Neuromuscular Disorders 33 (2023) 511–522

Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

254th ENMC international workshop. Formation of a European network to initiate a European data collection, along with development and sharing of treatment guidelines for adult SMA patients. Virtual meeting 28 – 30 January 2022

Maggie C. Walter[a,*], Pascal Laforêt[b], W. Ludo van der Pol[c], Elena Pegoraro[d], on behalf of the 254th ENMC Workshop Study Group[1]

[a] Friedrich-Baur-Institute at the Department of Neurology, University Hospital, LMU Munich, Ziemssenstr. 1, Munich 80336, Germany
[b] Department of Neurology, Nord/Est/Ile de France Neuromuscular Reference Center, AP-HP, Raymond-Poincaré Teaching Hospital, Paris Saclay University, Garches, France
[c] Department of Neurology, University Medical Centre Utrecht, Utrecht University, Utrecht 3584 CX, the Netherlands
[d] Department of Neuroscience DNS, Neuromuscular Unit, University of Padova, Italy

ARTICLE INFO

Article history:
Received 18 February 2023

1. Introduction

The 254th ENMC international workshop on the "Formation of a European network to initiate a European data collection, along with development and sharing of treatment guidelines for adult SMA patients" was held virtually from 28th to 30th January 2022.

29 clinical researchers from 12 different countries (Belgium, Canada, Denmark, France, Germany, Greece, Italy, Netherlands, Poland, Spain, Switzerland, UK), 2 SMA patients, one representative of a patient advocacy group and 2 industry representatives from Biogen and Roche met for a virtual workshop in the weekend of 28–30 January 2022. The Workshop aimed at the formation of a European network to initiate a European data collection, along with development and sharing of treatment guidelines for adult SMA patients. This workshop was supported by the 10 ENMC partner organisations.

Spinal muscular atrophy (SMA) is caused by homozygous loss of function of the survival motor neuron (SMN) 1 gene on chromosome 5q13. SMA is characterized by degeneration of the anterior horn cells of the spinal cord resulting in muscle atrophy and predominantly axial and proximal muscle weakness. The prevalence of healthy carriers of the disease in the general population is high (1/50-80) and with an incidence of 1/10,000 to 1/6000, SMA is the second most common fatal autosomal recessive disorder after cystic fibrosis and the leading genetic cause of death of infants and toddlers due to respiratory muscle failure (Mercuri et al. [6]).

Depending on the severity of symptoms, age of onset, and the best motor acquisition achieved, SMA is classified into different subtypes depending on age at onset and the best motor acquisition achieved, although it is now accepted that the SMA phenotype rather spans a broad continuum without a clear delineation of subtypes. The severity of the disease varies greatly and is closely related to the age at onset of symptoms. However, this classification has limitations as the disease has a continuous severity spectrum with cases of onset before birth (Type 0) and intermediary subtypes (1 a–c, 2 a-b, etc.). The arrival of new effective DMTs has led to a significant increase in survival and therefore the prevalence of the disease is likely also likely to increase in coming years. To stress the importance of the functional level rather than the achieved motor milestones at the time of diagnosis, the current classification is based on the best motor function that the patients experience now rather than in the past, and patients are now differentiated in non-sitters, sitters and walkers [1].

The *SMN1* gene in the telomeric part of the duplicated region in 5 q13 contains a centromeric copy gene in the centromeric part, the *SMN2* gene. The *SMN1* and *SMN2* genes are highly homologous and only differ by 5 nucleotides [2,3]. In healthy individuals, the SMN protein is produced mostly by the *SMN1* gene but also in small amounts by the *SMN2* gene. An inverse correlation exists between the number of copies of the *SMN2* gene and phenotype

* Corresponding author.
E-mail address: maggie.walter@lrz.uni-muenchen.de (M.C. Walter).
[1] Listed at the end of this report.

https://doi.org/10.1016/j.nmd.2023.03.011
0960-8966

severity: 80% of patients suffering from SMA1 have 1 or 2 copies of the *SMN2* gene, 82% of patients suffering from SMA2 have 3 copies of the *SMN2* gene, and 96% of patients suffering from SMA3 have 3 or 4 copies of the *SMN2* gene [4]. However, the association is strongest at the edges of the spectrum with large variation in severity in individuals with 3 and to a lesser extent 4 copies [5].

From the time point of diagnosis, and without SMN-restoring treatment, patients with SMA rarely achieve improvements of motor function or acquire additional motor developmental milestones. The treatment and management of the disease are multidisciplinary because of the progressive loss of muscle force, gradual progression of respiratory and gastrointestinal symptoms, and vertebral column and limb orthopedic deformities. Technical advances in recent decades have significantly improved the survival of many patients with ventilatory support and enteral nutrition. In 2007, an international consensus statement was published on the management of pediatric SMA and in 2018, the recent revision of the consensus statement was made available [6,7]. Nevertheless, there is considerable variability in the care of patients suffering from SMA in different countries, although national guidelines are in development (https://register.awmf.org/assets/guidelines/022-030l_S1_Spinale-Muskelatropie-SMA-Diagnostik-Therapie_2021-07_1.pdf).

State of the art treatment of SMA in the adult patient population is a combination of supportive care and medical treatment with either Nusinersen or Risdiplam. Efficacy of Nusinersen treatment has been shown in RCTs that allowed inclusion of children with SMA type 1–2 up to the age of 12 years [8], and efficacy of Risdiplam was shown in a wider range of patients up to the age of 25 years in several RCTs and open label trials [9,10]. Regulatory authorities in the United States and Europe allowed market access for both drugs for all patients with SMA, irrespective of type or age, or disease duration. Real-world data from neuromuscular clinical centers suggest a benefit for both drugs beyond the populations investigated in trials [11], but data on treated adults remain patchy at best. Regular systematic evaluation of the motor status with validated instruments for adequate monitoring of the therapeutic effects is therefore crucial.

Currently, there is still no generally accepted approach towards treatment of adult SMA patients, even though majority of them is older than 18 years, and there is an urgent need for consensus on standards of care and monitoring of efficacy of SMN augmenting drugs.

Compared to drugs in common diseases, approval of orphan drugs is frequently based on a limited amount of evidence. After approval, it is often not feasible to conduct further placebo-controlled clinical trials. However, to evaluate the long-term effect of these drugs in a broad spectrum of patients, it is crucial to collect clinical data on the respective patients systematically and independent of commercial partners. Therefore, the aim of the French, German, Dutch, Spanish, and Italian registries is to include all SMA patients independent of their current treatment regime. Disease-specific registries are favoured by all stakeholders over product-specific registries to allow meaningful analysis across both treated and untreated SMA patients. A comprehensive collection of post-marketing data is challenging not only due to paucity of data but also due to the lack of options to use the existing data. There is an international consensus on the need of data sharing, implementing the FAIR principles of data (Findable, Accessible, Interoperable, Reusable). The interoperability of different approaches establishing SMA registries to collect real-life outcome data throughout the world is crucial. Harmonization of existing international SMA registries based on formats as put forward by TREAT-NMD (www.treat-nmd.eu) and others are crucial for speeding up the identification of those characteristics, biomarkers and genetic modifiers that might help in predicting the effects of drug treatment in different subgroups of SMA patients.

The SMA literature is biased towards pediatric SMA, despite the effects that most patients who are alive are adults. The classification suggested by the recently revised SoC [6,7] has limited relevance and specific heath issues reported by adult patients are still to be studied in detail [12]. Moreover, 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 SMA-related medical attention due to respiratory or orthopedic problems; therefore, in contrast to pediatric SMA patients, motor function was not always 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, although some studies on disease course in adults have recently been published [5,13]. Relative lack of natural history data in adults complicates the interpretation of treatment effects.

In several European countries, efforts have been made to implement data bases / registries, such as SMArtCARE in Germany (www.smartcare.de). SMArtCARE aims to collect longitudinal data on all available SMA patients as disease specific SMA registry [14]. The Dutch SMA registry (www.smaonderzoek.nl) that was founded in 2010 has been an important tool to get more insight in the natural history of SMA in treatment-naïve patients, especially at older ages. These data proved vital to secure reimbursement for Nusinersen and Risdiplam treatment under the condition of continued monitoring of the disease course. The documentation in SMA registries enable systematic development of a database for further development of the novel treatment paradigm. Relevant aspects of SMA therapy start and stop treatment criteria, management of expectations, and follow-up assessment should be discussed with international experts.

2. Background, experience of treatment in children, recent therapeutic advances in SMA, lessons of pediatric trials for adults: what could we learn as adult neurologists from pediatric trials?

Valeria Sansone from Italy gave an overview on the clinical classification of SMA. The 2018 standards of care had already identified the need to cluster patients according to their functional status rather than traditional type 1, 2 or 3, and have classified non-sitters (typically patients with SMA1), sitters (typically patients with SMA2 and SMA3) and standers (typically patients with SMA3 and 4). With the advent of new therapies, the functional classification has changed. Patients with SMA1 can still fit the 'non-sitters' group if now older children or young adults from the pre-treatment era, but the majority of SMA1 patients on treatment or pre-symptomatic patients with 2 SMN2 copies are now in the 'sitters' group and some are moving to the 'walkers' group (Fig. 1).

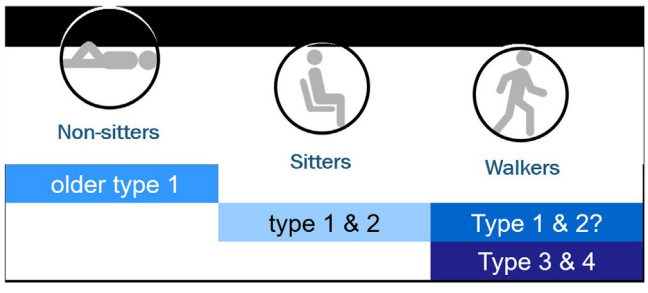

Fig. 1. Patient segmentation and new classification.

