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Meeting Report

Measuring Outcomes in Adults with Spinal Muscular Atrophy – Challenges and Future Directions – Meeting Report

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Abstract. Spinal muscular atrophy (SMA) is a progressive autosomal recessive motor neuron disease which affects 1 in 6,000–10,000 live births, caused by loss of the survival motor neuron 1 gene (SMN1). A major focus of therapeutic developments has been on increasing the full-length SMN protein by increasing the inclusion of exon 7 in SMN2 transcripts, enhancing SMN2 gene expression, stabilizing the SMN protein or replacing the SMN1 gene.

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In June 2017, FDA and EMA have approved the antisense oligonucleotide Nusinersen as the first treatment for all SMA subtypes without age restriction. While prominent treatment effects have been observed in the earlier stages of the disease and in patients up to 15 years of age, there is only limited data from clinical trials in adult SMA patients. First real-world data from neuromuscular clinical centers suggest a therapeutic benefit of nusinersen with a favourable safety profile also in adult SMA patients: in several cases, relevant improvements of motor function is achieved, which might lead to enhanced autonomy in daily life activities and improved quality of life. Systematic follow-up of the motor status with validated instruments is crucial for an adequate monitoring of the therapeutic effects but most of the widely used scales and scores have been developed and evaluated for the pediatric population only. International neuromuscular experts have met in Frankfurt/Main, Germany in May 2019 to discuss relevant aspects of the diagnostic pathway and patient management in adult SMA. The recommendations and challenges in this patient population are discussed.

Keywords: 5q-SMA, adult SMA, spinal muscular atrophy, motor neuron, nusinersen

INTRODUCTION

Nusinersen, a first causative treatment for 5q-associated spinal muscular atrophy (SMA) has been available in Europe since June 2017, following two successful randomized controlled double-blind studies in early- and later-onset SMA [1, 2]. While the data from the pivotal trial in SMA type 1 included infants enrolled before the age of 7 months, the first real world data were obtained in several countries as part of the worldwide expanded access program (EAP) and show a significant increase in survival and overall improvement of motor function even in older kids and with longer disease duration. More recently, real-world data from neuromuscular clinical centers in US, Germany and Italy are increasingly suggesting a therapeutic benefit of nusinersen also in adult SMA patients: in several cases, stabilization and even relevant improvements of motor function are achieved, potentially leading to enhanced autonomy in activities of daily life and to improved quality of life [3, 4]. A systematic follow-up evaluation of the motor status with validated instruments is crucial for an adequate monitoring of the therapeutic effects. While there is general consensus on which neuromotor scales and outcomes to measure in the pediatric population, there is still no standardized protocol to assess neuromotor function and progression in adult SMA [5].

A group of 9 neuromuscular specialists with broad expertise in SMA from 7 countries (France; Belgium; Germany; Switzerland; Italy; Spain and Canada) met in Frankfurt/Main, Germany in May 2019 to discuss relevant aspects of the diagnostic and management pathways in adult SMA in this novel therapeutic era. Specifically, the aims of the workshop were to discuss (I) appropriate patient reported outcome measures (PROMs), quality of life (QoL) and medical assessments as a minimal dataset collecting harmonized data on adult SMA patients, considering different clinical presentations across the disease continuum based on current SMA registry data; (II) current gaps of knowledge for the most meaningful outcomes measures and PROMs, appropriate for the different clinical presentations, and (III) set up a sustainable platform to collect the data gaps; (IV) and define a plan and set a timeline for developing the standard of care (SoC) for different clinical presentations of adult SMA; (V) to define a strategy to drive awareness and education withinall SMA stakeholders.

SESSION 1: DEFINING *ADULT* SMA AND PATIENT PROFILES

The first part of the discussion focused on the definition of *adult* SMA in the era of novel standard of care and disease-modifying treatments.

