"Not only has she survived, but she lives a happy life" – Parents' perspectives and experiences of a novel disease-modifying therapy for spinal muscular atrophy in Sweden

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ABSTRACT

The objective of this prospective cohort study was to explore parents' perspectives of patients' experiences of the first available novel disease-modifying therapy for SMA in Sweden. Patients with SMA and their parents/legal guardians were identified in the National Patient Register and the Multi-Generation Register. Data was recorded using an electronic questionnaire administered at baseline, and after 6, 12, and 18 months. In total, 47 parents to 33 children with SMA (mean patient age: 9 years, 59% female; 27% with SMA type I, 33% with type II, and 39% with type III) participated. All parents reported that they wished their child to be treated with nusinersen and most parents (81%) reported that they had sufficient information to make an informed treatment decision. Across follow-up, almost all parents reported having a positive experience of nusinersen. Our study provides unique insights into caregivers' real-world experiences of a novel disease-modifying therapy for SMA.

Keywords: Clinical Decision-Making; Information Sources; Caregiver Burden; Treatment Outcome; nusinersen

1 Introduction

The arrival of disease-modifying therapies (i.e., nusinersen, onasemnogene abeparvovec, and risdiplam) has dramatically transformed the treatment landscape for spinal muscular atrophy (SMA), a rare, genetic neuromuscular disease characterised by highly variable progressive muscle atrophy and weakness, disability, and in severe cases death.[1] In Sweden, nusinersen was introduced for clinical use in December 2017, risdiplam in December 2021, and onasemnogene abeparvovec in February 2022. However, due to limited evidence of real-world tolerability and effectiveness, particularly in the long-term, the introduction of these treatments has posed new challenges for affected families, as well as healthcare practitioners. As an alternative to palliative care, parents now face the decision of whether or not to consent to an innovative treatment of their child, with little to no information about expected long-term outcomes. In SMA type I, the most severe form of the disease, this dilemma has been described as "an impossible decision between the early death of their child and the risk that treatment will not allow their child to live independently."[2]

Currently, only a handful of studies have investigated caregivers' views on disease-modifying therapies for SMA. There is a paucity of information on, for example, factors influencing the therapeutic decision process, parents' sources of information, and families' experiences of these treatments, in particular over time. To help bridge these evidence gaps, the objective of this longitudinal study was to explore parents' perspectives and experiences of the first available novel disease-modifying therapy for SMA in Sweden.

2 Patients and Methods

This was a prospective cohort study of parents to patients with SMA in Sweden.

2.1 Sample population

Patients with SMA in Sweden were identified in the National Patient Register, a nationwide administrative database encompassing data on all inpatient admissions and specialised outpatient care managed by the National Board of Health and Welfare in Sweden. The following inclusion criteria were imposed for study eligibility: (i) Documented diagnosis of SMA (i.e., ICD-10 code: G12.0, G12.1, or G12.9) in calendar year 2018; and (ii) <18 years of age. Parents or legal guardians were identified in the Multi-Generation Register, a nationwide register listing Swedish individuals with links between children and biological parents managed by Statistics Sweden.

2.2 Study procedures

Parents to children with SMA were sent an invitation letter to participate in the study via regular post. The letter described the study aim and contained a link to an online website for registration. Parents who registered were subsequently sent a link to an electronic study questionnaire by email. The questionnaire was developed in conjunction with family members of children with SMA and clinical and academic healthcare professionals. Upon providing informed consent, parents completed the questionnaire on four occasions (i.e., at study entry/baseline, and after 6, 12, and 18 months). The study was approved by the Ethics Review Board in Stockholm (DNR: 2018/651-31).

2.3 Collected data

The study questionnaire encompassed questions (categorical, as well as free text forms) covering patients' and parents' demographic characteristics, as well as questions concerning parents' perception of the decision to initiate treatment with nusinersen, sources of information informing their decision, experiences with nusinersen, and thoughts about the future.