This new way of classifying largely depends on the treatments now available, on the timing of first dosing and very importantly, on the functional status at baseline. An additional determinant to consider is the number of SMN2 copies, being this the strongest genetic modifier so far known. Some differences were found in the functional abilities of the upper limbs and degree of Cobbs' angle between adults who had been regularly followed in dedicated neuromuscular clinics and new patients coming to specialized clinic after hearing about new treatment options ("newcomers"). The regularly followed patients had better upper limb residual function and a less severe scoliosis compared to newcomers. Finally, looking into the SMA3 patients, the age at onset was highly predictive of loss of ambulation emphasizing that SMA3 may include sitters and walkers with very different clinical pictures. There was consensus that the classification into non-sitters, sitters, and walkers still holds for adults. In general, a revised classification for SMA should include *pre-symptomatic kids*, especially considering the newborn screening programs available in many countries and *possibly standers* [5]. It might happen that non-sitter phenotype will disappear as treatment becomes available for all patients in all countries. Treatments have emphasized this clinical heterogeneity because responses vary according to the baseline functional status and functional levels go beyond types that were traditionally confined to one subgroup (sitters are now not only SMA2, but also SMA1) [1].

Eugenio Mercuri gave an overview of the results from clinical trials with Nusinersen and Risdiplam in children and adolescents with SMA and elucidated the issue on how to extrapolate pediatric trials to adult population. Real world data suggest the efficacy of the drug even in a real-world setting including older patients who had been excluded from clinical trials. The results are better interpreted in comparison with natural history studies, and longer follow-up of all the available drugs will provide better understanding of the new natural history of the disease [15].

Maggie Walter from Munich gave an overview on the results from clinical trials and real-world data in adult SMA patients. Only seven patients in the Nusinersen CS2/CS12 trial were age $\geq$ 13 years at enrolment and age 18−22.5 years at last visit, while the Risdiplam Sunfish trial included patients up to age 25. Three multicenter studies in Germany and Italy [16–18] showed safety and efficacy outcomes in 274 adults on Nusinersen for up to 14 months of treatment, overall resulting in mild improvement even in patients with longstanding disease. Although the treatment effect is mild, still it is the first time that improvement has been seen in the natural history of this otherwise progressive disease. All three studies showed that a lower disease severity at baseline correlated with greater improvement in motor function, and that preserved motor function prior to onset of treatment is key to largitude of improvement. It is challenging to show differences in patients with slowly progressing disease, and traditional outcome measures do not capture all aspects of the patient experience. Participation in registries, where data can be standardized and pooled, is vital, and the multidisciplinary team is critical for the optimal management of adults with SMA.

Juan F Vazquez-Costa discussed what could be learnt from clinical trials in ALS. "Time to event" endpoints (e.g., ventilation-free survival), disease stages, strength measurements with dynamometry, respiratory function measurements (such as forced vital capacity (FVC), bedside multidimensional scales (such as ALSFRS-R), and patient reported outcome measures -PROMs- (such as ROADS) are used in both clinical trials and clinical practice in ALS. Given the slow progression, some outcomes such as "time to event" endpoints or disease stages may be difficult to apply in clinical trials to adult SMA patients, but other outcome measures could be useful. Thus, ALSFRS-R has been validated in all phenotypes [19], although some items are of limited use in SMA patients (e.g. orthopnea). Similarly, the Egen Klassifikation Scale version 2 (EK2) has been found sensitive to detect changes in non-ambulant patients, but it is not applicable to walkers [19]. Strength measured with the MRC scale is an outcome measure with valuable natural history data [5], but its reliability and sensitivity are limited. Promising results have emerged with innovative devices that quantify strength in a reliable manner (e.g. myotools, neuromyotype), even in non-sitter patients, but more research on them (including longitudinal data) is needed [20,21]. Suitable PROMs for SMA are SMAIs, SMA-HI or SMA-TOOL, but there is still lack of natural history data for these scales [22]. FVC and use of non-invasive ventilation may constitute an important outcome measure in sitters and non-sitters, along with QoL and caregiver burden, but again more longitudinal data are needed [23]. Despite real-world studies, many adult SMA patients currently have no access to DMT or symptomatic treatments, due to the lack of clinical trial data. Therefore, the implementation of clinical trials in this population should be encouraged. While some outcome measures are already available and easy to implement, most of them focus on motor function and are applicable only to a subset of patients (ambulant vs non-ambulant). Thus, a SMA-specific multidimensional functional scale, which could be used in all phenotypes should be eventually developed. Finally, ALS is a highly heterogeneous disease, as it is SMA. Several innovations are being implemented in ALS clinical trials to control for this heterogeneity and speed up the therapy development, including the use of multivariable prediction models to stratify patients and the implementation adaptive platform trials [24]. To succeed in the implementation of clinical trials in adult SMA patients, the collection of large amounts of natural history data, new biomarkers (see below) and the implementation of a network of centers is needed.

Eugenio Mercuri gave an update on treatment with the gene replacement therapy Onasemnogene Abeparvovec in SMA children up to 24 months of age and 15 kg. Along with efficacy, durability over 5 years has recently been demonstrated [25]. However, side effects increase with age and weight of the patients; mainly liver dysfunction and thrombocytic microangiopathy (TMA) [26]. In heavier children and adults, intravenous administration is therefore not an option, clinical trials in older patients (STEER and STRENGTH) with a one-time intrathecal administration are still running.

Ksenija Gorni from Roche and Ben Tichler from Biogen gave an industry perspective on future SMA therapies. Ksenija Gorni emphasized that pediatric patients may receive treatment as soon as they are diagnosed, whereas adult SMA patients face significant barriers to care and even in countries with access to treatment, up to 60% of adults remain untreated. This is likely due to physicians not convinced of the risk-benefit ratio, lack of sense of urgency to treat adults, or lack of sensitive outcome measures. In addition, patients may have safety concerns, problems with reimbursement or may live far from treatment centers. Multiple studies have shown that SMA is a lifelong progressive disease. Apart from the Sunfish and Jewelfish data, where 85 patients $>$ 18 years are involved, there are alternate treatment approaches such as the MANATEE trial, a global phase 2/3 clinical study to evaluate the safety and efficacy of an investigational anti-myostatin antibody targeting muscle growth in combination with Risdiplam in SMA. Ben Tichler illustrated that there are still many open questions – appropriate comparison of efficacy of DMTs, combination and sequencing of DMTs, efficacy beyond clinical trials, biomarkers of disease activity, different delivery, improved outcome measures and future improved molecules. Apart from clinical trials, patient registries, biomarkers, and smartphone apps will play an important role.

3. Nusinersen and Risdiplam in adults with SMA: techniques, assessments, and initial experiences in European countries

Tim Hagenacker presented the challenges of Nusinersen administration in patients with difficult spines because of severe scoliosis previous spine surgery in which conventional lumbar puncture is not feasible. In these cases, the available techniques can be subdivided into radio-guided and ultrasound-guided injections. For radio-guided techniques, it is important to consider the short- and long-term risks of procedure-related radiation exposure and dosimetry should be monitored. He presented a case series of 12 SMA type 2 and type 3 patients undergoing successful radiological imaging-assisted injections. In the course of the treatment, a significant decrease in the effective radiation dose was observed and showed a reduction in radiation exposure during the treatment suggesting that increased experience contributed to the optimization of the procedure [27]. The relevance of reducing the radiation dose to avoid the risk of cancer or genotoxic effects has also prompted the development of ultra-low radiation dose protocols that showed that radiation doses can be significantly decreased in CT-guided intrathecal Nusinersen administration maintaining a high technical success rate [28]. In few cases where the previous spinal surgery and rotoscoliosis resulted in unsuccessful CT-guided procedure, a transforaminal, intrathecal administration of Nusinersen has proven feasible and safe [29]. The ultrasound-guided lumbar puncture is emerging as an alternative to radio-guide procedure. The ultrasound-guided lumbar puncture, following an interlaminar parasagittal approach, is a safe and effective approach for intrathecal treatment with Nusinersen in children, adolescents and carefully selected adult SMA patients with complex spines and could be considered the first option in them [30]. Finally, to decrease the radiation risk and time-consuming procedures an off-label use of an intrathecal catheter system may also be considered. In conclusion, both radio-guided and ultrasound-guided procedures have pros and cons. The ultrasound-guided procedures show no radiation exposure, and are safe and secure but on other hands require technical equipment and training by experienced users. The radiation-guided procedure is also reproducible and safe but concern of radiation exposure and challenging logistic are detrimental.

Robert Muni Lofra presented the challenges in defining outcome measures in SMA. A large variety of scales are currently available to measure body structure and function, activities, and participation but each of these is feasible in a subset of patients according to their functional status and no scale is relevant across the entire spectrum of SMA. There is a lack of outcome measures able to capture changes in adult non-sitter patients. For these very weak individuals the Adapted Test of Neuromuscular Disorders (ATEND) scale has been developed based on the CHOP ATEND scale to allow evaluation of patients in sitting position to avoid unsafe transfer or the prone position. The CHOP ATEND scale derives from the CHOP INTEND removing those items that are not appropriate in an adult population (items 11, 15 and 16). The ATEND is an assessment based on semi-reclined and sitting position. It is a 14 items scale ranging from cervical, trunk strength to distal strength including arm and hand function based on contractures. Test construct is based on a total score of 46 with items derived from CHOP INTEND, RHS, MFM-32, PUL 2.0, EK2 (all information about this scale at https://med.stanford.edu/day-lab/atend.html).

