Childhood spinal muscular atrophy: controversies and challenges

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Spinal muscular atrophy is an autosomal recessive disorder characterised by degeneration of motor neurons in the spinal cord and is caused by mutations of the survival of motor neuron 1 gene *SMN1*. The severity of spinal muscular atrophy is highly variable and no cure is available at present. Consensus has been reached on several aspects of care, the availability of which can have a substantial effect on prognosis, but controversies remain. The development of standards of care for children with the disorder and the identification of promising treatment strategies have changed the natural history of spinal muscular atrophy, and the prospects are good for further improvements in function, quality of life, and survival. A long-term benefit for patients will be the development of effective interventions (such as antisense oligonucleotides), some of which are in clinical trials. The need to be prepared for clinical trials has been the impetus for a remarkable and unprecedented cooperation between clinicians, scientists, industry, government, and volunteer organisations on an international scale.

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Introduction

Spinal muscular atrophy is a neuromuscular disease characterised by degeneration of α motor neurons in the spinal cord, resulting in progressive proximal muscle weakness and paralysis. The classical form of the disorder is caused by a genetic mutation[1] in 5q11.2–q13.3, affecting the survival of motor neuron (*SMN*) gene.[2] The severity of classical spinal muscular atrophy is highly variable and patients with heterogeneous clinical features can be classified into four phenotypes on the basis of age of onset and maximum motor function achieved.[3] No cure for spinal muscular atrophy is available but improved understanding of the mechanisms underlying the disease has enabled the development of preclinical models to test potential therapeutic approaches.[4] Some compounds are already being tested in clinical trials and others are likely to be available for testing in the next few years. These advances have provided the prospect of a possible cure for physicians and families who are willing to proactively manage the disease.

The increased attention to early diagnosis and to several aspects of management of spinal muscular atrophy has stimulated the development of clinical guidelines and standards of care,[5,6] which have affected survival and the disease's natural history. Studies of the most severe form of spinal muscular atrophy (type 1) have shown that survival beyond 1 year of age has improved as a result of the introduction of non-invasive ventilation and enteral feeding.[7,8] By contrast with older investigations, which provided evidence of a progressive disorder, more recent studies of the course of type 2 and 3 spinal muscular atrophy have shown that motor and respiratory function do not change over a 12 month period.[9,10] However, no consensus exists for numerous clinical aspects (eg, management of scoliosis or fundoplication in type 1 spinal muscular atrophy) of the disease.[5]

Our aim is not to provide a comprehensive Review of spinal muscular atrophy or therapeutic approaches—such reports are already available.[5,6,11] Instead, we focus on the most recent advances in the field of spinal muscular atrophy, and particularly on aspects of care and methods of assessment that can be used both in clinical practice and as trial outcome measures. We discuss aspects of care for which consensus has been reached and those that are still controversial. We review natural history data for the different forms of spinal muscular atrophy with paediatric onset, aiming to establish how earlier diagnosis, and improved understanding of the complications of the disorder and how to prevent and treat them, have affected patients with this debilitating disease.

Diagnosis and classification

The first diagnostic test for a patient with a normal or only mildly increased serum creatine kinase concentration who is suspected to have spinal muscular atrophy should be a search for a homozygous deletion in *SMN1*. The absence of *SMN1* exon 7 (with or without deletion of exon 8) confirms the diagnosis of spinal muscular atrophy. The test has 95% sensitivity and nearly 100% specificity.[5]

If mutation analysis is negative, laboratory investigations including electrophysiological tests such as electromyography and nerve conduction tests should be done. If electromyography suggests a motor neuron disease, then further testing for *SMN* mutations should be undertaken. Genetic tests offer quick and reliable *SMN1* gene copy-number testing by multiplex ligation-dependent probe amplification or real-time PCR. Semiquantitative assays improve diagnostic sensitivity up to 98%.[12,13] If the patient has one copy of *SMN1*, the coding region of the undeleted allele should be sequenced to identify the second causative mutation, usually subtle sequence variations such as point mutations, insertions, and deletions. Sequence analysis of *SMN1* is recommended for patients who have typical symptoms, two copies of *SMN1*, and who are born to consanguineous parents or originate from genetic isolates. Patients homozygous for minor point mutations in *SMN1* have been reported, albeit rarely.[14]

