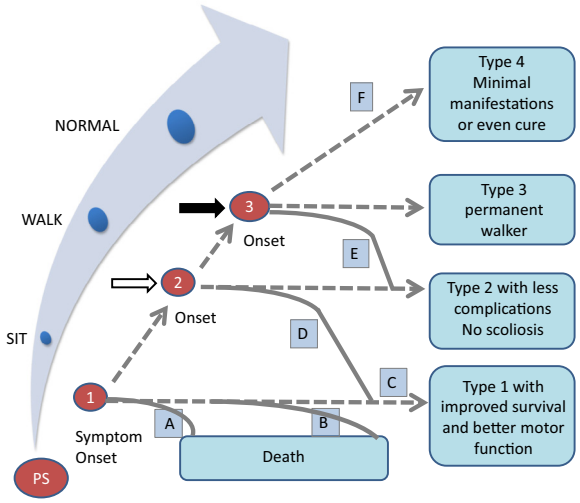

Fig. 1. Hypothetical changes in Type 1 SMA phenotypes. Circles represent SMA types ranging from presymptomatic (PS) to Type 3 disease. A typical Type 1 patient under treatment may not be responsive to therapy and has its natural history to death. Alternatively, it could reach more survival or better motor function without changing the SMA type or change the SMA type in onset and evolution time. A similar trajectory can be hypothesized for a Type 2 (starting in the white arrow after sit) or Type 3 patient (starting in the black arrow after walk). A: Parabolic curve, with brief period of maximal motor function followed by rapid decline and death. This represents a Type 1 infant who received palliative care. B: Plateau phase at maximal motor function, followed by a more gradual decline and eventual death. This is the projected curve for a typical SMA Type 1 infant who received pro-active nutritional and ventilation support. C–E represent increasing levels of response to a therapeutic drug. C: Sustained plateau phase, without loss of motor function or related feeding and respiratory status. D: Type 1 attains sitting (i.e. becomes a Type 2), then loses that skill and reverts to a Type 1, but is stronger overall and with a better survival. E: Type 1 becomes a Type 2, then attains walking (i.e. becomes a Type 3), or a Type 2 attains walking, with a plateau phase then a more gradual loss of function back to a Type 2. F: Functional cure – no motor, respiratory, feeding or orthopedic impairment, with sustained benefit over time.

2. The impact of improved supportive care

Clinical care for infants and children with SMA has advanced significantly over the past two decades. Newer technologies, such as cough assist devices, non-invasive ventilation support, and gastrostomy tube placement, now offer home-based pulmonary and nutritional management that previously was only available in hospital. These interventions have increased the survival of Type 1 infants, albeit often at the cost of ventilator and feeding tube dependence [14]. Motor function, however, fails to improve in Type 1 infants despite these supportive measures [15]. A consensus statement for standard of care guidelines in SMA, published in 2007 [16], summarizes suggested approaches to the diagnosis and management of patients with SMA. An updated version has a goal of minimizing the diagnostic odyssey and optimizing quality of life and independent function for these patients [17]. In addition, clinical trials in SMA have typically stipulated that participants adhere to these standard of care guidelines. As such, these guidelines have assumed a larger role of defining what is meant by optimal or even required care. The actual impact of implementing these uniform guidelines, however, remains unclear [18,19,20]. Physicians and parents of Type 1 infants have struggled with the ethical quandary of deciding between palliative (comfort) care and proactive (supportive) care when there was no effective treatment available for the underlying disorder, and prolonged survival was without the prospect of improvement in motor function [15].