Another function that is not captured by standard evaluation scales is bulbar dysfunction, which is often present in adult SMA. The development of an international SMA bulbar function assessment for inter-professional administration has been presented. This scale engaged speech-language therapists, physical therapists, neurologists, occupational therapists, and dentists to achieve consensus on objective measures and PROs. Key aspects of bulbar function were identified and categorized into 6 domains: oral intake status, oral facial structure and motor function, swallowing, voice, speech, and fatigability. For each domain appropriate items were identified and stratified upon age and functional status.

Hélène Prigent presented an overview of the main parameters of the pulmonary function tests (PFTs) used in assessing respiratory function in neuromuscular patients. She stressed that in neuromuscular diseases (NMDs) a restrictive respiratory failure presents as a decrease in pulmonary volumes. She illustrated the tools available to assess the diaphragm function (supine VC), the inspiratory muscles (maximal inspiratory pressure, MIP, sniff nasal inspiratory pressure, SNIP), and the expiratory muscles (maximal expiratory pressure, MEP, and peak cough flow, PCF). In SMA restrictive syndrome, the main impairment is of expiratory rather than inspiratory muscles while diaphragmatic involvement is not predominant. As a consequence, there is no additional benefit of measuring FEV or FVC in supine position [23]. The peak cough flow may be the more sensitive index of respiratory impairment in SMA and it is reliable in patients with intact bulbar function. Pulmonary function tests (including VC, Expiratory Reserve Volume, Inspiratory Capacity and PCF) are easily performed with simple spirometer, but additional material is needed to assess pressure with MIP, MEP or SNIP.

Piera Smeriglio presented advancement in biomarkers discovery and validation in SMA. The discovery and use of biomarkers can be useful from diagnosis to the prognosis in SMA and can further help in better stratifying patients to predict their potential response to treatment. Once treatment is started, biomarkers help to monitor the patients' response and possibly optimize dosing and timing of treatment in order to formulate a personalized medicine approach. There are several biomarkers that are currently being explored in SMA, namely electrophysiologic parameters to measure the nerve and muscle activity, the imaging biomarkers and the molecular biomarkers. For the latter group, few research groups in the last years have used multi-omics approaches to identify neuroprotective proteins associated with a better prognosis in SMA patients or biomarkers correlated with functional score [31–33]. Piera Smeriglio's lab has focused on the analysis of neurofilaments which are proteins abundantly expressed in the axons of motor neurons and are released in the body fluids during the degenerative processes in SMA. Two portions of the neurofilaments can be dosed: the light chain and heavy chain, whose phosphorylated (pNF-H) form seems more stable and better correlated with the response of SMA type I patients to Nusinersen treatment [34]. No significant pathological alterations in levels of pNF-H detected in cerebrospinal fluid (CSF) or blood samples under baseline conditions or during loading with Nusinersen was observed in a cohort of 11 SMA type 3 patients [35]. Similarly, NfL levels did not change in response to Nusinersen in adult with SMA and were not different from controls. An age-related increase in CSF NfL in patients and controls was observed suggesting the Nf are not predictive or prognostic biomarkers in adult SMA [36]. Piera Smeriglio also presented data from her group on pNF-H level in the cerebrospinal fluid (CSF) and plasma in a cohort of 17 adult SMA patients (8 SMA type 2, 9 SMA type 3). pNF-H were measured at loading doses and first two maintenance doses. The levels of pNF-H in the CSF, measured by Elisa assay, were significantly reduced starting from the 3rd injection in both females and males and with no correlation between the age of patients and the level of neurofilaments. Only two patients did not reveal a decrease in pNF-H after the loading doses. Correlation between locomotor changes and pNF-H levels for 3 patients (two SMA type 2 and one SMA type 1c) did not reveal a direct link between the level of the biomarker (reduction) and the locomotor functions – no change in the MFM scale, and no change in respiratory function except for 1

patient. Meanwhile, 2 out of the 3 patients showed improvement in the post-motor changes and in their subjective feeling about their QoL. Unfortunately, the concentration of pNF-H in the plasma was not changed upon treatment suggesting that the use of this biomarker cannot be extended to the systemic compartment or that changes in plasma might be recorded only at later time points.

Janbernd Kirschner presented the infrastructure of the SMArtCARE registry. In addition to randomized controlled trials (RCTs), registries provide an important source of evidence. Randomized trials are truly experimental, select homogeneous patient population and reduce the risk of bias and confounding. Registries, on the other hand, are non-invasive, observational studies, that collect routine data to assess long-term safety and effectiveness outside of the controlled setting of a clinical trial. Both RCTs and registries are important sources of evidence because they each provide unique and complementary information. By combining the evidence from RCTs and registries, a more complete and accurate picture of the benefits and risks of different treatments can be obtained. Ideally, registries should be disease specific, use meaningful and validated outcome measure and cover a large part of the population of interest to avoid selection bias. The exact definition of data fields, the use of classification systems (e.g. ICD, International Classification of Diseases, or MedDRA, Medical Dictionary for Regulatory Activities) along with source data verification can further improve quality of the registries. In addition, pre-specifying the statistical analysis plan for registries helps to reduce the risk of biased or selective reporting of results. This includes handling of missing data and potential adjustment for confounders. Another relevant aspect to keep in consideration is the sustainability of registries to allow for long-term observation. While adequate funding is important, it should not have an impact on data ownership, analysis and interpretation. Patient involvement is essential to help the design of the registry, to select outcome measure meaningful for patients and for the governance of the registry itself.

SMArtCARE (https://www.smartcare.de/en) is a joint initiative of neurologists, child neurologists, and patient organizations. The aim of SMArtCARE is to collect longitudinal "real-world data" on all available SMA patients independent of their actual treatment regimen to create a disease specific SMA registry. For this purpose, an online platform has been developed to collect data on SMA patients from their health-care providers and this platform can be shared by other countries (i.e. CuidAME network in Spain). Austria and Switzerland use the SMArtCARE registry and combined data analysis is possible if agreed by national networks. Data are collected during routine patient visits and items for data collection are aligned with the international consensus for SMA registries. Different pharmaceutical companies provide financial support for this registry. However, the contractual basis has been regulated in such a way that data collection, analysis and interpretation are independent of these companies.

The SMArtCARE network has developed recommendations for the clinical evaluation of patients with SMA and provide corresponding documentation sheets for participating centers.

More than 60 neuromuscular centres have joined the SMArtCARE registry. Recruitment started in 2017 and about 1488 patients have been enrolled: SMA1 24.1%, SMA2 41.4%, SMA3 24.1%. More than one third of registered patients are adults. Compensation is provided for the documentation efforts of the participating centres and is contractually guaranteed. A steering committee was implemented to oversee the registry activities and to approve data analysis and pre-specified SAPs. In summary, registries for SMA support the development of effective and safe treatments, help to identify meaningful changes and thereby facilitate clinical decision making for patients with SMA.

4. European treatment experience with Nusinersen and Risdiplam in adults with SMA: numbers regulatory and practical issues

Belgium: Peter van den Bergh stated that Nusinersen was approved in September 2018 for genetically identified 5qSMA, without permanent ventilatory support and the patient had not been treated with Nusinersen before or the patient was treated with non-reimbursed Nusinersen. Prolongation of reimbursement was granted if the treatment had a favourable effect, the patient did not need permanent NIV, patient evolution was documented with HINE, CHOP INTEND; HFMSE, and the patient agreed to cooperate with the Belgium Neuromuscular Disease patient registry BNMDR. Since 2008, a specific SMA sub-registry exists with regard to the TREAT-NMD Global Database. The registry collects longitudinal data from SMA patients, recruitment works through the Belgian NMRCs of all SMA patients irrespective type and treatment regimen. Time points for data collection recommended for patients treated with Nusinersen are at baseline, six months after initiation of treatment, then every 8 months until the end of the observation period. For untreated patients, time points are baseline and every 12 months until the end of the observation period. In 2020, a total of 231 SMA patients with a final diagnosis were registered in the BNMDR SMA registry; 140 patients received Nusinersen, 63 of them adults; 30 patients had received Risdiplam, and 3 patients Onasemnogene Abeparvovec.

Denmark: John Vissing reported on 150 SMA patients in Denmark. About 20 are on gene modifying or gene replacement therapy treatment. SMA1 patients who are not permanently ventilated can be treated with Onasemnogene Abeparvovec, Risdiplam or Nusinersen, SMA2 $<$ 6 years with Risdiplam or Nusinersen, while SMA3 $<$6 years receive Risdiplam. Presymptomatic children with $\geq$ 2 SMN2 copies have access to Risdiplam or Nusinersen, presymptomatic children with $\leq$ 2 SMN2 copies to Onasemnogene Abeparvovec. The Danish Medicines Council recommended to change all patients on Nusinersen to Risdiplam. At the time of the workshop, adults could not be treated.

France: Pascal Laforêt explained that for treating SMA patients with Nusinersen or Risdiplam, a prescription made by a neurologist or neuropediatrician is mandatory. Nusinersen as a first-line treatment should be reserved for patients with SMA1 whose symptoms began after 3 months of age, as well as for patients with SMA2. The decision to prescribe should be discussed on a case-by-case basis: in severe SMA1, having started before the age of 3months of age, in early SMA3, taking into account the walking capacity. Nusinersen has no place in the therapeutic strategy for the management of SMA4. Risdiplam is indicated in patients aged 2 months and older with a clinical diagnosis of SMA1–3, in case of failure, intolerance or impossibility of administration of the available therapeutic alternatives, following the opinion of national multidisciplinary meeting (pediatric or adult) of the Filnemus network. Follow-up data should be collected into the French SMA Registry. Clinical assessment of treatment benefits is done by functional scales (MFM32, HFMSE, RULM), Myotools (assessment of hand weakness), PROMs (Goal Attainment Scaling (GAS) and Canadian Occupational Performance Measure (COPM)).