A large study[15] based on data from 68 471 individuals showed that high-throughput population testing for carriers

is feasible. The results showed a carrier frequency of one in 54 and a disease incidence of one in 11000. Carrier frequency was slightly higher in white US (one in 47) and Taiwanese (one in 48) participants than in African Americans (one in 72).[15,16]

Spinal muscular atrophy is conventionally classified into four phenotypes on the basis of age of onset and highest motor function achieved, with an additional phenotype (type 0) to describe the severe forms of antenatal-onset spinal muscular atrophy (table 1).[3] This classification has several clinical advantages but is not always adequate to provide prognostic information or to facilitate stratification of patients in clinical trials.

In clinical trials, type 3 patients who have lost the ability to walk independently in childhood are often grouped as non-ambulant, or sitters, because they can be assessed with the same outcome measures. The number of copies of *SMN2* might correlate with the severity of the phenotype and could be used as a biomarker in classifying patients for clinical trials. Although studies have shown that patients with a higher number of copies have, as a group, milder phenotypes, prediction of phenotype is not always accurate in individual cases.[12,17,18]

Standards of care and controversies in management

A consensus statement[5] for standards of care was published in 2007, and is being updated. The document provides guidelines for aspects of diagnosis, assessment, and monitoring for which there was consensus among experts. Table 2 summarises aspects of assessment and management for which consensus was reached. Agreement has not been reached for several areas of care. The lack of agreement about some questions of assessment and management, such as management of scoliosis, is the result of different approaches in different countries and an absence of controlled comparative studies. For other aspects of care, such as the choice between palliative care and intervention in type 1 spinal muscular atrophy, the absence of consensus is related to difficulties in defining standards of care without considering caregiver burden and ethical and personal issues. The application of practice standards can be limited by cost or different health-care delivery systems.

Palliative care in type 1 spinal muscular atrophy

Intervention in type 1 spinal muscular atrophy increases survival,[7] but the choice between intervention and palliative care is not always easy. The best practice is to provide accurate information. The palliative care team should meet the family soon after diagnosis to help them to understand the difference between prolonging life and improving quality of life in terms relevant to their choices for intervention. The team can facilitate discussion between family members who might differ in their opinions about what might be best for the child. They can liaise between the clinicians directing the child's care and the family, who might have many questions but be reluctant to challenge the primary care provider. They might also help to put the child's family in contact with other families who have been faced with similar challenges in the past and with advocacy support groups that can provide information for the families of newly diagnosed patients with spinal muscular atrophy.

Ventilatory support in type 1 spinal muscular atrophy

The natural history of type 1 spinal muscular atrophy has changed substantially in the past decade because of the availability of new technology and the implementation of an aggressive approach to improve survival and quality of life.[19] Non-invasive ventilation can be used at a very young age—as early as the neonatal period—because interfaces are now available for small infants.[20] Bi-level positive airway pressure ventilation can be provided at home with a face mask. Such technology enables the introduction of non-invasive ventilation while the infant is still reasonably healthy, as soon as or before paradoxical respirations are visible. Some infants might object to using a mask but most adjust quickly and sleep easily while being ventilated.[21]

As weakness progresses, the requirement for ventilation might increase from 4–6 h per night to almost 24 h