SMA has been categorized classically into five subtypes (0–4) based on the age of onset, the severity of motor decline and life expectancy. There is small group of most severely affected adult patients with SMA type 1, who survived due to an early mechanical-ventilation and a GItube to adulthood, but were never able to sit independently (“non-sitters”); adult SMA type 2 patients usually reach sitting as their best motor function, suffer from severe scoliosis and frequently require at least part-time non-invasive ventilation (“sitters”). SMA type 3 comprises the milder end of the spectrum with an age of onset between 18 months and 18 years of age; patients typically achieve the motor milestone of walking (“walkers”) at least for some time in life [6]. Natural history studies have shown a slowly progressive decline of motor function across all subtypes even in adulthood [7, 8]. Until now, adult SMA frequently

included patients who had previously been classified as SMA type 4, since they only were diagnosed in adulthood when symptoms of motor involvement became more disabling. However, careful exploration of the medical history often points towards an earlier onset in late childhood or adolescence, and the majority of patients also harbor 3–4 SMN2 copies, same as seen in patients with SMA type 3, so the existence and frequency of a SMA type 4 phenotype is controversial. The new therapeutic options have led to new SMA phenotypes, including SMA type 1 patients sitting and some SMA type 2 patients walking independently, especially if treatment was started early and patients were only moderately affected prior to therapy [9]. Because both, the progressive nature of the disease and the emergence of new therapeutic options, the panel agreed that the classification suggested by the recently revised SoC [10] based on function rather than on type would also be preferable for adult SMA, including "non-sitters", "sitters"and "walkers". It is worth reminding that motor milestones can also be lost in adulthood in the course of the disease.

Prior to approval of nusinersen, the majority of adult patients with SMA have not been regularly followed by adult neurologists in clinic, since patients mainly needed medical attention for respiratory or orthopedic problems; in contrast to pediatric SMA patients, motor function was not regularly assessed in the adult SMA population. Patients were considered as chronically disabled and the lack of specific treatment options did not prompt regular and rigorous data collection over time. This created a gap in the natural history of adult SMA and complicates interpretation of treatment effects.

Revised patient profiles

Non-sitters

Adult non-sitters usually comprise of SMA type 1 and 2 patients, although some older type 3 also belong into this category. Patients usually display severe weakness, are flexia and hypotonia with some trace movement in distal limbs. While facial and bulbar weakness and respiratory impairment typically leads to limited communication in SMA type 1 patients, those originally classified as SMA type 2 or 3 usually have no or only minor restrictions on communication. Contractures and severe scoliosis are common, frequently requiring (spinal) surgery. SMA type 1 patients suffer from a severe restrictive respiratory insufficiency requiring ventilator support for >16 hours/day or tracheostomy, which can also be observed in severely affected SMA type 2 patients. Recurrent pneumonia and aspiration are amongst the most threatening and challenging issues in this group of patients. The respiratory complications and additional nutritional difficulties, frequently requiring a GI tube along with weight deviations represent the major cause of morbidity and are burdensome for the patients and their caregivers.

Sitters

The group of sitters mainly comprises type 2 and 3 patients, including thosewho stand assisted but are unable to walk. Some minor leg movements may be present. Arm weakness is usually severe, with proximal muscles weaker than distal ones. Reflexes are usually absent. Contractures and scoliosis are common features. Respiratory involvement may be present, but to a lesser extent than in the non-sitter group, and patients may either not require non-invasive ventilation or use it only at night. Bulbar weakness can be present affecting facial and jaw muscles leading to problems with mouth opening, chewing and swallowing. Weight deviations and gastrointestinal problems due to immobilizationare frequently seen.

Walkers

Patients with SMA are defined as "walkers" if they are able to walk 10m unassisted.SMA walkers are always type 3or type 4 patients. Weakness is typically more evident in the lower than in the upper limbs, proximal muscles are predominantly affected. Interestingly, in the upper limbs, triceps and deltoid muscles are more affected than biceps brachii, and in the lower limbs, gluteus maximus, iliopsoas, quadriceps and gluteus mediusmuscles are more affected than hamstrings [7]. Reflexes are usually absent in the lower limbs and may be either normal, weak or absent in the upper limbs. There may be some mild facial or bulbar weakness and most patients present a normal respiratory function.

