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Original article

2024 update: European consensus statement on gene therapy for spinal muscular atrophy

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ABSTRACT

Spinal muscular atrophy (SMA) is one of the most common genetic diseases and was, until recently, a leading genetic cause of infant mortality. Three disease-modifying treatments have dramatically changed the disease trajectories and outcome for severely affected infants (SMA type 1), especially when initiated in the presymptomatic phase. One of these treatments is the adeno-associated viral vector 9 (AAV9) based gene therapy onasemnogene abeparvovec (Zolgensma®), which is delivered systemically and has been approved by the European Medicine Agency for SMA patients with up to three copies of the *SMN2* gene or with the clinical presentation of SMA type 1. While this broad indication provides flexibility in patient selection, it also raises concerns about the risk-benefit ratio for patients with limited or no evidence supporting treatment.

In 2020, we convened a European neuromuscular expert working group to support the rational use of onasemnogene abeparvovec, employing a modified Delphi methodology. After three years, we have assembled a similar yet larger group of European experts who assessed the emerging evidence of onasemnogene

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abeparvovec's role in treating older and heavier SMA patients, integrating insights from recent clinical trials and real-world evidence. This effort resulted in 12 consensus statements, with strong consensus achieved on 9 and consensus on the remaining 3, reflecting the evolving role of onasemnogene abeparvovec in treating SMA.

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disease caused by biallelic pathogenic variants in the *SMN1* gene, characterized by loss of motor neurons and progressive muscle weakness. The disease encompasses a broad spectrum of disease severity, and the main predictor of severity is the number of *SMN2* copies. *SMN2* is a highly homologous gene, which can partially compensate for the lack of functional *SMN1*. The majority of patients display 2 copies of *SMN2* and present with the most severe form of the disease that starts during the first six months of life. Higher *SMN2* copy numbers are associated with later onset and less severe course – although all forms of SMA are degenerative and are associated with progressive and severe motor disability [1–3].

Since 2017 three different drugs have been approved for the treatment of SMA. While nusinersen and risdiplam increase SMN protein production by modifying the splicing of *SMN2*, onasemnogene-abeparvovec is a one-time gene therapy, which adds a fully functional copy of the *SMN1* gene. For all three drugs it has been shown that early or ideally presymptomatic treatment is associated with best outcome. Therefore, an increasing number of countries have introduced a genetic test for SMA as part of their national newborn screening programs. Availability of disease-modifying treatments and introduction of newborn screening have dramatically changed the course of disease, so that these treated patients do not follow the traditional course of the disease. For example, patients with three copies of *SMN2*, who typically present with SMA type 2 and would normally never walk, often achieve walking ability following early treatment. Similarly, patients with two *SMN2* copies, who usually develop SMA type 1 and would not be expected to sit independently, often attain autonomous sitting, and many eventually become ambulant. In addition, these patients may not require respiratory or feeding support, in striking contrast with the natural history of the disease [4]. Patients who are not identified through newborn screening and receive treatment in advanced stages of the disease often continue to experience a significant disease burden, despite the use of disease-modifying treatments [5,6].

In 2020 the European Medicine Agency (EMA) approved onasemnogene-abeparvovec (Zolgensma®) for the treatment of SMA. Onasemnogene abeparvovec is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9) based vector containing the cDNA of the human *SMN1* gene under the control of the cytomegalovirus enhancer/chicken-β-actin-hybrid promoter.

The EMA label includes two groups of patients for treatment with gene therapy.

- patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1
- patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene.