	Age of onset	Maximum function achieved	Prognosis	Proposed subclassification	*SMN* copy number
Type 0 (very severe)	Neonatal with prenatal signs	Never sits	If untreated, no survival beyond the first months after birth	..	..
Type 1 (severe)	0–6 months	Never sits	If untreated, life expectancy <2 years	1A, head control never achieved, signs in the neonatal period; 1B, head control never achieved, onset after neonatal period; 1C, head control achieved, onset after neonatal period	One or two copies of *SMN2* in 80% of patients
Type 2 (intermediate)	7–18 months	Sits but never stands	Survival into adulthood	Decimal classification according to functional level, from 2·1 to 2·9	Three copies of *SMN2* in >80% of patients
Type 3 (mild)	>18 months	Stands and walks	Survival into adulthood	3A, onset of weakness before 3 years; 3B, onset of weakness after 3 years	Three or four copies of *SMN2* in 96% of patients
Type 4 (adult)	10–30 years	Stands and walks	Survival into adulthood	..	Four or more copies of *SMN2*

Table 1: **Classification of spinal muscular atrophy**

	Pulmonary		Gastrointestinal and nutritional		Orthopaedic and rehabilitation	
	Assessment and monitoring	Assistance and intervention	Assessment and monitoring	Assistance and intervention	Assessment and monitoring	Assistance and intervention
Non-sitters	Assessment of cough effectiveness; respiratory muscle function tests; overnight oximetry; standard oximetry	Airway clearance; cough assistance; chest physiotherapy; nocturnal non-invasive ventilation (if nocturnal ventilatory failure); non-invasive ventilation (if daytime ventilatory failure)	Assessment of feeding (speech or occupational therapist); videofluoroscopy (if indicated); search for signs of reflux	Gastrostomy (if aspiration or poor efficiency of feeding); Nissen fundoplication (if appropriate)	Physical and occupational therapy assessment (posture, contractures); hip and spine radiography; bone health	Equipment and devices for posture; splinting to preserve range of motion should be considered; no consensus on orthosis or surgery in scoliosis
Sitters and ambulant patients	Assessment of cough effectiveness; respiratory muscle function tests; forced vital capacity (patients >5 years); overnight oximetry	Airway clearance; cough assistance; chest physiotherapy; nocturnal non-invasive ventilation (if sleep-disorder breathing); immunisation and respiratory syncytial virus prophylaxis (when appropriate)	Assessment of feeding (speech or occupational therapist); videofluoroscopy (if indicated); search for signs of reflux	Optimise caloric intake with supplements (if not adequate intake but safe swallowing); gastrostomy (only if aspiration or poor efficiency of feeding after calories supplemented orally); medical management (when appropriate)	Physical and occupational therapy assessment (posture, contractures, strength); assessment of power and manual mobility	Contracture management and exercise; orthoses

Table 2: **Standards of care for pulmonary, gastrointestinal, nutritional, and orthopaedic care and rehabilitation**

per day. With full-time ventilation the upper airway can become damaged, resulting in oedema, increased secretions, and bleeding. Such complications in the airway or intercurrent infection can necessitate intubation. Whether to proceed to tracheostomy with long-term invasive ventilation is an individual choice for the child's family. Many centres ask the palliative care team to offer support and advice to families who have to make difficult decisions. Most families opt to withdraw support when the child needs invasive ventilation. Children with type 1 spinal muscular atrophy who undergo tracheostomy and long-term ventilation remain dependent on ventilators for the rest of their lives. Some ventilator-dependent children attend school with the help of a carer. Some patients are at high risk of recurrent hypoxia, which is associated with brain injury.

The goal of intervention should always be to improve quality of life of the child, not to prolong life. Non-invasive ventilation in infants with spinal muscular atrophy can prevent or even reverse changes in the shape of the chest wall, increase lung growth, and slow the loss of chest wall compliance.[22] The ultimate aim should be a decreased rate of infection and hospital admission, both of which can affect the quality of life of the child and his or her caregivers. The cost-effectiveness of these approaches has not yet been assessed.

Parenteral feeding in type 1 spinal muscular atrophy

Decreased feeding is often the first sign of progressive weakness. When breastfeeding, the child might have prolonged feeding times, cough while feeding, and tire quickly. Weight gain slows and then halts, and eventually weight is lost. Because poorly nourished children become fatigued and are more susceptible to infection, early gastrostomy is recommended. The surgery can be done soon after diagnosis and while the infant is healthy, and nocturnal feeding can be initiated to supplement calories as oral feeding decreases. Even if the family decides against ventilation therapy, they might choose to proceed with gastrostomy. Gastrostomy can improve quality of life because the child will not be hungry even though he or she cannot safely eat. Fundoplication for type 1 patients at the time of gastrostomy placement is still controversial.