2.4 Statistical analysis

Replies to categorical survey questions were summarized using absolute and relative frequencies across response options. Replies to free text questions were analysed using content analysis,[3] in which the prevalence of principal words, themes, or concepts (coded at the question-level) were delineated and summarized, as well as text mining using the library polyglot[4] (for translation of texts from Swedish into English) and the packages tidytext[5] and ggwordcloud[6] in the R statistical language version 4.2.3.[7]

3 Results

A total of 47 parents to 33 children with SMA (mean patient age: 9.0 years [SD: 4.8, range: 2.6–17.6]; 59% female; *n*=9 [27%] with type I, *n*=11 [33%] with type II, and *n*=13 [39%] with SMA type III) provided informed consent and completed the baseline study questionnaire between September 2020 and March 2021 (response rate: 67% [47/70]). Demographic characteristics of the caregiver sample are provided in Table 1. All children with SMA were receiving disease-modifying therapy (i.e., nusinersen) and had, at baseline, been treated with an average of 10 doses (range: 4 to 20). One patient was not allowed to continue therapy after having received 15 doses due to dismissed reimbursement following lack of treatment effect (discontinued between the second and third follow-up). Two patients switched treatment to risdiplam between the second and third follow-up; the remaining patients continued on nusinersen during the entire study period.

3.1 The decision to initiate treatment with nusinersen

In total, 75% of parents first learned of nusinersen as a treatment option from their child's physician, 23% from parents to other children with SMA, and 19% from the Internet. All caregivers reported that they wished for their child to be treated with nusinersen and that they were in agreement about this decision with the other parent/legal guardian. However, the decision was accompanied by a range of interrelated positive and negative emotions, including hope, happiness, fear, uncertainty, scepticism, excitement, worry, and gratefulness. Many parents noted that this was a great opportunity, the only chance for the survival of their child, that they had nothing to lose, and that the decision to start treatment was a given. As emphasized by several respondents: "I had no doubts". At the same time, some parents noted fear about lack of treatment effect and side-effects, as well as being allocated to the placebo

arm of the clinical trial. One parent mentioned that the time he/she was waiting for approval of reimbursement for the disease-modifying therapy was the "worst period of my life".

3.2 Sources of information

The main source of information for the parents' decision to initiate therapy with nusinersen was the child's physician (reported by 79%). However, 47% of parents reported also considering information and experiences from parents to other children with SMA (in some cases via the Swedish SMA patient organization [NSMA]), and 15% from the Internet. Only 4% of parents reported informing their decision based on information from the scientific literature.

Overall, 81% of caregivers reported that they had sufficient information to make an informed decision about the treatment with nusinersen. Limited or inadequate information was noted concerning both the short- and long-term treatment effect, as well as side-effects, in particular weight gain. One parent noted that families may struggle to make a decision due to the acute emotional distress associated with receiving an SMA diagnosis: "A family goes into shock, so in the beginning it is still difficult to process new information. The focus should initially be on crises management".

In terms of other aspects that would be of relevance for healthcare practitioners helping families to children with SMA more generally, parents highlighted the importance of providing accurate, clear, straight-to-the-point information concerning expectations regarding the progression of disease (using, for example, pictures and videos showing the progressive impairment and disability over time) and the burden associated with caring for a child with SMA. As noted by one parent: "It was extremely good that they told you what to expect, that

is, how the disease progresses. It did not create high expectations and I was able to take what came, step by step." Many parents also emphasized the importance of visiting and talking to other caregivers to children with SMA for help and guidance. Timely information about clinical tools that can work preventively (e.g., inhalers and bilevel positive airway pressure [BIPAP] treatment) was also requested by several parents.

3.3 Experiences with nusinersen

Table 2 provides a summary of the caregivers' experiences of nusinersen across follow-up. Figure 1 shows a textmined wordcloud of parents' thoughts about nusinersen. Few parents (*n*=3) ever considered terminating the treatment with nusinersen. Of those who did, reasons included severe headache and vomiting following the administration of the first doses, as well as considerations of the treatment costs to society.

Almost all parents stated that they would advise other families to start treatment with nusinersen (Table 2). The rest noted that they would prefer not to give any advice (mainly due to limited experience of the treatment and the lack of long-term effect data). Concerning specific advise, parents noted that they would encourage other families to obtain as much information as possible (from the treating physician, as well as other sources), to initiate therapy as early as possible, to acknowledge that the effect – although significant and positive – may be variable and dependent on the type of SMA, that the treatment does not reduce the need for continuous work and support, to consult other parents to children with SMA, to not compare their child with other children with and without the disease, and to trust their intuition, never give up, think positively, and be optimistic.

3.4 Thoughts about the future and psychological support

Figure 2 shows a textmined wordcloud of parents' thoughts about the future. In total, 86% of parents stated that they talk to someone about their thoughts about the future, and 57% reported that they talked to clinical staff, primarily the treating physician, but also physiotherapists and occupational therapists. Only two parents stated that they had contact with a psychologist or counsellor.

