Rehabilitation in spinal muscular atrophy – a challenge for the future

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Introduction

Spinal muscular atrophies refer to a large group of genetic diseases of the lower motoneuron.

The most common form, which affects 1 in 10,000 individuals, is caused by a homozygous loss of function mutation of the Survival Motor Neuron () gene, which leads to muscle atrophy and weakness by premature death of motoneurons of the anterior horn. In 95% of cases, this mutation is a homogenous deletion of exon 7 of *SMN1*.

The first standards of care were established in 2007, and a new version has recently been published (1, 2, 3). The approval of new medications since 2018 and the presentation of new phenotypes, including patients treated before the onset of symptoms, both pose new challenges for rehabilitation.

Guidelines and management

The care of spinal muscular atrophy (SMA) patients must be planned and organised by reference centres, within structures capable of meeting all the needs for providing a standard of care and for the management of acute conditions related to the disease (1,2).

A neuromuscular reference centre brings together a multidisciplinary team of medical and paramedical experts in the field of neuromuscular diseases. In addition to the neurologist or neuropaediatrician, the team consists of specialists in physical and rehabilitation medicine, an orthopaedic surgeon, a cardiologist and pulmonologist, a physiotherapist, occupational therapist, speech therapist, psychologist and neuropsychologist, coordinating nurse, social worker and dietician, supported by a team of secretaries.

Belgium has 7 neuromuscular reference centres spread over 9 sites, located in Liège, Brussels (4 centres), Ghent, Edegem, Vlezenbeek and Leuven.

Until recently SMA patients only received supportive treatments, including non-invasive ventilation and nutritional support, which in recent decades have translated into an increase in life expectancy (3-5).

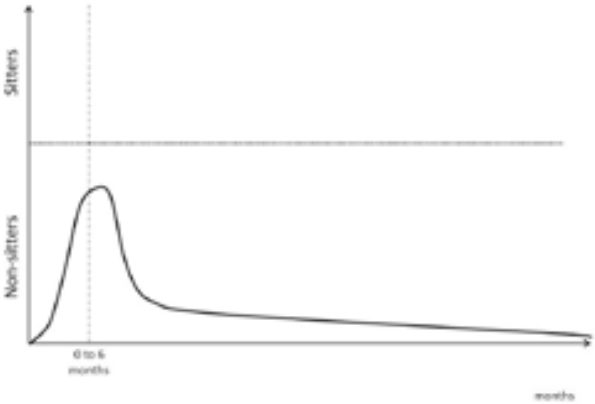
Patients' rehabilitation has for years focused on the functional ability to reduce impairments and preventing or treating complications. Good positioning, stretching, passive, assisted or active muscle work, respiratory physiotherapy and verticalisation have become individual key points in the management of SMA patients (6).

There are a wide range of phenotypes classified into clinical groups grounded on their current motor ability (non-sitter, sitter, walker) in the new standard of care or on their previous maximal achievement of motor function (type 1, 2, 3 or 4). Recommendations for physiotherapy are commonly expressed according to the patient's motor ability:

Non-sitters

For non-sitters, the goals of rehabilitation are improving motor functions, limiting deficits and improving the tolerance of the different positions (Figure 1).

Figure 1. Schematic evolution of type 1 SMA patients before the availability of disease-modifying treatments.



To achieve this goal, stretching and mobilisation, technical postural or communication aids, as well as respiratory physiotherapy are necessary. The latter is particularly important in maintaining bronchial clearance and improving alveolar recruitment.

In patients needing cough assistance, postural drainage as well as the use of intrapulmonary percussion with elastic belts can be offered. This method allows for the increase of ventilation parameters up to 30-40cmH2O. To further ensure upper airways clearance, nasobuccal aspirations should be performed on a regular basis by trained caregivers. Regular capnometry is needed to decide the onset of a non-invasive ventilation (NIV).

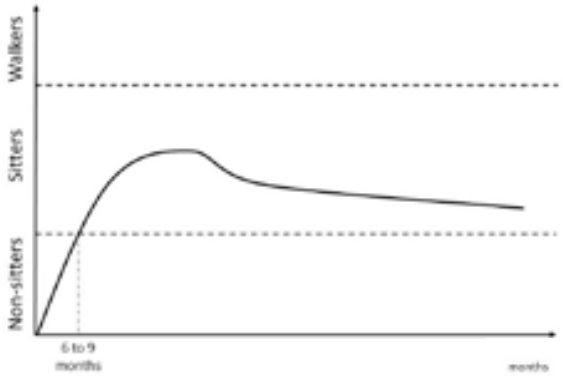
The participation of caregivers in the daily respiratory management is crucially important, and initial training as well as regular refreshment should be implemented.