SESSION 2: RECOMMENDED ASSESSMENTS IN ADULT SMA

Non-sitters

The CHOP INTEND scale was originally validated for infants and until now recommended to monitor motor function also in adult SMA non-sitters. For improved suitability in adults, items which are

not relevant and applicable to adults (e.g. items 6 and 7 "rolling", item 11 "hip flexion and foot dorsiflexion", item 15 ("head/neck extension/Landau sign"), and item 16 ("spinal incurvation/Galant sign") have been omitted, and the adapted score has been renamed recently as CHOP ATEND (now "A" for adults instead of "IN" for infants) (Congress report,CureSMA2018).

At baseline, a full respiratory work-up should be performed, including a clinical examination of the chest for detection of abdominal movements and paradoxic breathing. Nocturnal oximetry and capnometry is recommended. The criteria for non-invasive (NIV) or invasive ventilation (IV) should be applied according to current SoC and recommended international guidelines [11]. Importantly, respiratory insufficiency in SMA is a dynamic process, requiring regular assessment of ventilation parameters over time. The number of acute respiratory events per month or per year should be assessed, defined by episodes requiring hospitalization, medical assistance and/or antibiotic treatment. Caregivers should be instructed to document these events and the required medication, and to report these during follow-up visits. Follow-up assessments should be scheduled at least once every 12 months; but if patients are on NIV > 16 hours/day or are on IV; additional respiratory monitoring should be considered. Table 1 summarizes the core data set recommended in adult non-sitter SMA patients.

Table 1
Assessment of Non-sitters

Frequency: As per routine clinical follow-up, at least once every 12 months	
Measure	Practical challenges and considerations
CHOP INTEND *or* CHOP ATEND	• Some items in CHOP INTEND are not relevant for adult patients • Many NMD specialists are unfamiliar with CHOP ATEND
Respiratory function[a] • Mandatory full work-up at baseline • Most universal: nocturnal oximetry • Need for NIV or IV • Changes in time required for NIV • Number of recurrent pulmonary infections • Hospitalizations (number of days, • Number of prescribed antibiotics	

Sitters

Motor function should be assessed in muscles with residual movement, predominantly in the upper limbs. The Revised Upper Limb Module (RULM) and the Expanded Hammersmith Functional Motor Scale for SMA (HFMSE) are recommended to monitor motor function in these patients.

A full respiratory work-up is mandatory at baseline and every 12 months, including forced vital capacity (FVC) in sitting position and peak expiratory flow (PEF) and number of pulmonary infections.

Table 2 summarizes the core data set recommended for adult sitters with SMA.

Table 2
Assessment of Sitters

Frequency: As per routine clinical follow-up, at least once every 12 months	
Measure	Practical challenges and considerations
RULM	• Training • Equipment • Time consuming
HFSME	• Training • Time consuming
Respiratory function[a] • Mandatory full work-up at baseline • Minimum requirement: • FVC sitting [mandatory] • FVC lying [recommended] • PEF	

Walkers

For the assessment of motor function, RULM and HFMSE are recommended; the Six-Minute-Walk-Test (6MWT)is suitable to monitor walking performance and fatigue in these patients [12, 13]. Respiratory assessment should be performed at baseline including FVC in supine and sitting position and PEF; depending on the results, lung function should be monitored over time.

Table 3 summarizes the core data set recommended for adult walkers with SMA.

SESSION 3: INITIAL EXPERIENCE WITH TREATMENT IN ADULT SMA PATIENTS

France

Shahram Attarian presented the experience of the Reference center for Neuromuscular disorders and

Table 3
Assessment of Walkers

Frequency: As per routine clinical follow-up, at least once every 12 months	
Measure	Practical challenges and considerations
6 MWT	• Time consuming • Space required • Training needed • Impact of comorbidities, for instance pulmonary dysfunction • Reimbursement
HFSME	• Training • Time consuming
RULM	• Training needed • Equipment • Time consuming
Respiratory function	

ALS, Timone University Hospital in Marseille and for France as coordinator of the French Neuromuscular diseases network (Filnemus; www.filnemus.fr). In Marseille, 85 SMA patients are followed-up regularly among them 35 adult SMA patients. In total, 30SMA patients are on treatment with nusinersen. Patients with severe scoliosis or with spine fusion are treated by using CT-guided injections. Untreated adult SMA patients are followed once a year systematically and, if necessary, every 6 months. Under treatment, the follow-up is scheduled every four months.