Cardiac findings in type 1 spinal muscular atrophy

Some patients with severe type 1 spinal muscular atrophy (usually those who have one copy of *SMN2*) have heart defects,[23,24] mostly atrial and ventricular septal defects, and possible involvement of the autonomic system, which might cause arrhythmia and sudden death. Some reports suggest that cardiac assessments should be done in patients with type 1 spinal muscular atrophy, but larger studies are needed to obtain more information about the prevalence, onset, and severity of cardiac symptoms.

Management of respiratory function in non-ambulant patients

Respiratory complications in type 2 or non-ambulant spinal muscular atrophy patients are less severe than in type 1. Implementation of standards of care and use of non-invasive ventilator support have substantially improved survival and quality of life. The methods of assessment and monitoring are quite similar to those used in type 1. Physical examination and assessment of cough effectiveness with respiratory muscle function tests should be routinely undertaken. Forced vital capacity should be measured in children older than 5 years. Overnight oximetry should be regularly done, especially in patients with severely reduced vital capacity (<65% predicted) or with clinical signs of nocturnal hypoventilation. Nocturnal hypoventilation should be treated with non-invasive ventilation.[25]

Airway clearance is important and there is evidence that assisted cough has a role in both prevention of infections and reduction of treatment duration. Availability of mechanically assisted cough varies by country and although widely accepted as a part of the management of severe cases, its use in less severe cases is limited by cost. Further studies are needed to test the extent to which daily assisted cough can decrease the number of infections requiring hospital admission and to provide evidence for overall cost-effectiveness.

Feeding and nutrition

Feeding and swallowing difficulties are not uncommon in sitters and walkers. Gastro-oesophageal reflux might be present but a questionnaire investigating subjective symptoms of reflux did not support the routine diagnostic use of oesophageal pH monitoring.[26]

Growth failure can occur for various reasons, from reduced intake because of masticatory muscle fatigue or prolonged meal times, to recurrent respiratory infections. Development of dysphagia because of progressive weakness of bulbar and oesophageal muscles can be insidious in adolescents with type 2 spinal muscular atrophy.[27] Video swallow studies are helpful in the assessment of a patient's chewing and swallowing.

At the other extreme, reduced activity and low energy expenditure increase the risk of obesity even in patients who have an apparently adequate nutritional intake for their age. Little evidence exists about how best to monitor these patients, partly because of difficulties in obtaining accurate measures of height or body mass index in patients with spinal muscular atrophy in whom lean body mass is reduced.[28–30] Further work is required to reach a consensus for the most appropriate methods with which to measure body composition and to define optimum nutritional management,[29] including the advantages and disadvantages of supplements and special formulas for patients with inadequate nutritional intake.

Scoliosis surgery

Scoliosis occurs in almost all non-ambulant spinal muscular atrophy patients. Spinal fusion is the treatment of choice but different centres have different policies about when to do it and the role of orthotic management.[5] No consensus exists for the efficacy of braces or other trunk orthoses to slow the progression of scoliosis.[31–33] Additionally, braces might compress the thoracic cage or have a negative effect on respiratory function.[31,34]

Scoliosis surgery should ideally be done in children older than 10 years. When progression of spinal curvature allows a delay until age 10 years or older, results are satisfactory for posture but no agreement among experts exists about the effects of surgery on pulmonary function.[35–37] There is no consensus about children who develop severe and rapidly progressive scoliosis before age 5 years and new surgical treatments have been suggested for the management of skeletally immature patients. Growing rods[38] or vertical expandable prosthetic titanium ribs[39,40] can be used to prevent progression of scoliosis in very young children if bracing is unsuccessful. These techniques have been effective in controlling progressive early-onset scoliosis before definitive spine fusion,[41–43] although the specific role of each surgical technique has not been elucidated. Although growth rods can control early scoliotic curve and pelvic obliquity in young patients with spinal muscular atrophy, they do not halt rib collapse.[43] Thus, a possible role for vertical expandable prosthetic titanium ribs might be to increase the space available for lung growth and chest compliance.