3. The therapeutic landscape in 2017

Several targeted treatment strategies have evolved over the past decade to increase SMN protein in at least motor neurons of the spinal cord and brain stem. From a therapeutic perspective, a precise focus in drug development has targeted the *SMN* genes in two ways: (1) transfer of a correct version of the *SMN1* gene using a scAAV9 vector [21], and (2) the modulation of *SMN2* pre-mRNA splicing by antisense oligonucleotides (ASO) [22] or by small molecule drugs to increase the amount of full-length SMN2 transcript [23]. Recent approval of nusinersen, an ASO, is a landmark event [24]. This drug is delivered by repeated intrathecal injections. Improved survival without need for permanent ventilation and improved motor function were demonstrated in an open label study [25]. Preliminary positive results have been reported from two phase 3 randomized sham-controlled clinical trials of symptomatic infants (ENDEAR) [26] and children (CHERISH) with SMA [27]. On the other hand, systemic delivery of the scAAV9 vector and the oral splicing modifier drugs now under clinical development may offer added benefit to muscle and other tissues. That is, targeting motor neurons is necessary but may not be sufficient to achieve an optimal response. Nor is the durability of the effect of these treatments known. Furthermore, SMN-independent strategies, such as neuroprotection [28], enhancement of neuromuscular transmission [29] or myoactivation [30], are also under clinical investigation (For SMA ongoing human protocols see

Table 1
Issues on therapy in SMA: whom, what, where and when (w.w.w.w.).

Whom:
1. **All SMA patients?** Severe Type 1 SMA and chronic Type 2 and 3. Type 1A (or 0) may be beyond rescue at the time of birth. The effect of therapy on long term survival in type I patients is unknown. Adults with type 3b or 4 need to be considered as well, with attention to the burden of the therapy versus the potential benefit to be accrued.
2. **Pre-symptomatic patients?** This raises the topic of newborn screening. Feasibility has already been demonstrated. Relevant ethical considerations and protocols should be established to decide therapy in pre-symptomatic cases with 3 or more SMN2 copies.
Changes are expected in the corresponding predicted trajectories of each SMA type (Fig. 1).
What:
1. **SMN dependent**: SMN1 replacement, SMN2 splicing modulation
2. **SMN independent**: Neuroprotection, enhancement of neuromuscular transmission, myoactivation/muscle trophic agents.
Current measures for standard of care would continue to be part of the following-up strategies and interventional measures (Fig. 2).
Where:
1. **Central therapy.** Clearly motor neurons need to be targeted. This can be accomplished with intrathecal ASOs, intrathecal or systemic neurotrophic vectors, or oral small molecule drugs. Other neuronal types may be targeted.
2. **Peripheral therapy**. There is evidence from research in animal models and patient observations that peripheral therapy including neuromuscular junction and muscle would be necessary.
Combined central and peripheral therapy seems reasonable (Fig. 2).
When:
1. **Therapeutic window:** There is an interval of time in which dysfunctional MN and NMJ function determines part of the patient's symptoms, followed by MN death. The sooner the treatment is initiated implies a better residual capacity of MN response. An argument can be made for neonatal treatment in early detected cases, at least for those individuals with a SMN2 copy number of 2 or 3, and not to wait until the patient becomes symptomatic.
2. **Frequency of administration**: Gene transfer therapy may be a single dose treatment with life-long benefit. It is unclear if retreatment will be needed or is possible. Other strategies such as ASOs or small molecule splicing modifiers are envisaged to be administered life-long to the patient (Fig. 3).

Abbreviations: ASO, antisense oligonucleotide; MN, motor neuron; NMJ, neuromuscular junction.

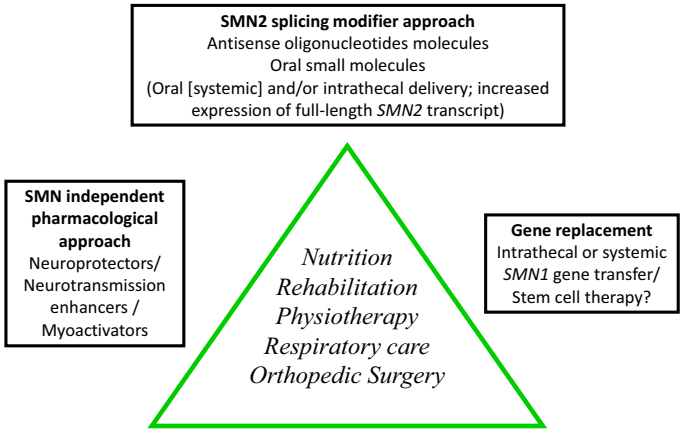

Fig. 2. The combination of therapies in SMA (part 1): The interior of the triangle includes the current standard of care measures. Different approaches are represented outside the triangle which will be integrated into the triangle when the efficacy is clearly proven.