Belgium

Stephanie Delstanche presented the experience of the Neuromuscular reference center of Liege, University of Liege.

This center follows 65 SMA patients, 17 of them adults. Among adult patients, 5 of them decided to remain without treatment with nusinersen for different reasons. Seven adult SMA1c patients have initiated treatment in this center.

Since the approval of nusinersen in Belgium (September 2018), motor function of treated patients has been evaluated every 4 months as well as ventilatory function FVC, MIP and MEP. For non-treated patients motor function is evaluated every 6 months. All patients also benefit from a follow up by a nutritionist, an orthopedic surgeon and a speech therapist at least every 1 year. Nocturnal oxymetry and capnometry is also performed at baseline and followed up according to SoC reviewed in 2018 [10, 11].

Germany

Maggie Walter presented the experience of the Friedrich-Baur-Institute in Munich. Currently, 60 SMA patients are followed-up regularly, 30 of them are on treatment with nusinersen. The remaining 30 decided against treatment for different reasons: difficult spine situation, planned pregnancy, fear of side effects (hydrocephalus), expectation of an oral medication. Patients are followed-up according to the SMArtCARE initiative (www.smartcare.de). SMArtCARE collects longitudinal data on all available SMA patients independent of their actual treatment regime as disease-specific SMA registry. For this purpose, we provide an online platform for SMA patients seen by health-care providers in Germany, Austria and Switzerland. The timing and frequency of follow-up visits and assessments depend on the actual treatment regime. SMA patients are normally seen once or twice a year in aspecialized outpatient clinic for neuromuscular diseases. Under treatment with nusinersen, for example, follow-up visits are scheduled every four months [22]. Recommendations for the clinical evaluation of SMA patients are summarized in Table 4.

Christoph Kleinschnitz and Tim Hagenacker presented the experience of the Department of Neurology, University Hospital in Essen. Currently, 62 adult SMA patients are followed-up regularly, 52 of them are on treatment with nusinersen. Especially patients with complex spine anatomy (scoliosis with or without spinal fusion) have to be treated by using fluoroscopy or CT-guidance. In these patients, treatment is feasible in >90%[23]. In single case a lumbar port system was implanted for treatment with nusinersen (off-label use). Using CT-guidance or fluoroscopy is accompanied with further logistic and radiation exposure challenges (see Section 4).

Italy

Valeria Sansone presented the experience of three Italian centers, specifically the Neuro Muscular Omni service Clinical Centers (NEMO Centers) in Milan, Rome and Messina. All 3 Centers are part of the international SMA consortium (iSMAc, Italian Coordinator Prof. Mercuri). All patients on nusinersen treatment are regularly followed for motor, respiratory and nutritional status every four months, while untreated patients are followed-up every six months. The same tests and procedures are applied in both groups and regular training of PT allows for quality control of data collection at each site. Over 160 adult SMA patients are now regularly followed in the outpatient clinic. Natural history data on detailed

Table 4
SMArtCARE recommendations for the evaluation of patients with SMA

	Patient visits (days)					
	1	14*	28*	63*	180	Every 6 months (every 4 months*)
Baseline data including genetic test results	X					
Current medical history and clinical examination	X	X	X	X	X	X
– including motor milestones in children <12 years of age						
Administration of nusinersen[a]	X	X	X	X	X	X
Physiotherapeutic assessments:	X			X	X	X
CHOP INTEND						
• All children <2 years of age						
• All patients >2 years of age without ability to sit						
HFMSE						
• All patients >2 years of age with ability to sit						
• If CHOP INTEND score >50: CHOP INTEND and HFMSE						
• If CHOP INTEND score >60: HFMSE instead of CHOP INTEND						
RULM						
• All patients >2 years of age with ability to sit (in a wheelchair)						
6 MWT						
• All ambulant patients >3 years of age						
ALS Functional Rating Scale(in adult patients)	X			X	X	X
Pulmonary function	X				X	X
Documentation of adverse events				Ongoing		

[a]Additional recommendations under treatment with nusinersen (grey); [b]If the patient is sufficiently cooperative due to age.

motor function and respiratory function are available for these patients.