Osteoporosis

It is still a matter of debate whether reduced bone mineral density in spinal muscular atrophy is related to reduced mobility or to pathophysiological aspects of the disease. Comparative studies with other disorders such as Duchenne muscular dystrophy do not provide concordant results.[44] In studies assessing dual-energy x-ray absorptiometry in children with type 2 and 3 spinal muscular atrophy, decreased bone mineral density seemed to be related more to increased age than to the ability to walk.[44] Another comparative study of 79 children with different neuromuscular disorders, particularly Duchenne muscular dystrophy and spinal muscular atrophy, showed that bone mineral density was lowest in patients with spinal muscular atrophy.[45] Bone mineral density has been used as a secondary outcome in clinical trials in patients with spinal muscular atrophy.[46]

Results of a study of the *Smn*$^{-/-}$ *SMN2* mouse model of spinal muscular atrophy showed a significant decrease in the concentrations of osteoblast differentiation markers, and an increased rate of osteoclast formation and bone resorption capacity (46%) compared with wild-type mice, indicating that *SMN* function might be involved in bone remodelling and skeletal pathogenesis in spinal muscular atrophy.[47] Improved understanding of the mechanisms of osteopenia is necessary to identify novel targets for therapeutic interventions and to establish standards of care, including clinical aspects of management, such as the promotion of weight bearing, that might help to prevent bone loss and reduce the risk of fracture.

Maintenance of independence

About half of patients with type 3 spinal muscular atrophy will lose independent ambulation by age 14 years.[48,49] Only a small fraction are ambulatory throughout life—independent mobility can be severely affected by even the mild form of the disease. The decision to recommend wheelchair use depends on several factors, one of which is how often the patient falls. Daily falls often mean that the child needs a wheelchair but possibly only for part-time use. Another factor is fatigue, whether it occurs at the end of the day or is related to distance walked. A wheelchair might only be used for long distances such as for shopping. If the child is too weak to self-propel or

becomes easily fatigued operating the chair, then a motorised chair is recommended. In some cases, the motorised chair might be necessary only for school, while the child remains ambulant at home.

For adolescents, an important part of independence is the ability to drive a car. Technology to aid driving exists for all but the completely quadriplegic. Depending on the severity of paralysis, hand-activated or voice-activated controls make independent driving possible. The patient should be assessed by a qualified occupational therapist with standardised assessment protocols and recommendations made about modification of the steering wheel, accelerator, and brake controls. Such modifications are often expensive and not covered by insurance but many families are willing to pay the cost.

Transitional care

Treatment and management for nearly all chronic diseases of childhood have improved greatly such that children are surviving into adulthood with diseases that are not well known to health-care providers for adults. Moreover, insurance coverage for childhood disease and its complications after the age of 21 years can be problematic. Children with severe chronic disease tend to be isolated, immature, and dependent on their parents.[50] Therefore, the primary provider should take the lead in initiating the transition of care from paediatric clinics to an adult service. Around 16 years of age, patients can be placed in adolescent clinics, where they see other patients of their age and where they can learn to give their own interim histories and ask questions of their providers. In some centres, adult neuromuscular medicine and pulmonary specialists attend the adolescent clinics, making the transition from paediatric clinics easier. Patients should be encouraged to learn about their disease, to focus on life after school (especially higher education), and to discuss sexuality and family planning.

Pregnancy and childbirth

All patients with spinal muscular atrophy should be counselled about the risk of having affected children. Since the disease mutation is autosomal recessive, the risk is usually very low. However, patients should be aware of the risk that their partner might be a carrier of the gene and the partner should consider genetic testing before starting a family.