In contrast to the US, where the Food and Drug Administration (FDA) defined an age limit of two years, the EMA label does not include any age or body weight limit. Nevertheless, at the country level, many payers have introduced limits primarily related to age or functional status. The fact that at the time of approval clinical data where only available for SMA patients treated during the first six months of life with a body weight below 8.4 kg, prompted the authors in 2020 to publish an ad-hoc consensus statement to provide some guidance on the use of gene therapy for SMA in Europe in the context of a broad label and limited available evidence [7]. In that statement, we cautioned against the uncritical use of onasemnogene-abeparvovec in older and heavier patients and called for the collection of additional data from clinical trials and real-world use. Following our initial publication, the patient organization SMA Europe issued a response that supported our statements, while also highlighting the challenges parents encounter in making life-determining treatment decisions, the varying individual perspectives on quality of life, and concerns that statements about limited benefits could lead to restrictions on availability [8].

Since the 2020 publication of these statements, significant new data have emerged, with over 3700 SMA patients worldwide treated with onasemnogene abeparvovec [9]. Given the growing evidence of its effectiveness and safety, the authors have found it necessary to revisit the original statements and present an update that reflects the current treatment landscape.

2. Methodology

The methods used to develop this updated consensus statement were similar to those used for the original publication. To broaden representation across Europe we have added additional experts from countries that were previously not represented (19 authors in the current effort, while 13 in the previously published consensus). The consensus process included a series of virtual meetings. After an initial kick-off meeting, we performed an anonymous voting on the previous consensus statements from 2020. For each of the 11 statements participants could vote and decide if the statement should remain unchanged, be adapted, or deleted. In case of a request for change, participants were asked to make concrete suggestions. In addition, the questionnaire provided an option to suggest additional new statements. After this initial voting, we separated in three subgroups to discuss the results of the voting and individual statements in more details. In addition, we organized an ad-hoc meeting with Novartis to allow the company to share interim results of the ongoing SMART study (NCT04851873) evaluating the use of gene therapy for SMA patients with a body weight of up to 21 kg. Even though results have not been published yet in a peer-reviewed journal, we were aware that interim data would have been released at the end of June 2023 at the Cure SMA meeting in US, we deemed the effort to gather information from this trial appropriate, as the observations are highly relevant for this updated consensus. To conclude the consensus process, the whole group performed two additional meetings to discuss the results from the working groups and adapt the statements accordingly.

In January 2024, we finalized the consensus process with the second and final round of anonymous voting on the statements, using a three-point scale: 'fully agree', 'partly agree', and 'do not agree'. If more than 95 % of responses were 'fully agree', this was considered a 'strong consensus'. If between 75 % and 95 % responded 'fully agree', it was categorized as 'consensus'. Between 50 % and 75 % was considered 'majority consensus', and less than 50 % 'fully agree' was labelled as 'no consensus'.

3. Results

Nineteen neuromuscular disease experts from 17 countries across Europe participated in the consensus process. Response rate in both anonymous surveys was 100 % (19/19). During the initial voting on the original statements from 2020, a majority of participants requested an adaptation of statement 3 (15/19) and statement 10 (10/19). For statement 11 all participants voted to keep it unchanged. For the remaining statements (1, 2, 4, 5, 6, 7, 8, and 9) a minority (between 2

and 7 of 19 participants) suggested a revision. One expert suggested to delete statements 9 and 11, respectively. For detailed results of initial voting see Supplementary Table 1. Results of the final voting are mentioned after each statement in the following section.

3.1. Consensus statement 1

Traditional SMA types (e.g. type 0, 1, 2, 3, 4) alone are not sufficient to define patient populations who might benefit most from gene therapy. In symptomatic patients, age at onset, disease duration and motor function status at the start of treatment are the most important factors that predict response to treatment.

Voting results: Fully agree: 19 (100 %)

Comment: This consensus statement remained unchanged. For rationale see original consensus publication [7] and supplemental material.

During the process, it was also suggested that in addition to motor function, bulbar and respiratory function are also relevant for capturing the broader range of severity of SMA patients. However, it was concluded that additional data from a larger number of patients would be required before having a full picture of the role of these different variables.