United Kingdom: Chiara Marini Bettolo showed the TREAT-NMD UK SMA patient registry (patient-based) along with SMAREACH UK and ADULT SMAREACH, both clinical databases for natural history with physician-based data. Currently, 16 SMA1, 115 SMA2, 139 SMA3 and 5 SMA4 patients were registered, 94 treated with Nusinersen, 160 with Risdiplam. PROMs used are Quality of Life EQ-5D-5 L, Global Impression of Change (patient- & caregiver-reported), SMA Independence Scale (SMAIS, Roche, non-ambulant),

free text, and EK2. There are Managed Access Agreements (MAA) for Nusinersen (5 year program) and Risdiplam (3 year program).

Germany: Simone Thiele gave an overview on the German-Austrian SMA patient registry (www.sma-register.de), where currently 886 SMA patients are registered along with their genetic report including SMN2 copy number and motor function data. Registered patients are regularly informed on new research findings and approval of new treatments via regular newsletters. For the last 10 years, there was an increasing interest in the utilization of registries regarding longitudinal data on disease progression and treatment outcome. Age and sex distribution are fairly similar across all age groups. The majority of patients has a genetically confirmed diagnosis; 22% of patients have 3 SMN2 copies, 10% 4 SMN2 copies, and 8% 2 SMN2 copies, while in 29% of patients, the copy number is still not identified. So far, 354 registered patients still do not receive a disease modifying therapy in Germany – however, there are also 251 patients without genetic report in the registry, thus are not eligible for treatment until the diagnosis is molecularly defined, leaving 100 genetically proven SMA patients without therapy. 221 receive Nusinersen, 21 Risdiplam and 6 have so far received gene replacement therapy; 5 patients have switched from Nusinersen to GRT (Gene Replacement Therapy) or Risdiplam. Presumably, there are many more patients receiving treatment, but have not yet entered this information into the SMA registry. A huge part of the registry work is communication and follow-up with patients to encourage them to update their data regularly, which needs a lot of time and manpower. Data on treatment are collected in more detail in the SMArtCARE Registry, which Janbernd Kirschner has already presented.

Regarding regulatory issues in Germany - with treatment approval by EMA, insurance has to reimburse the cost; one year following approval, the price of the treatment has to be negotiated between GBA and company. Nusinersen and Risdiplam are broadly approved for genetically defined 5q-SMA and can be prescribed, there is no need for pre-approval by insurances. For GRT, approved for 5q-SMA up to 3 copies or SMA1 phenotype, an individual application at the insurance is still needed, although the treatment is approved – this is due to the cost of the treatment, where the hospital cannot provide advance payment. All SMA patients, no matter if treated or not, are regularly assessed within the SMArtCARE initiative (www.smartcare.de).

Italy: Elena Pegoraro discussed the Italian experience with Nusinersen and Risdiplam in Italy. The EAP (Expanded Access Program) of Nusinersen started in November 2016 and included about 115 SMA type 1 patients. The European Medicine Agency (EMA) granted a marketing authorization valid throughout the European Union for Nusinersen on May 2017 and Nusinersen obtained reimbursement status by the Italian Medicine Agency on September 2017 for the treatment of all 5q SMA. Risdiplam was available through a CUP program to SMA 1 since Q1/2020 and SMA2 since Q2/2020. Risdiplam received a EMA conditional approval on march 2021 and a marketing authorization in Italy on January 2022. In Italy, Risdiplam has been approved for SMA patients older than 2 months diagnosed with SMA type 1, 2 or 3 carrying 1 to 4 SMN2 copies. For both Nusinersen and Risdiplam the Italian Government identified referral centers authorized to prescription and administration. To access these therapies free of charge the patients need to be enrolled in the National Registry of Rare Diseases. The registry has been established in 2001 as a network of regional registries and it attained a full coverage of the Italian territory during 2011. Beside the National Registry of Rare Diseases, the ITASMAc registry has recently been established. The registry, coordinated by Eugenio Mercuri, is a nation-based registry including 35 referral centers for SMA. Over 1200 SMA patients are enrolled in the ITASMAc registry with 281 classified as type 1, 451 as type 2 and 442 as type 3. Approximately 80% of these patients are receiving one of the available treatments.

The Netherlands: Ludo van der Pol discussed the Dutch experience regarding treatment with *SMN2* splicing modifiers of adults with SMA. The UMC is the only hospital in the Netherlands (population 17.6 million) that offers treatment with Nusinersen and Risdiplam to an estimated 450–500 patients with SMA. Centralization of treatment is considered a way to facilitate the collection of data during treatment and is an example of government policy that aims to maximize cost-efficacy of treatment with expensive orphan drugs. The coverage lock, a policy tool that postpones reimbursement of highly expensive (orphan) drugs until after detailed analysis of their added value and cost-efficacy followed by price negotiations, explains delays in reimbursement of Nusinersen (August 2018 for children younger than 9.5 years at the start of treatment) and Risdiplam (no reimbursement as of February 2022, not expected earlier than mid 2023) after-market authorization. Access to treatment in 2022 therefore also depends on additional conditional reimbursement arrangements for Nusinersen for children older than 9.5 years at the start of treatment and adults with SMA (January 2020) and compassionate use programs (Risdiplam, 2021). Although this patchwork made treatment possible for a majority of patients (260 with Nusinersen, 75 with Risdiplam), it leaves out a considerable number of non-ambulant patients with SMA type 3 for whom treatment with Nusinersen was not an option.

Switzerland: Andrea Klein reported that adult patients with spinal muscular atrophy (SMA) in Switzerland are seen in either the six recognized centers for neuromuscular disorders or some by specialists in private practices or regional hospitals. Access to Nusinersen for adults in Switzerland was available on individual decisions by the insurers since 2018, and by a national guideline since July 2020 for all type 2 and 3. Risdiplam was available through a compassionate use program since 2020 and is reimbursed for type 1–3 since December 2021. For both treatments, patients on permanent ventilation or with tracheostomy are excluded. Worsening of motor function without an alternative explanation is a stopping criterion for reimbursement. The registration in the Swiss-Reg–NMD, treatment at a neuromuscular center and the collection of the motor scores at four to six monthly intervals is a prerequisite for reimbursement. The Swiss Registry for Neuromuscular Disorders (Swiss-Reg-NMD), a clinician reported registry, collects data on SMA patients since 2008, prospectively with a predefined case report form (CRF) since 2018. It has implemented the TREAT-NMD Core Dataset for SMA. There are currently 130 SMA patients registered, half of them older than 18 years old, mostly type 2 and 3, a quarter ambulant, a minority with feeding tube or ventilation. Reports and CRFs are much less frequently available for adult patients than in the pediatric age group. Preliminary data collected in the registry show an effect of the treatment in adults for both medications, but missing data is an obstacle for analysis. To improve data collection, motivation of patients and physicians to measure and report data needs to be improved. Access to treatment and the collection of data at a neuromuscular center as a condition for reimbursement will help to harmonize care and data collection of adult patients with SMA in Switzerland in the future. Outcome measures that are simpler to administer (for example in the wheelchair if not ambulant) and able to show small changes would improve motivation for the patients.

Greece: Constantinos Papadopulos explained the situation in Greece. The approval of Nusinersen for the treatment of SMA has greatly increased the number of patients regularly followed in his institution, from about 2 patients per year in 2018 to 33 patients per year in 2022. This sudden change posed a challenge both in terms of human resources and on how to evaluate and

treat them, as most of these patients are highly complicated and usually need a multidisciplinary approach. Currently, in Greece, there is reimbursement of Nusinersen to all patients with a genetic diagnosis of SMA . In the 1st department of Neurology of the University of Athens, 16 patients (8 SMA type 2 and 8 SMA type 3/5 walkers) are under Nusinersen therapy, for a median of 14,6 months. Type 2 SMA and type 3 non-ambulant patients are evaluated mostly through patient reported outcome measures and report a benefit of the treatment on fatiguability, an increase in their voice volume and better neck movement. Type 3 ambulant SMA patients are evaluated through a battery of tests, including 6MWT, RULM, RHS, ALSFRS-R and dynamometry of selected muscle groups. A meaningful improvement of 3 points in RHS and an increase of 1 point in RULM were evident in 3 and 2 out of 5 patients, respectively, while all patients had an improvement in the distance covered in 6MWT. Respiratory evaluation with spirometry showed an improvement of parameters in type 2 and 3b patients. There are currently only 2 SMA 2 patients receiving Risdiplam in Dr. Papadopulos center through an early access program. Dr. Papadopulos underlined the need of validated outcome measures and biomarkers for severely affected patients and the implementation of European consensus guidelines for SMA treatment.

Poland: Anna Kostera-Pruszczyk discussed the situation in Poland, a country with 38 million inhabitants. Based on data from their national SMA Registry and epidemiological studies, there are approximately 1000 SMA patients (children and adults) in Poland, half of them are adults. In Poland, the TREAT-NMD SMA registry was established over a decade ago. It is curated by a team at MUW, with a mixed model – data is provided by the patients and curated by a neurologist with expertise in SMA. No data is directly fed into the registry by the patients.