4 Discussion

The first disease-modifying therapy for SMA, nusinersen, was introduced in Sweden in December 2017 (followed by risdiplam in December 2021, and onasemnogen abeparvovec in February 2022). In this prospective cohort study, initiated in September 2020, we recorded parents' perspectives and experiences in conjunction to the arrival of these treatments, which at the time of marketing authorization were characterized by limited evidence of real-world tolerability and effectiveness, especially in the long-term. Taken together, the results show that parents were optimistic to try the new therapy, perceived to be generally well-informed, and had overall positive experiences of the treatment over time.

To the best of our knowledge, only a handful of studies have previously investigated caregivers' views related to the initiation of disease-modifying therapies for SMA. In summary, parents have described the decision process as stressful and characterised by great uncertainty,[2,8,9] with concerns about risk factors and side-effects, high cost, insurance coverage, time involvement, frequency and administration method, post-treatment monitoring, and/or lack of data about efficacy as factors influencing their assessment.[9-12] Similar themes were observed in our study, except for insurance coverage, which is expected considering Sweden's universal health system (by which only a minor proportion of individuals opt for private insurance). However, contrary to the US study by Pacione et al.,[10] in which all participating parents (100%, 3 of 3) were uninterested in nusinersen, and the French study by Boursange et al.,[2] in which 39% (7 of 18) of caregivers were identified as "hesitant", all participants on our study were optimistic and excited about the new therapy. Indeed, many Swedish parents described the decision to consent to therapy as an obvious choice. A similar finding was reported by Kiefer et al.[8] in their analysis of experiences of

caregivers of children with SMA participating in the expanded access program for nusinersen in Germany, as well as van Kruijsbergen et al.[12] in their study of perspectives among Dutch caregivers to children with SMA treated with nusinersen.

In previous research, parents have indicated that they did not have the information necessary to make an informed decision, or that the information accessed was difficult for them to understand.[9,10,12] In contrast, in our study, 81% of parents stated that they had sufficient information. Nonetheless, many caregivers advised families to also consult parents to other children with SMA for guidance. This was a consistent theme among replies across follow-up. The importance of peer-to-peer information was also reflected in the fact that 23% of parents first learned of nusinersen from parents to other children with SMA, and that 47% reported also considering information and experiences from parents to other children with SMA (in some cases via the Swedish SMA patient organization [NSMA]) when making their decision.

On the topic of information sources, in our study, almost 80% of participants reported that the main source of information for their decision to initiate nusinersen therapy was the child's physician, with only 15% mentioning using the Internet for this purpose. Similar observations were reported by van Kruijsbergen et al.,[12] who noted that the treating physician played a major role in facilitating their decision-making process. This is contrary to observations made by Pacione et al.,[10] in which participants reported learning about nusinersen mostly through parent/patient testimonials on SMA-specific social media groups. However, the importance of the Internet has also been emphasized by parents in other studies. For example, in the work by Boursange et al.,[2] after the diagnosis and treatment proposal, one of the main sources of information was the Internet, and in van Kruijsbergen et al.,[12] most parents stated that they searched for information on the Internet to get an idea of the effect of and experiences with

nusinersen. As a word of caution, however, Pacione et al.[10] also reported that some individuals received misinformation from social media sources. Finally, in our study, only 4% of parents reported informing their decision based on information from the scientific literature. This is in line with findings from Kruijsbergen et al.,[12] in which few parents reported that they searched for information about nusinersen in medical articles.

Across follow-up, almost all parents in our study reported having a positive experience of nusinersen and noted that they would advise other families to start treatment, with very few ever considered terminating the therapy (Table 2). Similar evidence was noted in the study by Boursange et al.,[2] in which the majority of parents described a high degree of satisfaction with the effects observed in their child following the start of treatment, as well as Kiefer et al.,[8] in which children participating in the expanded access program for nusinersen was perceived to have a stabilized clinical situation, with some parents noticing signs of positive motor development. At the same time, it is important to acknowledge that some parents in our study did raise concerns about complications following the administration, as well as a high morbidity burden due to infectious diseases. Concerns about administration has been reported in previous studies,[2,12] noting that "some parents worried about their child's ability to cope with the treatment physically; they reported being afraid that treatment would cause too much suffering and effort for their child".[12]

There is well-established evidence that early intervention of disease-modifying therapies, such as nusinersen, is associated with better efficacy.[13-15] As a result, the decision to initiate therapy is often urgent and made in relation to the confirmation of the SMA diagnosis. However, similar to our study, previous research has found that many parents have difficulty processing information provided during their first clinic appointment due to its complexity

and their emotional state at the time.[9] These findings indicate that it may be appropriate to not discuss therapeutic options with parents immediately at the initial diagnosis confirmation visit.