3.2. Consensus statement 2

In truly presymptomatic patients, *SMN2* copy number is the most important predictor of clinical severity and age of onset. As long as no better biomarkers or predictors are available, treatment decisions for presymptomatic patients should primarily be based on *SMN2* copy number. Determination of *SMN2* copy number needs to be performed in an expert laboratory with adequate measures of quality control.

Voting results: Fully agree: 19 (100 %)

Comment: This consensus statement remained unchanged. For rationale see original consensus publication [7] and supplemental material. With increasing number of patients identified by newborn screening, it should be stressed that some of these patients are already symptomatic at birth or treatment initiation [4] and are thus not “truly presymptomatic” in the sense of this statement.

3.3. Revised consensus statement 3

An important aspect to consider when assessing the possibilities to treat with onasemnogene abeparvovec older and heavier patients compared to the younger, lighter, and less chronic patients, is that while the risk-benefit ratio for those younger age group is well documented from multiple published studies, there is still limited data on the efficacy of onasemnogene abeparvovec in the older and heavier population. In this patient population it is particularly important for physicians to discuss with families the fact that the risk-benefit ratio is still unknown, and to carefully manage parents’ or patients’ expectations.

Voting results: Fully agree: 18 (95 %), partly agree 1 (5 %)

Comment: When the original consensus statement was developed in 2020, it was mainly based on the pivotal studies in infants up to 6 months of age and some real-world evidence from the US where onasemnogene abeparvovec was approved for patients up to two years of age.

Meanwhile additional data became available on treatment of older and heavier patients. Weiss et al. reported a series of 76 patients treated with onasemnogene abeparvovec with a mean age of 16.8 months (range 0.8–59.0) and a mean body weight of 9.1 kg (range 4.0–15.0). Pane et al. reported 67 patients aged up to 72 months including many patients with a body weight between 8.5 and 13.5 kg and one patient with a body weight of 17 kg. The risk of liver enzyme elevation was associated with higher age and body weight [10].

Novartis has recently concluded a study (NCT04851873) in which 24 children with a body weight between 8.5 and 21 kg were recruited and treated with intravenous onasemnogene abeparvovec. Preliminary results were first presented at an international meeting in June 2023 (Cure SMA) and were recently content of a press release [9].

The previous statement has been revised to reflect the growing body of evidence concerning older and heavier patients. The updated version now emphasizes the uncertainties in the risk-benefit ratio for older patients. Furthermore, emerging evidence suggests that age may be a more significant risk factor than weight [11].

After the final consensus voting, a UK-based series of 99 patients with body weights ranging from 3.2 to 20.2 kg was published. The authors found that increase in transaminases and the need for higher steroid doses were correlated with body weight, being more pronounced in heavier patients [5]. Thus, further research is needed to determine whether the risk of side effects increases with age, body weight, or both. Meanwhile, both factors need to be considered.

3.4. Consensus statement 4

In patients presenting symptoms at birth, treated after a long disease duration, or with already severe evolution, parents should be clearly made aware that despite the use of gene therapy there is a high risk of living with a very severe disability. Palliative care should be discussed as an alternative treatment option in these circumstances.

Voting results: Fully agree: 19 (100 %)

Comment: This consensus statement remained unchanged. For rationale see original consensus publication [7] and supplemental material.

3.5. Revised consensus statement 5

Since the risk of gene therapy increases with the dose administered and since the dose is proportional with the weight and age, heavier and older patients should be treated very cautiously as the data available in these patients are very scarce. Treatment with other disease-modifying treatments or future intrathecal administration of onasemnogene abeparvovec if it shows an acceptable efficacy-safety ratio, should be considered as a valuable alternative, and discussed with parents.

Voting results: Fully agree: 19 (100 %)

Comment: In our initial 2020 consensus statement, shortly after approval of onasemnogene abeparvovec, we suggested a body weight limit of 13.5 kg. This recommendation was based on the lack of experience with heavier patients [7]. Given the expanding body of evidence, the somewhat arbitrary body weight limit for the use of onasemnogene abeparvovec seemed questionable. Instead, the group has chosen to emphasize the importance of conducting individual risk/benefit assessments that also consider other available treatment options.