Spain

Juan F Vázquez-Costa presented the experience of the University Hospital La Fe, in Valencia. Currently, all SMA patients (22 children and 43 adults) are followed-up every 6–8 months in this center and39 of them are on treatment with Nusinersen (20 children and 19 adults). The remaining 24 adults decided not to receive Nusinersen for similar reasons to those exposed previously. Patients with complex spines are treated with ultrasound-guided lumbar punctures. Blood and CSF samples are being collected for biomarker studies and compound muscle action potentials (CMAP) are obtained in all treated patients. These as well as other clinical data and patients reported outcome measures (PROMs) will be collected in two multicenter registries: one registry sponsored by the patient's association FUNDAME; and another registry (CUIDAME), which will be aligned with the German SMArtCARE initiative.

Switzerland

Christoph Neuwirth reported 4 treated patients over a 1-year period. All patients remained stable and even increased in functional outcome measures like RULM, HFMSE or 6 MWT. Further, electrophysiological measurements like the CMAP in arm muscles (partially also in leg muscles in "walkers") increased over time as well as the Motor Unit Size Index (MUSIX), while the Motor Unit Number Index (MUNIX) remained stable.

Data of adult Swiss SMA patients are entered into the Swiss database for SMA patients (Schweizer Register für neuromuskuläreErkrankungen, Institut für Sozial- und Präventivmedizin, Universität Bern) and is planned to be entered into the database of the SMArtCARE initiative.

SESSION 4: CHALLENGES

Selection of outcome measures

The lack of specific tests for the adult SMA population constitutes a major problem - the scales which are commonly used for assessment of motor function in the pediatric SMA patients are mostly validated in children and are unfamiliar for neurologists. Additionally, these tests require specific training, are burdensome and time-consuming and personnel-intensive, thereby representing a barrier for data collection in general, and specifically compromising data quality, when assessed at unexperienced sites.

Moreover, most scores at hand are not sensitive enough to detect minor improvements, mainly in the

very mild and in the severe end of the spectrum due to floor and ceiling-effects.

However, the pediatric scales have been applied to the adult SMA patients despite these limitations since data have proven to be also robust in adults [7, 24, 25]. Therefore, adult neurologists treating SMA patients need to become familiar with the recommended scales and scores. A close cooperation between neuropediatricians and adult neurologist treating SMA should be implemented at the expert sites.

There is also an urgent need of functional scales that allow for an easy and reliable bedside testing.

Some centers use the EK2 scale, which was initially validated in 81 non-ambulant SMA patients. It has been translated to several languages and validated in different populations, showing adequate reliability and validity, and it is used in several countries and registries (the Danish Muscle Group, Italian SMA Group, UK Smart net, Pediatric Neuromuscular Clinical Research Network for SMA, and Spanish registries) [26]. Interestingly, the EK2 scale has been shown to correlate significantly with the forced vital capacity and a manual muscle strength test (MMT) [27]. Moreover, it was proved useful to evaluate subtle changes in upper limb function resulting from disease progression patients [28]. Finally, the EK scale, a previous version of the EK2 scale, detected functional changes in SMA patients after three years follow-up [27]. The EK2 scale seems to be useful in both sitters and non-sitters, but it is little sensitive in walkers [29]. Suggested ALS scales as substitute for the adult population are probably neither helpful nor evaluated, due to the different progression rate and pathophysiologic involvement of both, upper and lower motor neurons in ALS. The use of the ALS-FRS adapted for SMA (SMA-FRS) was discussed, but no consensus was reached on its regular use in adults with SMA, although a good positive correlation with the average MVICT sum score, 6 MWT and lean mass index has recently been described, along with a moderate positive correlation with ulnar CMAP amplitude. However, the data shows a ceiling effect in the high-performing patients. Never the less, the declining score over time suggests a potential ability to detect change over time (Elsheikh B, King W, Arnold WD, Kissel JT. Reliability of Spinal Muscular Atrophy Functional Rating Scale (SMA-FRS) in Ambulatory Adults with Spinal Muscular Atrophy. Poster presented at the Cure SMA Conference 2019). Additional data might be helpful to assess long-term outcomes and suitability in adult SMA.