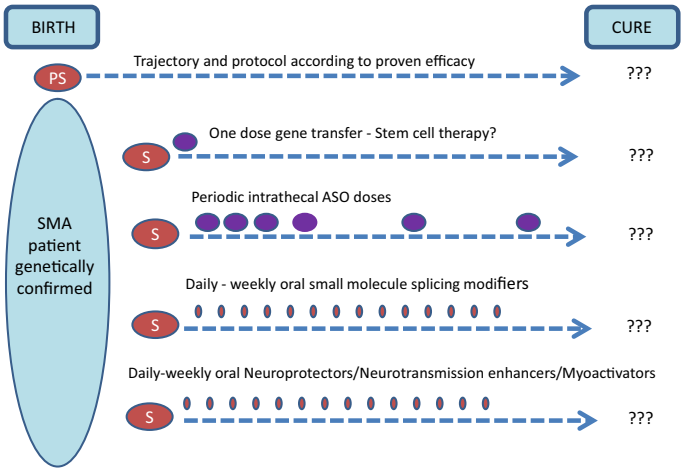

Fig. 3. The combination of therapies in SMA (part 2). Therapy approaches currently under clinical investigation in SMA show different mechanisms, administration route and administration schedule to apply in future protocols of treatment either in symptomatic (S) or presymptomatic cases (PS). ASO: anti-sense oligonucleotide.

www.clinicaltrials.gov). The developments of therapies with different targets (motor neurons, neuromuscular junction, muscle, other cells and organs) and different mechanisms of action (gene replacement, inclusion of exon 7 in SMN2, energy and metabolism of the cell) sow the field for future combinatorial approaches that could be strategized for specific SMA types and age groups (see Table 1 and Figs. 2 and 3).

4. Changing epidemiology and phenotype in severe SMA

Type 1 SMA, accounting for approximately 50–60% of all SMA [7,8], presents with severe, acute and life threatening disease and is perhaps the most suitable form to determine categorical changes in prognosis, course and outcomes [31].

Thus, with the advent of drug treatment for SMA it is timely to consider the different trajectories for survival and motor function that may result (Fig. 1). Clinicians need to be prepared to see a new phenotype of SMA evolve with altered motor repertoire. The classic pattern of proximal > distal weakness in the lower > upper limbs may be altered. The various aspects of the motor unit – motor neuron cell body, axon, neuromuscular

junction and muscle – may not respond to the drug treatment at the same time or be sustained to the same degree long-term. Clinicians will need to observe for new patterns of muscle fatigue that might evolve, e.g., a myasthenic pattern. A more comprehensive assessment of fine motor, language and cognitive development will also need to be considered.

Pre-symptomatic infants with SMA can now be identified either by pre- or post-natal testing of infants at risk (due to the parents having a prior affected child with SMA) or from newborn screening. Should such infants be treated pre-symptomatically several fundamental aspects of the disease may be altered: age of symptom onset; tempo of acquisition, retention or regression of motor milestones; bulbar, respiratory, and orthopedic (scoliosis, contractures) functions could be favorably impacted in various ways. These range from remaining asymptomatic and having normal growth and development (a cure), to having no impact whatsoever, and with several intermediate possibilities (Fig. 1): (1) delayed onset of SMA symptoms, but then develops the typical motor, feeding and respiratory features of type 1 SMA and rate of progressive deterioration; (2) delayed onset with a slower than normal acquisition of some unexpected motor function skills, such as achieving sitting or walking, but reaches a plateau; (3) delayed onset with slow but steady acquisition of full motor function. Maximal motor function may be sustained as the child grows or might falter over time. Change in motor function may or may not align with stabilization or improvement in bulbar function (ability to handle oral secretions, feeding, vocalization), respiratory function (need for ventilation support and effective cough) or orthopedic issues (scoliosis and joint contractures). Furthermore, longitudinal gains in weight, length, and muscle mass also need to be monitored and interpreted in the context of the response to treatment.

The basic concept is that these new treatments may transform Type 1 patients into a novel mix of motor function, respiratory, feeding and orthopedic features; generate progress into typical or new forms of Type 2 or 3 SMA, reverse the phenotype to allow the cure of the disease, or generate an entirely new form of SMA with different clinical features. The time necessary to observe this phenomenon is yet unknown. Such hypothetical changes may be transient then regress.