As outlined already in the context of consensus statement 3, recent publications and findings from the SMART study indicate that older and/or heavier patients face a higher risk of adverse events and require increased doses of steroids for longer durations [5,10–12]. In addition, clinical trials are exploring the intrathecal application of onasemnogene abeparvovec as an alternative strategy for older patients [13].

However, this approach remains in the clinical development stage and has not yet received regulatory approval.

3.6. Revised consensus statement 6

In absence of convincing evidence of published superiority of the combination of two disease-modifying treatments (e.g. gene therapy and nusinersen; or gene therapy and risdiplam), combinatorial therapies cannot be recommended at the moment. A controlled clinical trial

setting with head-to-head-comparison of one vs. two disease-modifying treatments is regarded as gold-standard to answer this open question.

Voting results: Fully agree: 18 (95 %), partly agree 1 (5 %)

Comment: Besides nusinersen, risdiplam has been available since 2021 as an additional disease-modifying treatment for SMA and has therefore been included in the statement. Risdiplam is an orally administered small molecule, that enhances SMN protein production by modifying the splicing of the *SMN2* gene [14,15].

Several combinations of disease-modifying treatments have been reported in the real world, and classifications that define "bridging" (using temporary nusinersen or risdiplam before gene therapy), "adding" and "switching" have been proposed [16]. While bridging might be appropriate in specific situations where one therapy is not readily available, our statement refers to the simultaneous use of two treatments. Although some clinical trials and publications report on the combination of different disease-modifying treatments (e.g. nusinersen or risdiplam after onasemnogene abeparvovec), they do not conclusively prove that a combination is superior to any single treatment due to the lack of an adequate control group [17,18]. Since all three approved treatments primarily exert their effects by increasing SMN protein levels, it remains questionable whether there is an additive benefit when targeting motor neurons. In addition, the significant cost of disease-modifying treatments questions the cost-effectiveness and the sustainability of this strategy, especially when the cost of the drug is added to the cost of standard of care [19].

3.7. Consensus statement 7

Centres performing gene therapy for SMA should have broad expertise in the assessment and treatment of SMA according to international standards. They should also have the ability and resources to deal with potential side effects of gene therapy. Personnel should be trained and have experience in the use of standardized and validated outcome measures for SMA to document treatment effects. Recognition as European Reference Centre (www.ern-euro-nmd.eu) or national accreditation as neuromuscular centre of expertise might serve as additional selection criteria.

Voting results: Fully agree: 19 (100 %)

Comment: This consensus statement remained unchanged. For rationale, please see original consensus publication [7] and supplemental material.

3.8. Revised consensus statement 8

There is convincing evidence that early initiation of any disease-modifying treatment, ideally in the presymptomatic stage of the disease, is associated with markedly better outcome as compared to later start of treatment. In newly diagnosed patients, including those identified by NBS, any delay of treatment should be avoided. Ideally, the time frame between diagnosis and initiation of a disease-modifying treatment should be the shortest possible. Patients with SMA type 1 and/or 2 copies of *SMN2* should be considered medically urgent.

Voting results: Fully agree: 19 (100 %)

Comment: Early treatment administration is crucial for infants expected to develop SMA type 1 due to the disease's rapidly progressive nature. In instances where events such as viral infections, vaccinations, or logistical challenges (e.g. travel, insurance issues) delay gene therapy, the immediate initiation of an alternative disease-modifying treatment must be considered as a bridge. Several real-world evidence publications have shown that any disease-modifying treatment, including onasemnogene abeparvovec, can be initiated in less than 14 days from diagnosis [4]. Given that infants with SMA, especially those with 2 copies of the *SMN2* gene, can develop or exacerbate symptoms within days, we have decided to replace the recommended time frame of 14 days with the term 'shortest possible'.