Sitters

For this clinical group, the main objective will be to gain and to maintain autonomy through the installation of electronic chairs and seat corsets (Figure 2). The same principle of rehabilitation and nutrition, this time with verticalisation, will be applied. Particular attention will be paid to the spine and the high incidence of deviation, but the amplitude of all joints must be checked on a regular basis and stretched accordingly (5).

The management of the respiratory aspect will be similar to that of non-sitters.

Figure 2. Schematic evolution of type 2 SMA patients before the availability of disease-modifying treatments.

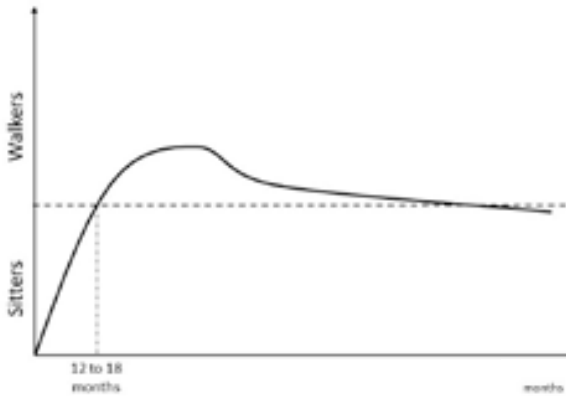


Walkers

Multidisciplinary care of the ambulatory clinical group aims to improve endurance, balance, and to maintain motor functions. Rehabilitation will ensure that good joint amplitudes are kept and that the patient is actively mobilised without causing excessive fatigue (Figure 3).

At the respiratory level, if no pro-active interventions are indicated, the maintenance of an effective cough, and the detection of hypoventilation or sleep apnea should be carefully reviewed.

Figure 3. Schematic evolution of type 3 SMA patients before the availability of disease-modifying treatments.



Disease-modifying treatments

European Medicines Agency (EMA) approval in April 2018 of nusinersen, followed by onasemnogene abeparvovec (May 2019) and risdiplam (pending), has changed the way patients and their families see the future of this disabling to fatal disease. This future is no longer about future losses but about future potential improvement, which translates into a major improvement of quality of life, even for minimal gain. Nevertheless, this raises new questions about the emergence of new challenges.

Emergence of new phenotypes and readjustment of paradigms

New therapies and clinical developments have shown that the earlier the treatment is administered, the better the results will be on the patient's motor functions and quality of life (7). For this reason, a pilot newborn screening program was launched in March 2018 in the Wallonia-Brussels Federation regions of Belgium, which screens 60,000 newborns per year. Several similar programs have also been initiated in Germany, Italy, Taiwan, the USA and Australia (8-11).

Disease-modifying treatments initiated in pre- or post-symptomatic patients have led to emerging phenotypes and thus to progressive and more proactive adjustments to standards of care. Indeed, the effects of innovative medication can be markedly different for motor, bulbar and respiratory functions. In this context, treated patients often show a rapid and clear improvement in their motor functions but remain at risk for bulbar, skeletal, respiratory and even vital progressive or rapid deterioration. A typical illustration of this concept is a young SMA1 patient with a rapid improvement in their motor skills, sometimes exceeding a weak SMA2 patient, but with severely compromised respiratory functions.

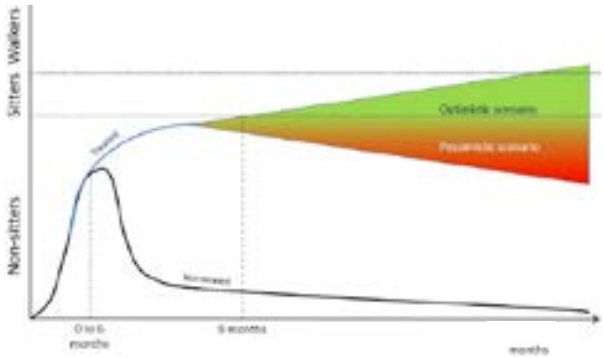
These emerging phenotypes further emphasise the importance of considering the motor achievement of patients, rather than the age of symptoms onset.