Descriptive assessments of individual patient achievements and PROMs are of utmost importance in the clinical practice and its use has been strongly suggested by regulatory authorities. The SMA Health Index, developed by Dr. Heatwole at the University of Rochester, NY might be an option to assess minor changes.

Hand and finger strength is of paramount importance to patients' autonomy and quality of life. Measurement of hand innervation, along with hand and finger strength assessment would eventually allow for a sensitive and objective monitoring [19]. Hand muscle innervation, measured by CMAP and Motor Unit Number Index (MUNIX) [30], has been described to correlate well with the overall disease severity and hand muscle strength. Therefore, these measures might be useful to measure disease progression or treatment efficacy, but longitudinal data are necessary to fully decide on their day-to-day suitability.

Criteria to Start and to Stop Treatment with Nusinersen

So far, there are two approved therapies for SMA, the *SMN*2 splicing enhancer nusinersen (Spinraza®, approved in US and EU) and the *SMN1* gene replacement therapy (GRT) onasemnogenabeparvovec-xioi (Zolgensma®, so far only approved in the US). Nusinersen is approved since June 2017 by FDA and EMA for SMA of all types and stages, also for presymptomatic patients identified via newborn screening; the GRT has been recently approved by the FDA for SMA of all types up to the age of 2 years; EMA approval is pending.

The general impression from the team of experts at the workshop and initial real-world data from the adult population [3] is that some adult patients improve with Nusinersen. In children, the degree of improvement of motor function seems to depend on the preserved motor function prior to treatment. Little is known on the impact of nusinersenon respiratory function or nutritional issues. In adult patients with little or no residual motor function, treatment efficacy can be expected to be low, although approval of nusinersen covers all SMA types, with no restrictions on the degree of severity.

The expert group agreed on criteria to start treatment: First, self- or physician-reported worsening motor function within the last months or years was agreed to be an important factor to start treatment. Second, treatment expectations and limitations, along

with potential complications following repeated lumbar punctures and repeated visits should be addressed. Third, the patient's and care's perspectives should be acknowledged and approached. What may appear irrelevant from a clinician point of view regarding effect size might be important for patients and caregivers: strength improvement of one finger may not change overall hand strength and function but may enable the patient to independently use a modified wheel-chair joystick or a touch tablet, resulting in increased autonomy and quality of life. Finally, decision for treatment should be achieved together with the patient. For evaluation of treatment efficacy, patients should be treated over twelve months minimum; however, patients may withdraw consent any time, and clinicians may stop treatment for medical reasons. Within a risk-benefit analysis, the age of the patient and lifetime-shortening comorbidities should also be considered. In patients with cerebral shunt or lumbar port systems, bioavailability and efficacy of nusinersen may be reduced, and this should also be discussed.

Managing expectations

Prior to treatment, realistic treatment goals should be agreed upon with the patient - a wheel-chair bound patient will most probably not start to walk independently, and ventilated patients will most probably still need this support. The majority of adult SMA patients are already well informed about treatment options and rate a stabilization of their current motor status as a satisfactory treatment effect [31]. The group agreed that so far, patient's adherence to nusinersen treatment is quite stringent.