Emerging data indicate that a proportion of infants identified via newborn screening (NBS) may already exhibit symptoms of SMA, and while their response to treatment is often impressive, it may not match the outcomes seen in truly presymptomatic patients [4,6].

3.9. Consensus statement 9

Data concerning effectiveness and safety of onasemnogene abeparvovec should be collected systematically for all patients treated. Treatment centres should be provided with adequate resources to perform long-term monitoring of treated patients with standardized outcome measures. Where available disease-specific registries should be used for data collection to allow comparison between different treatment regimens. Data analysis should be performed primarily by academic institutions and networks.

Voting results: Fully agree: 19 (100 %)

Comment: This consensus statement remained unchanged. For rationale see original consensus publication [7] and supplemental material. Since the approval of onasemnogene abeparvovec several manuscripts have reported real-world experience with its use [5,10,11,20,21]. These publications have significantly enriched our understanding of the safety and effectiveness of onasemnogene abeparvovec across different patient populations.

To further enhance the use of real-world data, additional efforts are needed to harmonize data collection across different countries (e.g. defining common data elements) and improve the prerequisites for joint data analysis (e.g. federated data analysis). Additionally, the implementation of rigorous statistical methods, such as pre-specified statistical analysis plans and careful management of confounders, is crucial to ensure that the conclusions drawn from real-world data are reliable and robust.

3.10. Revised consensus statement 10

Based on the currently available data and in light of existing effective treatment alternatives, intravenous gene replacement therapy with onasemnogene abeparvovec for older and heavier patients should only be performed under a rigorous protocol with continuous monitoring of safety and efficacy. Treatment of patients above 21 kg cannot be recommended.

Voting results: Fully agree: 19 (100 %)

Comment: In our 2020 consensus statement we recommended that patients with a body weight above 13.5 kg be treated within the structured setting of a clinical trial [7]. Subsequently, Novartis conducted the SMART study (NCT04851873) exploring intravenous treatment with onasemnogene abeparvovec in 24 patients weighing between 8.5 and 21 kg. While final results of the study have not yet been published, interim results have been shared with the authors of this consensus statement and were also made available through a recent press release [9].

In the revised consensus statement, we removed the weight limit of 13.5 kg but maintained the recommendation to continue collecting data on safety and effectiveness under a rigorous protocol. This ongoing data collection is crucial, as heavier and/or older patients are at higher risk for immune responses, as outlined in the rationale for statements 3 and 5. This information should aid in adapting and optimizing the immunosuppressive treatment regimen.

3.11. Consensus statement 11

As the use of onasemnogene abeparvovec will generate additional evidence during the coming years, pharmaceutical industry, regulators,

patient representatives, and academic networks should collaborate to ensure that any new data on effectiveness and safety are publicly available in an unbiased and timely manner. This growing body of evidence is indispensable for an improved risk-benefit assessment for future patients and should not be hampered by particular commercial or academic interests.

Voting results: Fully agree: 19 (100 %)

Comment: This consensus statement remained unchanged. For rationale see original consensus publication [7] and supplemental material.

3.12. New consensus statement 12

SMA should be included in newborn screening programs in countries where at least one disease-modifying treatment is readily available. Patients identified by newborn screening should be evaluated by a paediatric neurologist experienced with neuromuscular diseases as soon as possible. These patients require careful clinical evaluation and assessment of additional biomarkers (e.g. *SMN2* copy number). As soon as either symptoms or low *SMN2* copy numbers ($\leq$3) are detected, disease-modifying treatment should be initiated without any delay.