Nusinersen was first available in EAP for 26 pediatric patients (SMA1 only) in 2017. Reimbursement decision allowed to start treatment with Nusinersen in 2019 (Feb 2019 - children, March 2019 - adults). Reimbursed Nusinersen can be offered to SMA5q patients with acceptable intrathecal (IT) access without age limit, also for pre-symptomatic patients. Exclusion criteria follow the drug's label. Over 750 SMA patients are currently treated with Nusinersen at 30 sites (pediatric and adult neurology wards), 45% adults. IT procedures are allowed for hospitalized patients only. The patients are granted access to treatment following decision of Centralized Expert Committee (monthly meetings). Pediatric patients, including children diagnosed in NBS, are granted treatment access by emergency procedure (data review by single expert), to allow timely intervention (same day decision). Nusinersens treatment efficacy is monitored and reported to our national insurer (National Health Fund, NFZ) at baseline, 7th and each consecutive dose. CHOP-INTEND, HINE or HFMSE, depending on the age and clinical severity of the patients, are the scales used. As SMA is a progressive disease, treatment should lead to improvement or stop disease progression. Inefficacy of treatment is defined as deterioration in the functional scale appropriately matched for age and type of SMA: CHOP INTEND or HINE below baseline value persisting in two consecutive evaluations (performed every 4 months), and HFMSE more than 2 points below baseline value confirmed in two consecutive studies performed every 4 months. Until now, there were no discontinuations due to lack of efficacy of Nusinersen. Nusinersen treatment is supported by multidisciplinary care including physiotherapy, pulmonary, nutrition, orthopedic etc. For the patients with severe scoliosis sites provide CT- or ultrasound-guided administration. Risdiplam is available for patients in EAP (children & adults), and clinical trials (all –FISH studies, also adults in JEWELFISH). Overall estimated 850–900 SMA patients are currently treated in Poland with one of the DMTs: Nusinersen is reimbursed while reimbursement of Risdiplam is currently pending. Onasemnogene Abeparvovec is not reimbursed, but at least 25 children were treated with private funding (various fund rising initiatives).

Spain: Juan F Vazquez-Costa explained that in Spain, with 47 million inhabitants and 17 regions, there are approximately 800–1000 SMA patients, and two registries: CUIDAME (an academic, physician-reported registry) and REGISTRAME (patient-reported). Nusinersen is reimbursed since April 2018 for both children and adults, the first adults were treated in June 2018, with inclusion criteria type 1–3, 2–4 *SMN2* copies, HFMSE <54. Clinically advanced patients with NIV >14 h/day or EK2>47 or patients without lumbar access were excluded. Follow-up is mandatory every 8 months with HFMSE, RULM, EK2, FVC, collected in a central database of the Health Department (not in registries). Discontinuation criteria are lack of efficacy, e.g. for walkers an increase in HFMSE $\geq$ 3 + 6MWT $\geq$ 30, after 2 years (and maintained every 8 months afterwards), for non-ambulant patients an increase in HFMSE $\geq$ 3 and RULM $\geq$ 2 after 2 years (and maintained every 8 months afterwards), SAEs or any worsening which is considered to be clinically meaningful. Risdiplam was until recently only available via compassionate use program; 25 SMA non-sitters age 15–48 years were included, 5 of them after Nusinersen withdrawal. Since January 2023, Risdiplam is reimbursed in SMA patients older than 2 months, with type 1–3 and 1–4 *SMN2* copies. In 2022, a national consensus on the start/stop criteria of DMT and on the recommended outcome measures to assess the treatment response was reached by a group of neuropediatricians, neurologists and physical therapists experts on SMA [37].

Within the CUIDAME registry, 73% of SMA patients were treated and 63% within REGISTRAME. However, using population-based data in the Valencian region (with 5 million inhabitants), less than 50% of patients were on treatment, including 28% of patients on Nusinersen who had been discontinued. In total, it is estimated that less than 40% of patients are receiving DMT throughout Spain. It was concluded that access to DMT is unequal and limited in Spain, including initiation and discontinuation criteria of Nusinersen based in clinical trial protocols, which are not representative of the real-world population, and in results that have been often misinterpreted by regulators. The Spanish patient organization and SMA experts have therefore claimed for an initiative to promote the development of European guidelines and recommendations for the follow- up and use of DMTs in SMA patients [38].

5. Natural history studies and registries

Ludo van der Pol summarized the available literature of standards of care for adults with SMA and the natural history of SMA in adults. In contrast to the widely used (revised) standards of care for children, there is no such document for adults. Prof. Eugenio Mercuri announced that the authors of the standards of care for children have the wish to develop a guideline for adults with SMA. Needs of adults with SMA are different from those encountered in children and may be very individual. However, age appropriate, comprehensive, and integrated care and strengthened social and financial support systems were identified as generic terms that could be used as a starting point [39]. The nature of problems encountered by adults probably needs more attention - the Dutch patient organization and healthcare professionals developed a questionnaire that summarizes the wide variety of care needs of patients and that can help to set the agenda prior to consultations. This document that is only available in Dutch (www.levenmetsma.nl) is an example of tools that could help to facilitate personalized care.

Studies on the natural history of SMA after childhood are relatively few [5,13]. Natural history of SMA in children is age-dependent, with motor gains in the first years of life but patterns of decline of motor function in older children [40,41]. Decline of motor function and muscle strength has been documented in adults with all SMA types using HMSE, MRC sum score, MFM and more recently RULM [5,13,15,42]. The level of correlation of instruments for motor function and muscle strength is high, despite differences in floor- and ceiling effects [13]. Natural history studies of respiratory function show decline of FVC and FEV1 in children and adolescents with SMA type 1c-3a, followed by relative stabilization during adulthood [23], although more information is needed on the contribution of floor effects of lung function tests. The natural history of bulbar function is largely unknown. A cross-sectional study on maximal mouth opening supported by MRI suggested deterioration of bulbar muscle quality over time [43], but additional, validated clinical tests are needed to study natural history of bulbar function in more detail.

Shahram Attarian reported on the French SMA registry and natural history in adult SMA patients. In France, 72 centers are labeled Expert centers in NMD, and 32 centers as Reference centers (pediatric and adult). The French SMA patient registry is an observational (real-life) registry, collecting demographic data, genetic-clinical modules (motor, respiratory, neurological, nutritional, cardiac, metabolic), measures, motor outcome validated measures (MFM, HFSME, RULM, 6WMT), QOL interviews (QoL-gNMD), autonomy scales, therapy tolerance and safety modules. Data collection is historical, retrospective and prospective (2016–2025). All types of SMA from infant to adult with genetically confirmed SMA are included, treated or not by SMA specific therapies, followed in a center within the FILNEMUS network. In France, around 1000–1200 patients (50% adults) are estimated, currently, 775 patients from 55 centers are registered, 47% of them adults.

Hélène Prigent elucidated what we know on the respiratory function assessed by FVC, MIP, MEP and DEPt of adult SMA patients. 80 patients with SMA type 2 and 3 between 2 and 30 years of age were included. Results showed that respiratory dysfunction depends on the SMA type, expiratory muscle dysfunction remains predominant in adults, and does not seem progressive in adult SMA. Open questions are the impact of the new therapies on respiratory function [23].

5.1. Registries and data collection in adults with SMA

Eugenio Mercuri informed the group on current registries and data collections in SMA: Originally, the TREAT-NMD patient registries were developed for epidemiology and trial readiness. Patient registries can be run by patient advocacy groups, academia, industry or mixed models. Benefits to patients and families is a link to the research community, feedback on standards of care and new research development, along with feeling a sense of “belonging” to a broader community. Industry and academia benefit from an easy access to the patient community, a clear concept of the target market, feasibility and planning of clinical trials, recruitment of patients into these trials, and usage as a research tool. Disadvantages for academic registries are cost, monitoring accuracy of data, regular queries, regular trainings of physiotherapists and data entry, and an additional burden to routine assessments, and are therefore limited to few centres with more resources and a high number of patients. There is an increasing number of academic registries including most centres on a national level in Germany, UK, France and Spain. In Italy, ITASMAC is a national network including all SMA centres, maintaining strict methodology in data collection using a structured CRF. Challenges and future steps are improving the data entry quality (special apps for recording assessments and adverse events), privacy aspects, cost and sustainability, ownership of data, along with links to biobanks for biomarkers. In contrast to academic registries, industry registries are often a requirement from regulators, even though regulators claim that they prefer independent registries. Therefore, ownership issues and transparency of individual data for analysis may represent a challenge. Therefore, it would be crucial to find an agreement how these registries can live and work together to provide answers for all stakeholders.

Emmanuelle Salort-Campana spoke on the coordination of treatment initiation for adults with SMA in France. In October 2018, national multidisciplinary virtual meetings dedicated to SMA and involving neurologists, physiatrists, neuropediatrician and pulmonologists were initiated, to homogenize the criteria for starting treatment, follow-up and assessment of these patients. Between October 2020 to September 2021, 122 cases were discussed; treatment with Nusinersen was requested for 46 patients, and granted for 32, treatment with Risdiplam was requested for 54 patients, and granted for 26. Either treatment was asked for 5 patients, granted in 4, 3 received Nusinersen, 1 Risdiplam. Treatment switch was requested by 12 patients. In total, 109 patients age 16–62 years were presented, 41 SMA2, 63 SMA3. Most patients were presented only once, 12 patients were presented twice. Most frequently used outcome measures were MFM, FVC, RULM, 6MWT, Myotools, 10MWT, TUG, Clavitest, Brooke, Vignos, Walton Scales, Abilhand, Activlim, MIF, QoL-gNMD, FSS, personalized timing tests, 4-step climb test, GAS and MCRO. For each patient, stopping criteria are defined according to the initial objectives of the treatment and the patient’s disease progression. However, there is heterogeneity of recommendations over time, and analysis of the decision-making process making process is needed to improve the quality and homogeneity of decisions.