In the following sections, we will explain how concretely disease-modifying therapies influence the classical standard of care.

Non-sitters

A 1-year follow-up of non-sitting SMA1 patients treated with nusinersen, onasemnogene abeparvovec, and risdiplam demonstrates the acquisition of sitting position in approximately 60% of them (12-14). In longer term follow-ups, the proportion of patients acquiring standing position remains low (Figure 4).

Figure 4. Schematic evolution of a treated non-sitter (untreated indicated in black).



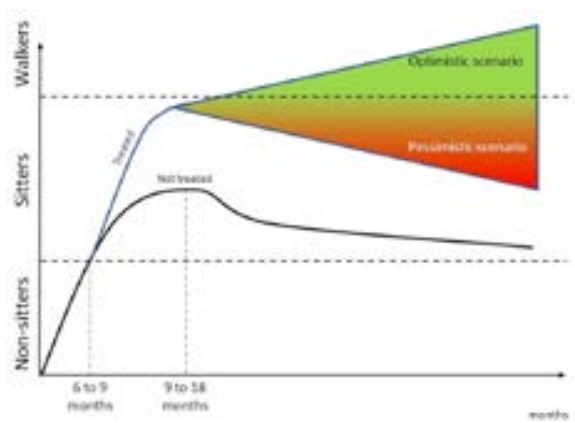
The aims of rehabilitation are to consolidate the acquired skills, by working the axial and proximal muscles and actively preventing contractures by regular and systematic stretching; and to facilitate the acquisition of new skills by active or active-assisted mobilisation. Changes of position, increasing autonomy by using chairs equipped with a seat-brace, or more simply, assisted active mobilisation and the use of standing frames are recommended. From a respiratory point of view, the emphasis is placed on the ability to achieve airways clearance on one's own, with or without technical assistance, and on the development of the lungs and the chest through the use of NIVs.

Sitters

Ambulation has been acquired in several strong type 2 patients following nusinersen treatment, leading to a specific emerging phenotype (16).

However, at least two significant issues that are not common to type 3 patients may present in type 2 patients who have become ambulant (Figure 5). Firstly, they are likely to present a lower bone density related to their previous condition of immobility (bone fragility and its treatment will be discussed later in the paper). A further issue is spine deformity, which continues to progress and requires adaptations to manage (18).

Figure 5. Schematic evolution of a treated sitter (untreated indicated in black).



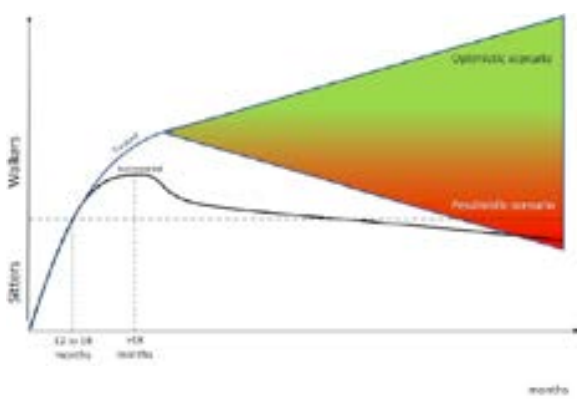
Therefore, the rehabilitation objectives will be:

1. To optimise upper limb function by passive stretching to avoid contractures, and active mobilisation to promote motor function.
2. To optimise airways clearance, especially in the context of respiratory infection, and to promote proactive pulmonary management.
3. To optimise lower limb active and passive mobility in order to facilitate potential walking acquisition. Furthermore, ankle and knee joint stretching is crucially important to avoid severe contracture limiting the chance of ambulation acquisition. Technical aids to develop ambulation autonomy such as Motilo.
4. To optimise axial strength and postural ability using technical devices to assist ambulation in the strongest patients, and suspension frames and standing frames in the weakest (15).

Walkers

There are only a limited amount of data regarding treated walkers. Nevertheless, as the natural history of ambulation in SMA is a long decline with an annual loss of 10 metres per year in the 6-minute walk test (6MWT), treated patients seem to be stable or even to increase mildly their 6MWT performance (19). The aims of rehabilitation for these patients will be to maintain ambulation on a positive trend, and to increase their walk perimeter (Figure 6). Avoiding contracture by regular stretching and exercising at moderate intensity should therefore be recommended.