Little information exists about women with spinal muscular atrophy enduring pregnancy and labour. Loss of respiratory function and mobility are the most important risks in pregnancy. During labour, the choice of anaesthesia might be affected by previous scoliosis surgery, which can preclude epidural injections. General anaesthesia might be associated with a high risk of pulmonary complications for patients who need ventilation. Lung function should be regularly monitored during pregnancy. Most women with spinal muscular atrophy have a caesarean section and are more likely to have a premature baby.[51]

Progress and controversies in translational research

In the past decade, clinical trials of several promising new therapeutic approaches have been undertaken in patients with spinal muscular atrophy,[46,52–58] reflecting the complexity of the mechanisms underlying the disorder (figure).[4,11,63–66] The escalation of clinical trial planning has raised concerns about readiness for such trials. Are enough patients identified who can be enrolled rapidly? Do we have reliable, valid, and sensitive outcome measures that can be implemented quickly and economically across many trial sites?[67–69]

Randomised double-blind placebo-controlled studies of rare disorders such as spinal muscular atrophy can only be done as large multicentre international trials. Numerous bottlenecks exist in undertaking such studies, related not only to difficulties in enrolment and stratification, but also to the need for common standards of care and consistent assessment methods and outcome measures to make data from different centres comparable.[67,70]

	Therapeutic targets	Therapeutic approaches	Trials completed or ongoing
***SMN1* gene mutation**	Replacement of *SMN1*	Gene replacement therapy	..
Alternative splicing of *SMN2* RNA	Inclusion of exon 7	Antisense oligonucleotides (new drugs developed by PTC Therapeutics, tetracycline)	New drugs developed by ISIS Pharmaceuticals
Decreased full-length SMN transcript	Increased amounts of SMN transcript	Histone deacetylase inhibitors, quinazolones, RG3039, aminoglycerides, albuterol, prolactin	Phenylbutyrate (randomised controlled trial)[52,53] Valproate (randomised controlled trial)[46,56,58] Hydroxyurea (randomised controlled trial)[59] Albuterol (open-label and ongoing randomised controlled trial)[54,60]
SMN protein deficiency	Stabilisation of SMN protein	Indoprofen, proteasome inhibitors, polyphenols	..
Loss of motor neurons	Neuroprotection	Neurotrophic factors	Gabapentin (randomised controlled trial)[61] Riluzole (open-label)[62] Olesoxime (TRO19622)
	Cell therapy	Stem cells	..
Clinical symptoms	..	..	..

Figure: **Relation between targets in the pathogenesis of spinal muscular atrophy and drug development**

Enrolment, inclusion, and stratification

International registries for patients with spinal muscular atrophy have greatly increased the chances of identifying and recruiting patients for clinical trials. Recruitment and retention in clinical trials can be difficult because families can be discouraged by invasive delivery systems (such as intrathecal injection), frequent study visits, the number of tests done, study duration, and the possibility of receiving placebo. These challenges can be addressed by multicentre international studies that require a small number of patients per centre, and by creative randomisation—eg, 2:1 randomisation or interim analyses—which is more appealing to patients and their families.

In view of the clinical heterogeneity within each type of spinal muscular atrophy, clinical trial investigators suggest that stratification should include functional measures to provide a fair representation of the different levels of activities of patients in the treatment and placebo groups. Because the number of copies of *SMN2* correlates with function,[12,18] copy number could also be used for stratification in clinical trials. Furthermore, in type 1 spinal muscular atrophy, survival and function differ between infants who receive different levels of care[7] and should be considered at stratification.

By contrast with early studies that provided evidence of a progressive disorder, more recent studies of patients who have received improved standards of care have shown that in type 2 and 3 spinal muscular atrophy motor and respiratory function do not change over a 12 month period.[71] This result should be considered when designing studies in these groups.