It is important to include the individual patient perspective into the discussion of treatment goals with the patient, e.g. preservation of finger function for independently using an electric wheelchair, smart phones or tablets. After one year of treatment, a re-evaluation of the therapeutic goals is warranted. For follow-up, scales and scores widely used in SMA are relevant, but should be amended with an individual clinical expert evaluation and supported by PROMs. One interesting option is the use of goal attainment scaling (GAS): a standardized method of scoring the extent to which patient´s individual goals are achieved in the course of intervention that allows statistical analysis (https://www.kcl.ac.uk/cicelysaunders/resources/tools/gas).

Challenges with repeated intrathecal administrations

Nusinersen is an ASO and cannot cross the blood-brain-barrier. In order to achieve sufficient concentrations in spinal motor neurons, nusinersen must be administered intrathecally in the subarachnoid space. Treatment starts with four loading doses on the days 0, 14, 28, and 63. Throughout the course of the maintenance therapy, nusinersen will be administered every four months. GRT so far is only approved for children up to age 2, but might become available for adults in the future with intrathecal delivery.

All experts agreed that intrathecal administration could be performed at any local site but that monitoring and assessments should only be performed in a neuromuscular center with extensive experience in SMA, ensuring adequate treatment for patients with respiratory insufficiency and experienced management of complications. However, in some countries such centers may not be readily accessible.

To date, side effects associated with lumbar puncture are not treatment-specific and consist of post-puncture syndrome (position-dependent headache, backache, dizziness, and nausea), after 10–40% of procedures in the expert centers. Serious complications have not yet been observed in any patients at the aforementioned centers. Communicating hydrocephalus not related to meningitis or bleeding has been reported so far in 6 patients, including children, treated with nusinersen; some of them were managed with implantation of a ventriculo-peritoneal shunt. Worldwide, more than 7.000 patients have so far been treated with nusinersen, and etiology of the hydrocephalus remains unclear. However, it could be part of the natural history of the disease, since the incidence of hydrocephalus is also increased in untreated SMA patients. Despite this, patients and caregivers should be informed about signs and symptoms of hydrocephalus before nusinersen is started. A systemic analgosedation for the administration of nusinersen is not necessary for adult patients in the majority of cases; however, a local anesthetic infiltration can be helpful in individual cases.

Non-invasive ventilation and monitoring of lung function during the procedure is only necessary in SMA patients with respiratory insufficiency.

CT prior to treatment for planning the administration route is only necessary in patients with severe anatomical complications (i.e. spondylodesis, scol-

iosis). Specific approaches and imaging procedures vary across the different centers, depending on the individual infrastructure and site preferences.

When conventional lumbar puncture is not possible due to spinal deformities, CT or fluoroscopy guided puncture can apply. Thus far, this method has been largely successful; there have only been a few cases where injections could not be administered. In these cases, alternative application technologies e.g. port systems offer an alternative; however, this would qualify as"off-label use" and eventual problems with reimbursement and insurance coverage should be considered beforehand.

Patients with severe spinal deformities requiring regular image-guided administration, or patients who plan a future pregnancy should be aware of the cumulative radiation exposure. Radiation exposure can increase morbidity and mortality due to future malignancies and should be clearly discussed prior to treatment [32, 33]. Similarly, potential fertility problems should also be addressed; secondary amenorrhea can be caused by exposure up to 10 Gray, while small doses of radiation exposure can trigger premature ovary failure.

Ultrasound guided punctures is a safer alternative avoiding radiation that has been successfully applied in patients with scoliosis and spinal fusion at La Fe Hospital, Spain (unpublished data). However, it requires specific training and experience.

Nusinersen for pregnant women and women of reproductive age

Animal experiments have not found signs for reproductive toxicity or infertility with nusinersen treatment; so far, no cases of pregnancy been reported during treatment. However, given the intrathecal delivery experts recommend contraception for female SMA patients in reproductive age during nusinersen treatment. If the patient became pregnant during treatment, the therapy should be discontinued.

Registries and data collection

The evaluation of real-life outcome data in a broad spectrum of SMA patients will lead to a better understanding of the natural history and the influence of drug treatment. This is crucial to revise and implement SoC for these patients. Furthermore, longitudinal data on all available SMA patients should be assessed and monitored in a disease-specific SMA registry for evaluation of a therapeutic benefit with different future drugs.