Figure 6. Schematic evolution of a treated walker (untreated indicated in black).



Additional points of attention are nutrition, bone calcification and sleep quality.

It is very likely that in the coming years, several pre-symptomatic patients who have been diagnosed and treated early will belong to the 'walkers' category, and exhibit either normal motor development, or mild SMA symptoms. Follow-ups for these patients will test for any sign of muscular weakness or fatigability that could prompt treatment change. This is especially true for patients treated by one-shot gene therapy, with still remaining uncertainty about gene expression duration, and for whom add-on treatment could be needed in the future. Further developments in add-on therapies are not yet clear, although some present clinical trials aim to study the potential of treatment combination (NCT03921528)

The evolution of patient prognosis in recent decades has shown that standards of care are of primary importance to improve patients' survival, quality of life and functional outcomes (4). The new disease-modifying treatments have all been validated in patients following SOC and should be used only in this context. The emergence of new phenotypes should prompt the recognition of until-now undescribed patient's trajectories, and the implementation of new rehabilitation plans and care.

Occupational therapy

The goals of occupational therapy are similar to those of physiotherapy, but more focused on technical aids and house adaptations.

For non-sitters, it is proposed that the correct installation should aim for comfort and optimization of tolerance to various positions by using custom and moulded-seating systems, custom wheelchairs, postural supports, and sleeping systems (2). These adapted systems allow the patient to use their upper limbs more efficiently, and to achieve a better level of motor development. It is also important to find a balance between stimulation and rest time, which is essential for child development.

For sitters, one goal is to prevent contractures and scoliosis by using brace, static, dynamic and functional orthoses (2). Seat-braces can be placed on frames with wheels for indoor and outdoor use, depending on the social environment and home accessibility. Monitoring of proper installation is necessary and seat-braces can be adapted to the child's growth.

To maintain, restore or promote function and mobility in these patients, the use of lightweight manual, power-assisted, or motorised wheelchairs is recommended to promote self-propulsion. Furthermore, depending on the patient and the muscle strength of their legs, a passive or active standing support should be considered.

For walkers, the key goals are to maintain, restore or promote function, mobility and adequate joint range; and to improve balance and endurance by using limb orthosis, lightweight manual wheelchairs, or for longer distances power-assisted or motorised wheelchairs (2).

The prescriptions for technical aids follow the International Classification of Functioning, Disability and Health according to the World Health Organization guidelines.

Management of bone health

In SMA patients, it is important to monitor bone health. Indeed, bone decalcification may be responsible for non- or pauci-traumatic fractures, bone pain, or deformities that will require invasive orthopaedic treatments. Reduced mobility, reduced exposure to sunlight, and nutritional issues – including reduced intake of calcium and vitamin D, as well as obesity – are factors that increase the risk of osteopenia.

Outside its primary role in motoneurons, SMN protein is ubiquitously expressed in many tissues where it plays an important role during early involvement. It has been suggested that the lack of SMN protein in the bone tissue could directly affect calcification, but this remains yet to be formally demonstrated (17). If so, this could be a rationale for the choice of medications that target not only the motoneurons, but also peripheral tissues.

In children, the risk of fractures cannot be predicted by low mineral bone density alone. Bone fragility is defined by the presence of a non-traumatic vertebral fracture, regardless of the mineral bone density or the occurrence of long bone fractures (fewer than 2 fractures or absence of traumatism) associated with a z-score of less than 2 SD.

The indications for treatment with bisphosphonates are not yet well defined. However, there is a broad consensus regarding basic prevention: calcium intake and vitamin D must be sufficient and appropriate to age, and dietary monitoring is recommended, as well as regular physiotherapeutic support with verticalisations. Since whole-body vibrations have been recommended in patients with cerebral palsy, this has also been suggested to be of benefit for SMA patients (20).

Although there are no evidence-based recommendations, some experts consider that treatment with intravenous bisphosphonates is indicated for children with

SMA having at least two of the following criteria: bone density less than - 2 SD, two or more multiple fractures due to minor trauma, and chronic bone pain (21). Maintaining the treatment over time should be evaluated regularly by performing bone densitometry and blood and urine phospho-calcium balances (21).

A proactive approach is very important considering that the proportion of walking patients will increase, and that patients with major bone fragility may start to walk and be at risk of falling.