	Type of SMA	Measure
Myometry[61,73]	2 and 3	Assessment of strength (Newtons)
Motor function measure (MFM)[74,75]	2 and 3	Functional scale, three domains
Gross motor function measure (GMFM)[76]	2 and 3	Functional scale
Children's Hospital of Philadelphia infant test of neuromuscular disorders (CHOP-INTEND)[77]	Non-sitters or very weak sitters	Functional scale
Test of infant motor performance (TIMP)[78]	Non-sitters or very weak sitters	Functional scale
Hammersmith functional motor scale for SMA (HFMS)[79]	Sitters	Functional scale
Upper limb module[80]	Sitters	Functional scale
Expanded HFMS[81,82]	Sitters and ambulant patients	Functional scale with items from GMFM
Extended HFMS[83,84]	Sitters and ambulant	Functional scale with add-on fine, gross motor, and timed tests
6-minute walk test (6MWT)[85]	Ambulant	Measure of endurance
Egen Klassification (EK)[86]	Non-ambulant	Questionnaire of functional abilities
PedsQL, neuromuscular module (NMM)[87]	Ambulant	Quality-of-life questionnaire

Tests included in this table have been used and validated in studies of SMA (see references). SMA=spinal muscular atrophy.

Table 3: **Outcome measures most commonly used in spinal muscular atrophy**

Outcome measures

Efforts are being made to implement training for investigators and assessors in multicentre networks and to improve inter-rater reliability across centres with different expertise.[10,72] Collaboration within international networks such as the International Coordinating Committee or Translational Research in Europe—Assessment and Treatment of Neuromuscular Diseases has accelerated the development and validation of disease-specific outcome measures (table 3).[67] One of the main advantages of this collaborative effort is that input from regulatory agencies and family advocacy groups has been taken into account, as well as the clinical views of investigators and statisticians, leading to the identification of measures that are not only statistically robust, validated, and suitable for multicentre studies, but also clinically meaningful for patients and their caregivers. Although in type 1 spinal muscular atrophy survival or time to ventilation are the most important outcomes,[88] in non-ambulant and ambulant patients functional motor scales seem to be the best methods to monitor clinically meaningful changes. Numerous clinical outcome measures have been promoted by investigators, including general scales that can be used across different levels of severity[63,76,89] and others developed specifically for non-ambulant or ambulant patients[79–81,83,85,90,91] or for young infants.[78,90] Neurophysiological techniques—such as compound muscle action potential—have proved to be reliable markers of the progression of motor neuron involvement.[9,92–94] Dual-energy x-ray absorptiometry can be used to assess changes in lean mass.[60] A paediatric questionnaire on quality of life in spinal muscular atrophy has been validated.[88]

The statistical robustness of functional motor scales currently in use is being determined, for example with Rasch analysis. Because scales are usually composed of different items, using ordinal data, new methods of analysis are being used for neuromuscular functional scales to establish how the scale works and to identify possible gaps in the scale or redundant items, with the goal of converting ordinal data to linear measurement.[95] The large Common Data Element project is underway—with funding and guidance from the US National Institute of Neurological Disorders and Stroke—in which case report forms and datapoints will be standardised according to disease. The first goal of this project is to save time and money by having a central source of case report forms that would be immediately available once a clinical trial was ready to proceed. The second goal is to make data transferable and shareable for post-trial analysis.

Molecular biomarkers

SMN gene products, either transcripts (both full-length and exon 7 deleted variants) or proteins, have been considered as biomarkers.[96–98] Large multicentre studies,

such as BforSMA, have explored other candidate biomarkers. A molecular approach seems appropriate when therapy is based on increasing the amount of SMN protein produced by the residual *SMN2* genes, through promoter activation or reduction of exon 7 alternative splicing, or both. However, the reliability of these molecular biomarkers is still being investigated and none is ready for phase 3 trials.[97]

Family care

Genetic counselling for couples who have one child with spinal muscular atrophy is commonly offered. In most cases, both parents are carriers of one mutated allele. However, rarely, de novo point mutations can occur in one or both parents. If parents choose to pursue a successful pregnancy, they should be referred to a qualified genetic counsellor associated with a high-risk pregnancy management team for a discussion of options, including carrier screening, prenatal diagnosis of the fetus, use of sperm or egg donors, and in-vitro fertilisation with pre-implantation testing.