Voting results: Fully agree: 18 (95 %), partly agree 1 (5 %)

Comment: There is now a compelling body of evidence suggesting that newborn screening for SMA can dramatically improve the prognosis for infants affected by the disease [4]. In addition-several health economic models have demonstrated that SMA newborn screening is a highly cost effective intervention [19,22,23]. An increasing number of countries have already implemented newborn screening for SMA or are in the process of doing so [24]. Given the accumulating experience with newborn screening, the authors have decided to include a specific consensus statement on this topic. Through this statement, we advocate for the implementation of newborn screening in all countries where at least one disease-modifying treatment is available [25]. It is imperative that patients identified through newborn screening require immediate and careful evaluation by an experienced physician. Many of these patients, particularly those with two copies of the *SMN2* gene, may already exhibit symptoms at birth or develop them within just a few days. Therefore, any delay in initiating treatment should be avoided.

In rare instances where symptoms are already severe at birth, palliative care might also be considered, as outlined in consensus statement 4. Consequently, managing these cases requires medical professionals who possess extensive experience and can act with the necessary expertise and urgency.

Authors' contributions

JK, FM and LS conceptualised the consensus process. All authors contributed to the development of the consensus statements. JK, FM and LS drafted the manuscript. All authors critically revised the article and approved the submitted version.

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Declaration of competing interest

JK has received honoraria for participating in advisory boards and/or symposia by Biogen, Novartis, Roche, and Scholar Rock. His institution receives funding for clinical research from Biohaven, Biogen, Novartis, Roche, and Scholar Rock.

GB has received honoraria for participating in advisory boards and/or symposia by Biogen, Novartis, PTC, Pfizer, Roche, and Santhera, and research support from PTC.

NB's institution has received funding from Biogen for equipment for the physiotherapy department and for a cough assist machine for patients.

LDW has received speaker and consulting fees from Novartis Gene Therapies, Biogen, and Roche, has worked as a principal investigator of SMA studies sponsored by Novartis Gene Therapies, Roche, Scholar Rock, and Biohaven, and has received research grants from Novartis Gene Therapies, Roche, and Biogen.

AFV has received honoraria for participating in advisory boards and/or symposia by Biogen, Novartis, and Roche. Her institution has received funding for a SMA registry from Biogen and for a pilot project of newborn screening for SMA from Novartis, Biogen, and Roche.

JH has received honoraria for participating to advisory boards and/or symposia by Biogen, Novartis, and Roche. Her institution receives funding for clinical research from Biogen and Roche.

TM has received honoraria for participating in meetings, formations and advisory boards from Biogen, Novartis, Roche, PTC, Astellas Gene Therapies, and Pfizer.

AK has received honoraria for participating in advisory boards and/or symposia by Biogen, Novartis, Roche. She serves as clinical lead of the Swiss-Reg NMD, that receives funding for clinical research from Biogen, Novartis, and Roche.

AKP has received honoraria for advisory boards and for speaking at educational events from Biogen, Novartis, PTC, and Roche; support for congress participation from Biogen, Roche, and Novartis; institutional grant support from Biogen, and support from Roche as principal investigator for SMA studies.

EM has received honoraria for participating to advisory boards and/or symposia by Biogen, Novartis, Roche, and Scholar Rock. His institution receives funding for clinical research from Biogen, Novartis, Roche, and Scholar Rock.

SQR has received honoraria for participating in advisory boards and giving lectures, as well as travel expenses from Novartis, Biogen, and Roche.

TS has received honoraria for lectures or consultancy from Biogen, Novartis, PTC Therapeutics, Sarepta Therapeutics, Roche, Hansa Biopharma, and Sanofi Genzyme.

EFT has received support to conduct clinical trials and research on SMA from Biogen and Roche, and has served as consultant to Novartis, Biogen, Biologix, Cytokinetics, Argenx, and Roche.

WLP is member of the scientific advisory board of SMA Europe, his employer has received a fee-for-service for scientific advisory boards and participation in educational activities by Novartis, Biogen, and Roche. He was principal investigator for SMA trials sponsored by Novartis, Biogen, and Roche.

SW has served as unpaid member on advisory boards for Biogen, Roche, and Novartis.

DZ has received honoraria for participating in advisory boards and giving lectures, as well as travel and research grants from Novartis, Biogen, and Roche.

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Appendix A. Supplementary data

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