Data should be collected according to the treatment schedule (Table 4); for untreated patients, natural history should be assessed in 6-months intervals. The expert group agreed that standardization and adequate training for tests and procedures is mandatory.

Data are already being collected in registries which vary amongst different groups (e.g. www.sma-register.de and www.smartcare.de in Germany; the International SMA Consortium including Italy, US and UK; the Italian SMA Consortium (iSMAc) and the CNDR in Canada [34].

All SMA patients independent of their current treatment regime should be included; disease-specific registries are favored by all stakeholders over product-specific registries to allow for a meaningful analysis across both treated and untreated SMA patients.

In the meantime, further research to identify robust objective and sensitive outcomes is needed to assist patients and physicians in the decision making of treatment continuation or termination.

Criteria for interrupting or terminating therapy

Generally, long-term nusinersen treatment for SMA does not have a definite duration.

Experiences thus far have found that most patients are treated on a long-term basis and very few patients choose to pause or terminate their treatment. The most commonly seen reasons for terminating therapy have been a progression of the disease, despite therapy and treatment efforts (such as the aforementioned side effects).

The presence of a functional deterioration does not imply termination of therapy, as the delayed progression throughout the course of the early stages of treatment is therapeutically beneficial and can be justified with further treatment. In this case, the medical indications should be examined critically. A rapid progression of the disease — as rapid as prior to therapy — should, at the very least, be handled by pausing therapy and should entail subsequent re-exposition and careful reevaluation. This underlines the importance of constant, careful documentation of the patients' motor an functional status.

Serious illness-related complications or inter current comorbidities could make interruption or termination of therapy necessary. Generally, whether or not therapy will be continued depends on whether the

complications have been managed. Therapy is should also be interrupted when patients become pregnant during their nusinersen treatment, as mentioned in a previous section.

The occurrence of lifetime-limiting comorbidities can justify treatment termination. Should radiation exposure through the controlled radiological application culminate to a significant level, especially in women, the decision to continue therapy should be questioned.

CONCLUSIONS

Recent clinical experiences find that even adult patients with SMA can benefit from Nusinersen therapy independent of patient´s age. In the absence of clinical trials in adult SMA patients, prospective clinical practice data of treated patients together with prospective and retrospective natural history data will be indispensable to determine the efficacy of new therapies and their impact on patient's autonomy and quality of life. In the next years, the phenotype of adult SMA patients in the light of disease modifying treatments will considerably change, with an increasing number of adult sitters among patients with SMA type 1 and walking SMA type 2 patients.

The effect of the treatment should be periodically monitored using proper instruments, particularly noting the treatment or improvement of critical residual functions on an individual basis. So far, there are no standardized protocols and procedures to test the progression of the disease in adult patients. This report emphasizes a minimal core data set that was discussed for each subgroup of adult patients, allowing for harmonization of care amongst patients across different countries and across centers with different levels of specialization in SMA. Functional scales and PROMs should be developed and validated to better evaluate the efficacy of nusinersen in adult SMA patients.

In general, intrathecal administration of nusinersen in patients with and without severe spinal deformation is feasible and received positively by patients. In order to assure the best possible treatment process, it is important for patients to continue multidisciplinary care at neuromuscular clinical centers.

Systematically compiling treatment process data into registries will lead to a comprehensive database to share treatment effects and to continue developing cumulative therapy approaches. A standardized bio specimen collection (biomarkers, innovative therapy approaches) should be strived for, especially, in the near future, untreated SMA patients will remain rare.

A number of open questions remain in the adult population including the lack of long-term natural history data. Therefore, registries will provide a valuable source of information on both natural history of the disease and effect of treatment in adults with SMA. Ongoing efforts aim at the harmonization of data collection; however, there is still need to define the most clinically meaningful data. Although regulators and payers primarily focus on quantitative data, qualitative data can be of high importance for patients and physicians. The expert group agreed that individualized PROMs are very important to consider on start and stop of treatment. Further education in the adult SMA field must be achieved by regular training and close collaboration with patient advocacy groups.

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