Little information exists about the frequency of use of in-vitro fertilisation and pre-implantation genetic diagnosis in families with spinal muscular atrophy. One report from Poland describes five families who had four healthy babies.[99] This procedure is prohibitively costly for most families and is generally done by private organisations with little regulation or oversight, especially in the USA. Anecdotal reports exist of affected babies being born after such procedures. Whether negative outcomes are caused by poor practice or for biological reasons is unknown.

Testing asymptomatic siblings is controversial. Several professional organisations have suggested that genetic testing in asymptomatic children might be unethical.[100] Many parents are anxious about the possibility of another child developing symptoms of the disease; since both severe and mild forms of spinal muscular atrophy can occur in siblings, their fear is not unfounded. Decisions about such testing should be made on an individual basis, taking into account each family's needs. All should be counselled that asymptomatic siblings have a 50% risk of being a carrier and so they and their partners should consider carrier screening before starting a family. Screening newborn babies is also controversial.

Conclusion

Spinal muscular atrophy is a rare disorder of infancy and childhood, the biology and pathophysiology of which have been extensively studied in the past decade. This scientific scrutiny has revolutionised our understanding of the disorder and has put an unprecedented focus on affected patients.

An immediate benefit for patients has been the development and distribution of standard-of-care recommendations. Data for improved survival in the most severely affected children with spinal muscular atrophy (type 1) are available. The long-term effect of the care guidelines on patients with type 2 and 3 spinal muscular atrophy is unclear, but some functional aspects—such as motor and respiratory function—are now reasonably stable over a 12 month period. A long-term benefit for patients will be the development of effective interventions, some of which are now in clinical trials. The need for clinical trial readiness has been the impetus for remarkable cooperation between clinicians, scientists, industry, government, and volunteer organisations on an international scale. This collaboration has resulted in improved understanding of the barriers to clinical trial readiness and the identification of possible strategies for overcoming them.

Search strategy and selection criteria

We searched Medline, CINAHL, PsycINFO, and Embase for all publications containing the term "spinal muscular atrophy" from 1990, to February, 2012. We included all relevant reports published after 2000 but papers judged to be seminal by us were included irrespective of their publication date. Articles published before 1990 were identified from PubMed and from our own files. Only papers published in English were reviewed.

Contributors

The authors contributed equally to the literature search and the writing and formatting of the Review, and to critically reviewing the manuscript.

Conflicts of interest

EM is a site principal investigator for the PTC Therapeutics (South Plainfield, NJ, USA) extension study of ataluren in Duchenne muscular dystrophy, for the TROPHOS (Marseille, France) clinical trial in spinal muscular atrophy, and for a GlaxoSmithKline study of exon skipping. He is also funded by Italian Telethon and SMA Europe for observational studies of outcome measures. He has been on the advisory board for Shire and PTC Therapeutics. EB is a site principal investigator for the PTC extension study of ataluren in Duchenne muscular dystrophy, for the TROPHOS clinical trial in spinal muscular atrophy, and for a GlaxoSmithKline study of exon skipping. He is also funded by Italian Telethon, the Italian Ministry of Health, and SMA Europe for observational studies of outcome measures. STI is a site principal investigator for the PTC extension study of ataluren in Duchenne muscular dystrophy and receives funding from GlaxoSmithKline, ISIS (Carlsbad, CA, USA), DuchEnne Muscular Dystrophy Long-term IdebenOne Study, and DART (Great Barrington, MA, USA) for clinical studies of spinal muscular atrophy and Duchenne muscular dystrophy. She has also received expenses from these companies for attendance at investigator meetings. She is co-principal investigator for the NeuroNEXT project funded by the US National Institute of Neurological Disorders and Stroke, for which she receives a salary. She is supported by the Muscular Dystrophy Association for her neuromuscular clinics.

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