The anatomic localization of motor neurons within the ventral horn and brain stem motor nuclei may be relevant to considering drug delivery to these target cells. Medially located motor neurons in the ventral horn innervate axial muscles and laterally located ones to limb muscles, where dorsal and ventral location is related to flexor and extensor muscles respectively [32]. Intravenous administration of a drug that crosses the blood–brain barrier needs to consider the vascular supply to the spinal cord, and intrathecal administration of drug depends on absorption of drug into these tissues. As such, both of these drug delivery techniques may result in uneven delivery of drug to motor neurons. These considerations could result in some muscle groups responding better than others, which in turn could affect the type and sequence of motor changes observed. These infants may not progress through motor development in the normal sequence, i.e. rolling over before sitting is achieved. Thus, changes in the SMA course are expected to make necessary a dynamic observation of the effect of therapies to determine the resulting phenotypes ranging from delayed onset, stopping, reversing or even rescuing or curing the disease (Fig. 1). This also raises a fundamental question about implementing palliative care or conversely, to adopt hard reactive measures if critical complications appear in these babies. In view of all these remarks and given that approximately 50–60% of SMA cases are Type 1 [7,8], the possibility of treatment would unavoidably increase the prevalence of Type 2 (or 3) cases, changing the health care scenario and the family burden facing the disease. Related ethical considerations would also need to be revisited.

5. The new phenotype

Non-CNS organ system dysfunction may become evident due to chronic SMN protein deficiency [33,34]. Autonomic nervous system dysfunction, chronic ischemic injury, and glucose dysregulation have been noted in animal models for SMA and in human observations, particularly in severe cases, and will need to be monitored [35]. Cardiac, renal, gastrointestinal, hepatic, endocrine and hematologic-immune systems will also bear close attention as these children grow. Subcellular issues such as mitochondrial dysfunction and re-dox stress may prove to have chronic secondary effects in children and adults living with SMA. As in the case of Pompe disease, the initial muscle weakness with prominent respiratory involvement may evolve to a condition that results in manifestations across body systems [36,37].

Neuropathology studies have demonstrated changes in the thalamus and other brain regions [11,38]; it is not known, however, if there is related cognitive impairment in the envisaged *new chronic* Type 1 children. Children with spinal muscular atrophy have a general intelligence in the normal range. By adolescence some environmentally mediated aspects of intelligence have been reported higher in patients with spinal muscular atrophy [39]. This topic has not been studied in detail in the type 1 population. Thus, if therapy is successful to improve motor function and to overcome complications, there may be opportunities to integrate these more chronic SMA patients into society.

The alert clinician will need to be prepared to identify these and other unsuspected issues as the face of SMA evolves. A multidisciplinary team, to include a neurologist, physiotherapist, dietitian, and pulmonary and orthopedic consultants, as well as psychological support should ideally follow up both the yet untreated patients as part of providing standard of care and patients that undergo specific therapies. These measures will help to warrant proof of benefit of “extended” therapies and proactive actions to avoid new unexpected clinical complications.

6. Changes in chronic intermediate and mild forms of SMA

In milder forms of SMA disease we deal with different scenarios. Type 2 intermediate disease manifests typically after 6 months of life, when babies have already achieved the skill of sitting. The clinical phenotype ranges from those weak

patients that could loss the capacity to sit later in life to the other extreme, strong cases that reach standing and may perform some walking with help. These Type 2 patients often have a long plateau phase of several years where there is no loss of milestones and only small declines in motor function scales are seen over a 2 to 4 year period [40]. These changes in motor function, both improvement and decline, focus mainly on trunk and lower limb function and are more likely to occur in younger children (2 to 5 years old) and in those going through the pubertal growth spurt [41]. Thus, certain children can be identified on the basis of age to be at higher risk of change in motor function. Improvement in upper or lower limb function may differ due to differences in strength and extent of contractures. Thus, a thorough motor function assessment needs to consider these domains with appropriate test measures.

Mild Type 3a cases manifest typically after 18 months of age and by definition are able to walk independently. The age of losing their ambulant status strongly depends on the age of onset and most of the patients maintain their ambulant capacity for decades if the disease manifestations present after the age of 3 years (type 3b) [42].