Hanns Lochmüller presented NMD4C, a pan-Canadian network bringing together the country’s leading clinical, scientific, technical, and patient expertise to improve care, research, and collaboration in neuromuscular disease. NMD4C aims to formalize and sustain a network of NMD stakeholders united around a cohesive 3-year work plan, train and educate the next generation of NMD stakeholders, raise the standard of care for NMD and access to therapies across Canada, strengthen biomedical and clinical infrastructure to build research capacity. Within NMD4C, SMA-centered initiatives are advocating for access to SMA treatment via CADTH Clinician Group Input submissions: access to Nusinersen (Spinraza) for adult SMA2 and SMA3 $>$ 18 years of age regardless of ambulatory status, access to Risdiplam for patients that are ambulatory, $>$ 25 years of age, or pre-symptomatic $<$2 month of age, generating a consensus statement on gene replacement therapy, developing of a decision aid for SMA treatments, and a CPD-accredited SMA webinar.

Victoria Hodgkinson is responsible for the TREAT-NMD affiliated Canadian Neuromuscular Disease Registry CNDR, where currently 290 SMA patients age 18–79 years are registered, 198 pediatric, and 92 adult patients, consisting of 31 SMA2, 53 SMA3, 2 SMA4 and 6 of unknown type. Unfortunately, access to DMTs is decided by postcode – Nusinersen is only reimbursed for adults in Saskatchenwan and New Brunswick, while use of Risdiplam – depending on where you live – can be restricted to only non-ambulatory patients age 2–25 years. Hopefully, new INESSS Monitoring Recommendations led by an expert committee of clinical experts may lead to revised recommendations.

Tim Hagenacker gave an overview on Start/Stop Criteria for SMA treatments in Germany. In general, there is an overall rational for therapy, since SMA is progressive over all subtypes, even in adults. Therefore, inclusion criteria of pivotal studies are not

suitable, because (mainly) no adults were included, and there are no widely consented criteria. In 2019, a Germany consensus was published with suggested start/stop criteria [44], and Hungarian recommendations also published [45]. However, the criteria are independent of reimbursement criteria – reimbursement criteria in many countries are unfortunately often without scientific rationale.

Hanns Lochmüller and Janbernd Kirschner reported on initiatives of the European Reference Network for Neuromuscular Diseases (ERN EURO-NMD) and TREAT-NMD in SMA data collections, emphasizing the importance of cross-registry collaboration. Data items and outcome measures must be harmonized, and relevant cofounders should be included to control for bias. Technical requirements for a combined analysis are common data elements with exact definition of data field, approval and patient consent for data exchange, FAIRification (Findability, Accessibility, Interoperability, and Reuse of digital assets), and federated models. With the start of TREAT-NMD in 2007 as EU-funded Network of Excellence, SMA registries were implemented in many countries. TREAT-NMD has significantly contributed to harmonization of data collection efforts and performed data analysis from participating registries. The SMA Core Dataset is available on the TREAT-NMD website (www.treat-nmd.eu).

The European Reference Network EURO-NMD (https://ern-euro-nmd.eu) is a Network of Health Care Providers (HCP) in EU member states to improve care for patients with rare neuromuscular diseases; a patient registry for the network is required by the European Commission (EC) to monitor impact of network activities. Participating institution in the development process are ERN EURO-NMD / Assistance Publique – Hôpitaux de Paris, Universitätsklinikum Freiburg, RADBOUDUMC, Stiching United Parent Projects Muscular Dystrophy, Stiching Duchenne Data Foundation, Association Institute de Myologie, Association Francaise contre les myopathies AFM. As rate of progression is slow in adults, generation of meaningful evidence will require long observation periods and large numbers which can only be reached by international collaboration. Registries have evolved from academic/research to health care/reimbursement; data collection at sites for real-world data is dependent on funding and training, and interoperability on European level helps to compare data between sites and countries.

6. Patient expectations, paving the way of a European consortium for care of adults with SMA and guidelines

Laetitia Ouillade recounted on patient experience of treatment, she is Eurordis patient advocate since 2018, and member of the adult committee of SMA Europe since 2021. Treatment options for adult patients are either Nusinersen or Risdiplam, with Nusinersen requiring 4-monthly injections and hospitalizations, and Risdiplam as a daily fluid available only through specialized pharmacies. However, no treatment can sometimes also represent a patient's choice. There is no uniform access across European countries – in France, Nusinersen is the first-line therapy, Risdiplam second-line if criteria are fulfilled. In the Netherlands, Nursinersen is only approved for children <9,5 years, although there is conditional reimbursement for older children and adults; for Risdiplam compassionate use was only possible for SMA type 1 and 2 when Nursinersen can not be adminstered. Even within the same country, not all patients have access, dependent on the treating physician. The clinical trials have forgotten the adult SMA population – few trials include adult patients and only up to age of 25 years, and the professional life of patients in clinical trials is not even considered. Treatment has to be balanced with daily life – adverse events must be managed, sometimes requiring hospitalization, and personal organization is key (Risdiplam always in fridge). Patients fears and questions concern treatment stop, lack of information on fertility and pregnancy issues, weight gain, constipation, treatment access and possible change of criteria, and treatment switch.

Rivka Smit shared her patient expectations in her different roles as a patient, volunteer, employer, employee, and just herself. She reports on her SMA symptoms – she is wheelchair-dependent, has muscle weakness in hands and arms, non-invasive ventilation since 2017, she suffers from fatiguability, mouth opening no more than 9 mm, she has mastication problems and pain in her lower back. She started with Risdiplam in July 2021, without major adverse events, she felt itch and hunger for two weeks. Her personal expectations were stabilization of mastication problems, no invasive ventilation and less or at least stable fatiguability. General expectations are a more personalized medicine in the future, along with a multidisciplinary approach, and more attention for 'new problems' (intestine problems, questions about feeding, healthy life, Qol, giving birth, kidney problems).

7. Harmonization of registries and data collection

Registries are in the center of everything; there is still need for harmonization of registries and data collections. In Germany, there is the national TREAT-NMD SMA patient registry (www.sma-register.de), which is patient-based, and aims on epidemiology and trial readiness, and the SMArtCARE (www.smartcare.de) data collection which assesses longitudinal functional data on the patients, both are complementary; SMArtCARE has been recently joined by Spain (CuidAME). RESTORE is an industry-owned registry by Novartis for patients treated with Onasemnogene Abeparvovec. In France, only physician-based data are collected. However, interoperability between registries remains a challenge, and the EURO-NMD ERN will soon set up an additional registry. A core minimal dataset will be mandatory for collaboration. Today, registries are predominantly industry-sponsored, which might be a problem for long-term sustainability since data requirement of regulators is minimal compared to academic requirements. Therefore, it is of utmost importance to keep academic registries alive. TREAT-NMD patient registries have been launched 15 years ago, and developed individually, but meta-analysis is still possible. Registries host an enormous amount of longitudinal data on natural history, which is valuable and should be published.

7.1. Minimal dataset for the follow-up of adults with SMA treated or non-treated

The TREAT-NMD core dataset has been harmonized within Europe, and most centres already collect these data. Minimal dataset should include motor function such as 6MWT, CHOP INTEND, CHOP ATEND, HFMSE, RULM, MFM, respiratory function (FVC, MIP/MEP, PCF), QoL measurements, PROMs, biomarkers and eventually MUNE/MUNIX. Importantly, regular training for the scales is mandatory, and keeping up with the patients is very time consuming, even in specialized centres due to many patients. It is also important to decide for harmonized testing intervals – every 6 months, or every 4 months according to the Nusinersen treatment schedule? Motor function scales often overlap, and it is difficult do decide which scale is the best for the individual patient. MFM is predominantly used in France, while HFSME and RULM are more frequently used in other countries. The CHOP-INTEND was initially used for non-sitting children, a recent adaption is the CHOP-ATEND for adult non-sitters (https://med.stanford.edu/day-lab/atend.html). It would be ideal to perform all these measurements, but unfortunately is not feasible regarding time and training, and the situation in each country and center is different; therefore,

development of a toolkit would be helpful for deciding, which outcome measure would be most suitable for which research question, e.g. a phenotype-related data set (CHOP-ATEND for adult non-sitters, RULM/HFMSE in sitters, HFMSE/6MWT in walkers, respiratory status (NIV, tracheotomy), FVC and PCF in all), optional ALS-FRS.

7.2. . Consensus draft protocol for monitoring of nusinersen and risdiplam safety and efficacy

Efficacy of either treatment should be assessed via the minimal data set. Male fertility problems and teratogenicity seen in Risdiplam animal data are important topics for patients in treatment decisions and should be proactively discussed with adolescents and adults regarding parenthood, pregnancy, and family planning.

8. Transition from pediatric to adult care

Maggie Walter presented the German AWMF guidelines for transition from pediatric to adult care (https://register.awmf.org/assets/guidelines/186–001l_S3_Transition_Paediatrie_Erwachsenenmedizin_2021–04.pdf). An individualized transition plan should be created for the transition process, which defines and terminates the individual action points. The willingness and ability to transition should be captured in a detailed clinical conversation. The time of transfer into adult care should consider the characteristics of the disease and the individual patient and should not be rigidly linked to the 18th birthday. The transition process should include training for the patient and, if necessary, his parents / caregivers on relevant aspects of the disease and the transfer. The transition process should be organized in an interdisciplinary manner. For the transfer, a structured epicrisis on the previous course of the disease with medical and psychosocial content as well as treatment-relevant preliminary findings should be provided to the patient and to the physician in adult care. One responsible contact person should chaperon the transition. To improve adherence and adherence to deadlines, low threshold offers should be used as reminders and information on suitable websites, apps, SMS, email and / or telephone, if available. In the case of younger adolescents, the parents / caregivers should be included into the transition process. Even after the transfer, it may be helpful to involve them in the process. In the case of patients with cognitive impairments, the involvement of parents / caregivers is mandatory. The offer of a joint consultation or case discussion involving paediatricians and adult care physicians who will provide further treatment can be considered. To support the transition process, not only individual action points should be applied, but several of the recommendations should be combined in a meaningful way. Transition talks should start early and in line with development. In the transition process, topics relevant to young people such as sexuality, family planning, sleep-wake rhythm, consumption of alcohol, nicotine and illegal substances and their interaction with the disease and its therapy should be addressed by the treatment team. Screening for psychological stress and abnormalities should be part of the routine treatment for chronic illnesses. Sufficient time (combined with appropriate remuneration) should be allowed for in-depth transition discussions in paediatrics, but also with the future adult care physician. The responsibility for disease management should gradually pass from parents to adolescents. Counselling for young people on professional and social issues related to the chronic disease should be offered. Young patients should be made aware of the support groups and patient organizations that are relevant to them. Support groups and patient organizations can be included in the design of the transition process.