Orthopaedic treatments

Since the emergence of new treatments, the vital and functional prognosis of SMA patients has improved, especially in SMA1 patients. Previously, orthopaedic management was more conservative with regard to managing congenital dislocation of the hips, tendon contractures, bone deformities, scoliosis and thoracic kyphosis.

Because an incidence as high as 60 to 90% of scoliosis deformities occur in childhood, management must be systematic. A clinical examination and radiography of the spine should be performed every 6 months until the patient is fully grown, then once every following year.

Treatment with braces from 20° of Cobb angulation is recommended to slow down progression, allow stable sitting positions, and facilitate respiratory function (2). Nevertheless, bracing is not effective to stop progression of scoliosis and should be discussed in regards with patient's vital capacity (22).

A surgical intervention is suggested if scoliosis is more severe than 50° or if progression is more than 10° per year.

In early-onset scoliosis, occurring before the age of 10 in skeletally immature patients (which is the case in most sitters), the use of instruments allowing for continued spine growth should be considered. Growing rods are the standard and most well-documented surgical technique.

To decrease the need for repeated surgery every 6 months and complications due to invasive procedures and exposure to general anaesthesia, magnetically-controlled growing rods have recently been implemented as an alternative to traditional growing rods. However, complications such as metallosis and a significant rate of implant failure requiring unplanned revision surgery have been reported (2, 23).

Good knowledge of the natural history of progression is essential to ensure optimal timing of therapeutic interventions (24). Because of the limited survival of non-sitters before the development of innovative therapies, the management of scoliosis was more conservative; even more so in patients with highly compromised respiration, or with severe bulbar issues. Braces could be proposed in respiratory stable patients. A more pro-active management is proposed with increasing life expectancy in SMA1 patients.

Spine deformity in SMA 2 patients who acquire ambulation is progressive; this should prompt surgical treatment, as is classically proposed to SMA2 patients. However, in ambulant patients with a limited walking perimeter, spinal surgery is likely to lead to loss of ambulation, and the indication is therefore much less obvious than in sitters. Proactive management of spine deformity with a conservative approach (such as a brace) should thus be proposed.

Due to new innovations in treatment, rehabilitative care will also need to adapt and follow this innovative trend. Besides the classic rehabilitative treatments which have proven their efficiency, there are various re-educative tools such as exoskeletons and virtual reality which have emerged in recent years.

Lower limb exoskeletons

Robotic lower limb exoskeletons have emerged in the last several years as a potent rehabilitation tool, mainly used by patients with spinal cord injury and injury to the central nervous system.

Their use is based on the principles of neuroplasticity and motor learning maximising afferent input from peripheral joints and providing task-specific stimulation to the central nervous system) and the beneficial effects of verticalisation and mobilisation (24).

The benefits proposed in relation to spinal cord injury include the strengthening of impaired muscles, increased walking speed and efficiency, quality of life, and a decrease in spasticity and pain. Positive changes in the cardiovascular system and metabolism, bowel, and bones have also been proposed; however, only a few patients were included in these studies (25).

Another meta-analysis studying the effects of exoskeleton use in spinal cord injury has shown a significant positive effect on ASIA lower extremity muscle score (LEMS), and the results of both the 6-minute walk test (6MWT) and 10-minute walk test (10MWT) (26).

These results are promising for patients with acquired injuries, although exoskeletons presently have prohibitive costs, limited accessibility, and require a high level of training for both supervisor and patient before they can be safely and independently used (26).

However, the usefulness of exoskeletons with regard to neuromuscular diseases such as SMA is still unproven There is presently no literature on this subject, with the exception of one case report studying supported treadmill therapy in 3 patients with limb-girdle muscular dystrophy (LGMD) (27).

Conclusions

Innovative therapeutic approaches for the treatment of spinal muscular atrophy have in recent years modified the prognosis for patients with this disease, increasing life expectancy and motor development.

The standard of care in spinal muscular atrophy was renewed and adapted in 2018, with the goal of minimising the consequences of the disease and to maintain, restore, and promote function and mobility. Nevertheless, as new phenotypes are still appearing due to the approval of new medications released after 2018, newborn screening, and pre symptomatic treatments, the standard of care will need to be more frequently adapted going forward.

A multidisciplinary approach is therefore essential and as vitally important as a proactive attitude in both medical and paramedical teams.

Conflict of interest statement

The authors report no conflicts of interest.

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