Thus, the latency period to clinical onset and ergo, the therapeutic window is larger in chronic Type 2 and 3 forms than in acute Type 1 SMA and there is a longer evolution of the neuromuscular phenotype with less involvement of other systems or organs. In chronic Type 2 disease the primary endpoint in clinical trials is related to changes in the score of a motor function scale, or on occasion the gain or loss of milestones. Results from an interim analysis of a phase 3 randomized controlled trial of nusinersen in Type 2 patients reportedly demonstrated benefit as defined as a significant difference in a motor scale as compared to the sham/control arm. However, for Type 2 patients categorical issues may appear after prolonged therapy, such as delayed onset or even prevention of scoliosis, improvement of respiratory function and better nutritional status. It is reasonable to presume that pre-symptomatic or very early therapy in these cases may result in ability to stand and walk in a patient that nowadays would be lifetime confined to a wheelchair (Fig. 1).

7. Changes in the extreme ends of the phenotype, type 0 and type 4

Given the wide label approval of nusinersen for treatment of SMA by the FDA and similar recommendation by the EMA, and due to the fact that the clinical trials have been conducted only in more typical SMA type 1 infants and type 2 children, no data are available on the effect in the extreme ends of the SMA phenotype: the most severely affected infants (type 0, presenting with joint contractures, profound weakness and need for ventilation support at birth) and adult patients (Type 4, who present with slowly progressive proximal limb weakness). This older age group and the milder type 3b patients, characterized by decades of ambulation, need to be carefully monitored in order to determine therapeutic effects and minimal changes in a rather stable chronic weakness phenotype. Issues on peripheral therapy and independent SMN strategies should especially be considered for this group of patients. In this context, some clinical meaningful changes for patients and families may be important for the patient's daily life and autonomy and surely will influence their quality of life. Thus, specific quality of life and disability scales are needed to capture these aspects of living with SMA. These tools are now under development.

8. The future of SMA: central and peripheral combinatory therapy

Current approaches under clinical investigation differ in administration routes, frequency of dosing, intrathecal versus systemic delivery, and mechanisms of action. As SMA is such a devastating disease, it is reasonable to assume that a unique therapeutic solution may not be sufficient. Once the efficacy of each alternative is demonstrated separately in randomized clinical trials, a combined protocol could be elaborated according to the type of SMA patient.

Considerations for different combined schemes may vary depending on the context of application and can be summarized as whom, what, where and when (w.w.w.w.) and are showed in Table 1 and Figs. 2 and 3. Although motor neurons ideally need to be targeted early, prior to when neurodegeneration and loss occur, the temporal requirement for SMN protein in other tissues, such as muscle, especially in the growing child, is unclear at this time. Systemic therapy would be necessary to address delivery to the drugs to non-CNS tissues. Of note is that current systemic gene therapy with scAAV [21] will target only post-mitotic cells, for example motor neurons, but would not be expected to have a sustained benefit in tissues with some cellular turnover, such as muscle. In addition to orally administered compounds that modify SMN2 splicing currently under clinical investigation, systemic treatment in dividing cells will also need to be considered and investigated with other therapeutic strategies under preclinical experimentation, such as gene editing [43].

9. Final considerations

It is clear that we are facing a rapidly changing landscape in SMA due to the perspectives of new therapeutic approaches as a result of a deep knowledge of the genetic basis of the disease, better understanding of the natural history and the impact of improved means of management. This has been the result of joint efforts of clinicians, researchers, families and advocacy groups, pharmaceutical companies and regulatory agencies. SMA is perhaps at the moment the rare genetic disease with the most specific therapeutic options under clinical investigation, with the prospect to tackle its burden on these patients and change its label as a devastating and untreatable disease. As a counterpoint, the high cost of these orphan drugs may emerge as a limitation to guarantee the world wide accessibility to all SMA patients. Combination therapies with expensive drugs may at some point be prohibitive. With this therapeutic scenario, a new SMA patient is coming and multidisciplinary teams should be prepared and versatile to face the many expected and unforeseen changes to warrant the best long-term results,

and deliver the optimal return on investment with improvement in the quality of life of patients and their families.

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