9. Future activities of the consortium and European data collection

Importantly, additional European countries should be included, e.g. Hungary, Portugal, and others). There is an urgent need for the development of suitable bedside functional scales, PROMs, wearables, and dedicated apps for SMA patients. Regarding data collection, Janbernd Kirschner suggested to provide a table to all participants in collaboration with SMA Europe to map for the existing registries and EURO-NMD, focusing on observational long-term data. Future activities consist of paving the way to access to treatments for adult SMA patients across Europe, updating standards of care, standardization of biomarker collection, and guidelines for switch of treatment.

10. Towards organization of a follow-up workshop dedicated to adult guidelines

The group agreed that there are still unmet needs for adult SMA patients, and a follow-up workshop dedicated to adult guidelines would be warranted and applied for, paving the way of a European adults SMA network.

Workshop participants / study group

Attarian, Shahram. Reference Center for Neuromuscular Disorders and ALS, AP-HM, CHU La Timone, Marseille, France

Bartels, Bart. Child Development and Exercise Centerm University Medical Center Utrecht, Netherlands

Gorni, Ksenija. PDMA Neuroscience and Rare Disease, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Goemans, Nathalie. Department of Pediatric Neurology, University Hospitals Leuven, Belgium

Gusset, Nicole. SMA Europe, Freiburg, Germany

Hodgkinson, Victoria. Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Canada

Hagenacker, Tim. Department of Neurology and Center for Translational Neuro- and Behavioral Sciences (C-TNBS), University Hospital Essen, Germany

Kirschner, Janbernd. Department of Neuropediatrics and Muscle Disorders, Faculty of Medicine, Medical Center-University of Freiburg, Germany

Klein, Andrea. Neuropädiatrie, Rehabilitation und Entwicklung, Universitätsklinik für Kinderheilkunde, Inselspital, Bern, Switzerland

Kostera-Pruszczyk, Anna. Department of Neurology, Medical University of Warsaw, Poland

Lochmüller, Hanns. Children's Hospital of Eastern Ontario Research Institute; Division of Neurology, Department of Medicine, The Ottawa Hospital; and Brain and Mind Research Institute, University of Ottawa, Canada

Marini-Bettolo, Chiara. The John Walton Muscular Dystrophy Research Center, Translational and Clinical Research Institute, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

Mercuri, Eugenio. Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy

Muni-Lofra, Robert. The John Walton Muscular Dystrophy Research Center, Translational and Clinical Research Institute, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

Ouillade, Laetitia. GI SMA, AFM Telethon, France

Quinlivan, Rosaline. National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, Queen Square, London, UK

Papadopoulos, Constantinos. Department of Neurology, Eginition Hospital, University of Athens, Greece

Prigent, Hélène. Department of Physiology and FHU Phenix, Hôpital Raymond Poincaré – GHU APHP University Paris Saclay – Garches, France

Salort-Campana, Emmanuelle. Service des maladies neuromusculaires et de la SLA, Hôpital de La Timone, Marseille, France

Sansone, Valeria A. Neurorehabilitation Unit, the NeMO Clinical Center in Milan, University of Milan, Italy

Smit, Rivka. SMA patient

Smeriglio, Piera. Biotherapies for Motor Neuron Disorders, Sorbonne Université, Center de Recherche en Myologie UMRS 974, Institut de Myologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France

Thiele, Simone. Friedrich-Baur-Institute at the Department of Neurology, University Hospital, LMU Munich, Germany

Tichler, Ben. Biogen Switzerland, Zug, Switzerland

Van den Bergh, Peter. Neuromuscular Reference Center, Department of Neurology, University Hospital Saint-Luc, Brussels, Belgium

Vazquez-Costa, Juan F. Neuromuscular Unit, Department of Neurology, Hospital Universitario y Politécnico la Fe, Valencia, Spain.

Vissing, John. Neuromuscular Clinic and Research Unit, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark

Declaration of Competing Interest

Maggie C. Walter has served on advisory boards for Avexis, Biogen, Novartis, Pfizer, Roche, Santhera, Sarepta, PTC Therapeutics, Ultragenyx, Wave Sciences, received funding for Travel or Speaker Honoraria from Avexis, Biogen, Novartis, Pfizer, Roche, Ultragenyx, Santhera, PTC Therapeutics, and worked as an ad-hoc consultant for AskBio, Audentes Therapeutics, Biogen Pharma GmbH, Fulcrum Therapeutics, Novartis, PTC Therapeutics, and consulted for Affinia, Biogen, BridgeBio, Edgewise, Pharnext, PTC Therapeutics, Roche.

Pascal Laforêt has served on advisory boards for Biogen, Roche, AMICUS Therapeutics, Sanofi-Genzymze, MAZE Therapeutics, received funding for Travel or Speaker Honoraria from Sanofi-Genzyme, and received research fundings from Sanofi-Genzyme and AMICUS Therapeutics.

W. Ludo van der Pol has served as an ad-hoc member on advisory boards for Avexis, Biogen, Novartis, Roche, Scholar Rock, Argenx and Takeda.

Elena Pegoraro has served on advisory board for Alexion, UBC, Sarepta, Biogen, Roche, Sanofi. Received funding for travel or speaking from Alexion, Biogen, Roche, Sanofi.

Acknowledgments

The workshop was made possible thanks to the financial support of the European Neuromuscular Center (ENMC) and ENMC main sponsors: Association Française contre les Myopathies (France), Deutsche Gesellschaft für Muskelkranke (Germany), Muscular Dystrophy Campaign (UK), Muskelsvindfonden (Denmark), Prinses Beatrix Fonds (The Netherlands), Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (Switzerland), Telethon Foundation (Italy), Spierziekten Nederland (The Netherlands), and Associated members Partners: Finnish Neuromuscular Association (Finland), Österreichische Muskelforschung (Austria), SMA Europe and World Duchenne Organization. In addition, we would like to thank the members of the ENMC Company Forum: Sanofi, Roche, Lupin Neuroscience, Amicus Therapeutics, Ionis Pharmaceuticals, Biogen, Novartis, PerkinElmer and Astellas.

References

[1] Sansone VA, Walter MC, Attarian S, Delstanche S, Mercuri E, Lochmüller H, et al. Measuring outcomes in adults with spinal muscular atrophy - challenges and future directions - meeting report. J Neuromuscul Disord 2020;7:523–34. doi:10.3233/JND-200534.

[2] Cartegni L, Hastings ML, Calarco JA, de Stanchina E, Krainer A. Determinants of exon 7 splicing in the spinal muscular atrophy genes, SMN1 and SMN2. Am J Hum Genet 2006;78:63–77. doi:10.1086/498853.

[3] Kashima T, Rao N, David CJ, Manley JL. hnRNP A1 functions with specificity in repression of SMN2 exon 7 splicing. Am Mol Genet 2007;16:3149–59. doi:10.1093/hmg/ddm276.

[4] Feldkötter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet 2002;70:358–68. doi:10.1086/338627.

[5] Wadman RI, Wijngaarde CA, Stam M, Bartels B, Otto LAM, Lemmink HH, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. Eur J Neurol 2018;25:512–18. doi:10.1111/ene.13534.

[6] Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018;28:103–15. doi:10.1016/j.nmd.2017.11.005.

[7] Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord 2018;28:197–207. doi:10.1016/j.nmd.2017.11.004.

[8] Mercuri E, Darras BT, Chiriboga C, Day JW, Campbell C, Conolly AM, et al. CHERISH study group. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med 2018;378:625–35. doi:10.1056/NEJMoa1710504.

[9] Darras BT, Masson R, Mazurkiewicz-Beldzinska M, Rose K, Xiong H, Zanoteli E, et al. FIREFISH working group. Risdiplam-treated infants with type 1 spinal muscular atrophy versus historical controls. N Engl J Med 2021;385:427–35. doi:10.1056/NEJMoa2102047.

[10] Mercuri E, Baranello G, Boespflug-Tanguy O, De Waele L, Goemans N, Kirschner JSUNFISH Working Group. Risdiplam in types 2 and 3 spinal muscular atrophy: a randomised, placebo-controlled, dose-finding trial followed by 24 months of treatment. Eur J Neurol 2022 online ahead of print. doi:10.1111/ene.15499.

[11] Gavriilaki M, Moschou M, Papaliagkas V, Notas K, Chatzikyriakou E, Papagiannopoulos S, et al. Nusinersen in adults with 5q spinal muscular atrophy: a systematic review and meta-analysis. Neurotherapeutics 2022;19:464–75. doi:10.1007/s13311-022-01200-3.

[12] Günther R, Wurster CD, Cordts I, Koch JC, Kamm C, Petzold D, et al. Patient-reported prevalence of non-motor symptoms is low in adult patients suffering from 5q spinal muscular atrophy. Front Neurol 2019;10:1098. doi:10.3389/fneur.2019.01098.

[13] Wijngaarde CA, Stam M, Otto LAM, Bartels B, Asselman FL, van Eijk RPA, et al. Muscle strength and motor function in adolescents and adults with spinal muscular atrophy. Neurology 2020;95:e1988–98. doi:10.1212/WNL.0000000000010540.

[14] Pechmann A, König K, Bernert G, Schachtrup K, Schara U, Schorling D, et al. SMArtCARE - a platform to collect real-life outcome data of patients with spinal muscular atrophy. Orphanet J Rare Dis 2019;14:18. doi:10.1186/s13023-019-0998-4.

[15] Coratti G, Pane M, Lucibello S, Pera MC, Pasternak A, Montes J, et al. Age related treatment effect in type II spinal muscular atrophy pediatric patients treated with Nusinersen. Neuromuscul Disord 2021;31:596–602. doi:10.1016/j.nmd.2021.03.012.

[16] Walter MC, Wenninger S, Thiele S, Stauber J, Hiebeler M, Greckl E, et al. Safety and treatment effects of nusinersen in longstanding adult 5q-SMA Type 3 - a prospective observational study. J Neuromuscul Disord 2019;6:453–65. doi:10.3233/JND-190416.

[17] Hagenacker T, Wurster CD, Günther R, Schreiber-Katz O, Osmanovic A, Petri S, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. Lancet Neurol 2020;19:317–25. doi:10.1016/S1474-4422(20)30037-5.

[18] Maggi L, Bello L, Bonanno S, Govoni A, Caponnetto C, Passamano L, et al. Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3. J Neurol Neurosurg Psychiatry 2020;91:1166–74. doi:10.1136/jnnp-2020-323822.

[19] Vázquez-Costa JF, Povedano M, Nascimiento-Osorio AE, Escribano AM, Kapetanovic-Garcia S, et al. Validation of motor and functional scales for the evaluation of adult patients with 5q spinal muscular atrophy. Eur J Neurol 2022;29:3666–75. doi:10.1111/ene.15542.

[20] Lizandra Cortés P, Poveda-Veru D, Ferriz AA, Nungo-Garzon NC, Domine MC, Sevilla-Mantecon T, et al. Validation of neuromyotype: a smart keyboard for the evaluation of spinal muscular atrophy patients. Neurología 2022 (English Edition)online ahead of print. doi:10.1016/j.nrleng.2022.05.001.

[21] Querin G, Lenglet T, Debs R, Stojkovic T, Behin A, Salachas F, et al. Development of new outcome measures for adult SMA type III and IV: a multimodal longitudinal study. J Neurol 2021;268:1792–802. doi:10.1007/s00415-020-10332-5.
[22] Vázquez-Costa JF, Branas-Pampillon M, Medina-Cantillo M, Povedano M, Pitarch-Castellano I, Lopez-Lobato M, et al. Validation of a set of instruments to assess patient- and caregiver-oriented measurements in spinal muscular atrophy: results of the SMA-TOOL study. Neurol Ther 2022;12:89–105. doi:10.1007/s40120-022-00411-2.
[23] Wijngaarde CA, Veldhoen ES, van Eijk RPA, Stam M, Otto LAM, Asselman FL, et al. Natural history of lung function in spinal muscular atrophy. OJRD 2020;15:88. doi:10.1186/s13023-020-01367-y.
[24] Paganoni S, Berry JD, Quintana M, Macklin E, Sabille BR, Detry MA, et al. Adaptive platform trials to transform amyotrophic lateral sclerosis therapy development. Ann Neurol 2022;91:165–75. doi:10.1002/ana.26285.
[25] Mendell JR, Al-Zaidy SA, Lehman KJ, McColly M, Lowes LP, Alfano LN, et al. Five-year extension results of the phase 1 START trial of onasemnogene abeparvovec in spinal muscular atrophy. JAMA Neurol 2021;78:834–41. doi:10.1001/jamaneurol.2021.1272.
[26] Day JW, Mendell JR, Mercuri E, Finkel RS, Strauss KA, Kleyn A, et al. Clinical trial and postmarketing safety of onasemnogene abeparvovec therapy. Drug Saf 2021;44:1109–19. doi:10.1007/s40264-021-01107-6.
[27] Kizina K, Stolte B, Totzeck A, Bolz S, Fleischer M, Mönninghoff C, et al. Clinical implication of dosimetry of computed tomography- and fluoroscopy-guided intrathecal therapy with Nusinersen in adult patients with spinal muscular atrophy. Front Neurol 2019;10:1166. doi:10.3389/fneur.2019.01166.
[28] Rosiak G, Lusakowska A, Milczarek K, Konecki D, Fraczek A, Rowinski O, et al. Ultra-low radiation dose protocol for CT-guided intrathecal Nusinersen injections for patients with spinal muscular atrophy and severe scoliosis. Neuroradiology 2021;63:539–45. doi:10.1007/s00234-021-02643-9.
[29] Spiliopoulus S, Reppas L, Zompola C, Palaiodimou L, Filippiadis D, Palialexis K, et al. Computed-tomography-guided transforaminal intrathecal Nusinersen injection in adults with spinal muscular atrophy type 2 and severe spinal deformity. Feasibility, safety and radiation exposure considerations. Eur J Neurol 2020;27:1343–9. doi:10.1111/ene.14245.
[30] Veiga-Canuto D, Cifrian-Perez M, Pitarch-Castellano I, Vazquez-Costa JF, Aparici F. Ultrasound-guided lumbar puncture for Nusinersen administration in spinal muscular atrophy patients. Eur J Neurol 2021;28:676–80. doi:10.1111/ene.14586.
[31] Rizzo F, Nizzardo M, Vashisht S, Molteni E, Melzi V, Taiana M, et al. Key role of SMN/SYNCRIP and RNA-Motif 7 in spinal muscular atrophy: RNA-seq and motif analysis of human motor neurons. Brain 2019;142:276–94. doi:10.1093/brain/awy330.
[32] Nizzardo M, Taiana M, Rizzo F, Aguila-Benitez J, Nijssen J, Allodi I, et al. Synaptotagmin 13 is neuroprotective across motor neuron diseases. Acta Neuropathol 2020;139:837–53. doi:10.1007/s00401-020-02133-x.
[33] Kessler T, Latzer P, Schmid D, Warnken U, Saffari A, Ziegler A, et al. Cerebrospinal fluid proteomic profiling in Nusinersen-treated patients with spinal muscular atrophy. J Neurochem 2020;153:650–61. doi:10.1111/jnc.14953.
[34] Darras BT, Crawford TO, Finkel RS, Mercuri E, De Vivo DC, Oskoui M, et al. Neurofilament as a potential biomarker for spinal muscular atrophy. Ann Clin Transl Neurol 2019;6:932–44. doi:10.1002/acn3.779.
[35] Totzeck A, Stolte B, Kizina K, Bolz S, Schlag M, Thimm A, et al. Neurofilament heavy chain and tau protein are not elevated in cerebrospinal fluid of adult patients with spinal muscular atrophy during loading with Nusinersen. Int J Mol Sci 2019;20:5397. doi:10.3390/ijms20215397.
[36] Pino MG, Rich KA, Kolb SJ. Update on biomarkers in spinal muscular atrophy. Biomark Insights 2021;16. doi:10.1177/11772719211035643.
[37] Pitarch Castellano I, Cabrera-Serrano M, Calvo Medina R, Cattinari MG, Espinosa Garcia S, Fernandez-Ramos JA, et al. Delphi consensus on recommendations for the treatment of spinal muscular atrophy in Spain (RET-AME consensus). Neurologia 2022;37:216–28. doi:10.1016/j.nrleng.2021.07.002.
[38] Vázquez-Costa JF, Martinez-Moreno M, Madruga-Garrido M, Munell F, Nascimento A, Pitarch-Castellano I, et al. Treatment of spinal muscular atrophy in European countries: a call to action. Eur J Neurol 2022;29:3475–7. doi:10.1111/ene.15522.
[39] Walter MC, Chiriboga C, Duong T, Goemans N, Mayhew A, Ouillade L, et al. Improving care and empowering adults living with SMA: a call to action in the new treatment era. J Neuromuscul Disord 2021;8:543–51. doi:10.3233/JND-200611.
[40] Mercuri E, Finkel R, Montes J, Mazzone ES, Sormani MP, Main M, et al. Patterns of disease progression in type 2 and 3 SMA: implications for clinical trials. Neuromuscul Disord 2016;26:126–31. doi:10.1016/j.nmd.2015.10.006.
[41] Kaufmann P, McDermott MP, Darras BT, Finkel RS, Sproule DM, Kang PB, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology 2012;79:1889–97. doi:10.1212/WNL.0b013e318271f7e4.
[42] Annoussamy M, Seferian AM, Daron A, Péréon Y, Cances C, Vuillerot C, et al. Natural history of type 2 and 3 spinal muscular atrophy: 2-year NatHis-SMA study. Ann Clin Transl Neurol 2021;8:359–73. doi:10.1002/acn3.51281.
[43] Wadmann RI, van Bruggen HW, Witkamp TD, Sparreboom-Kalaykova SI, Stam M, van den Berg LH, et al. Bulbar muscle MRI changes in patients with SMA with reduced mouth opening and dysphagia. Neurology 2014;83:1060–6. doi:10.1212/WNL.0000000000000796.
[44] Hagenacker T, Hermann A, Kamm C, Walter MC, Weiler M, Günther R, et al. Spinal muscular atrophy - expert recommendations for the use of Nusinersen in adult patients]. Fortschr Neurol Psychiatr 2019;87:703–10. doi:10.1055/a-0996-0994.
[45] Boczán J, Klivenyi P, Kalman B, Szell M, Karcagi V, Zadori D, et al. Consensus statement of the hungarian clinical neurogenic society about the therapy of adult SMA patients. [Article in Hungarian]. Ideggyogy Szle 2021;74:79–86. doi:10.18071/isz.74.0079.