Considering the detrimental nature of the disease, and the burden on affected families, the very low prevalence of psychological support to parents to children with SMA observed in this study is indeed concerning. We have previously shown that caregiving in SMA frequently is associated with reduced health-related quality of life, impaired family function, depression and anxiety, strain, and stress, as well as a substantial impact on work life and productivity.[16] Following the advent of disease-modifying therapies for SMA, which for some patients would be expected to dramatically prolong survival, informal caregiving demands are likely to increase, both in terms of intensity and duration. This is worrying, considering our work on the caregiver burden of other neuromuscular diseases, such as Duchenne muscular dystrophy, which has revealed that anxiety and depression among parents are significantly associated to both the number of hours of care provided, as well as the cost burden on the household.[17] Accordingly, increased attention on caregiver well-being in the SMA patient population appears warranted.

Strengths of our study include robust ascertainment of SMA in terms of clinically confirmed cases, as well as the longitudinal design, allowing for analysis of changes over time (which is particularly relevant for a progressive disease, such as SMA). In terms of limitations, our sample included 47 caregivers, which reduced possibilities to perform subgroup analysis (by, for example, SMA type). As an observational study, in which data were recorded directly from parents, it is also important to note that our results may be subject to information bias due to, for example, incorrect reporting. Because all patients were treated with nusinersen at

baseline, we were also not able to assess the effectiveness of different disease-modifying therapies on parents' experiences. Finally, our study was implemented during the COVID-19 pandemic, and it is important to consider this as a possible confounding factor.

5 Conclusions

Our study provides unique insights into caregivers' experiences of a novel disease-modifying therapy for SMA. The findings should be helpful to inform approaches for interactions with families to children with SMA at the timing of diagnosis and therapy initiation, as well as the development of information material about the disease, available therapies, and expected outcomes.

Statements and declarations

Ethical considerations

The study was approved by the Ethics Review Board in Stockholm (DNR: 2018/651-31).

Consent to participate

Informed consent to participate was obtained from all study participants before administering any study materials.

Consent for publication

Not applicable.

Declaration of conflicting interest

Thomas Sejersen reports receiving honoraria for lectures or consultancy from Biogen, Novartis, PTC Therapeutics, Sarepta Therapeutics, Roche, Hansa Biopharma, and Sanofi Genzyme, outside of the submitted work. The other authors have no conflicts of interest to declare.

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Availability of data and materials

The data supporting the findings of this study are not publicly available due to ethical restrictions.

Authors' contributions

CU, TS, and UK designed the study, and coordinated the ethical approval process, patient recruitment, and data collection. EL and MCB implemented and executed the statistical analysis. EL, CU, and UK led the interpretation of findings with input from the other authors. EL drafted the manuscript. All authors reviewed and revised the manuscript for important intellectual content and approved the decision to submit for publication.

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Tables

Table 1: Demographic characteristics of the caregiver sample

	Total sample (*n*=47)
Age, mean (SD (range) years	40 (8) (18–61)
Sex, female	24 (51%)
Country of birth*	
Sweden	34 (77%)
Nordics (excl. Sweden)	0 (0%)
Europe (excl. the Nordics)	4 (9%)
Outside Europe	6 (14%)
Education	
Elementary school	3 (6%)
Upper secondary school	20 (43%)
University/college	24 (51%)
Occupation	
Employed full-time	26 (55%)
Employed part-time	7 (15%)
Unemployed	0 (0%)
Student	2 (4%)
Sick leave	0 (0%)
Formal caregiver to my child with SMA	12 (26%)
Living situation	
Living with the other parent to my child with SMA	40 (85%)
Living with other partner	2 (4%)
Living alone	5 (11%)
Number of children living in household	
1	16 (34%)
2	18 (38%)
≥3	13 (28%)
Living area	
Urban city	21 (45%)
Smaller town	21 (45%)
Countryside	5 (11%)

More than one child with SMA	3 (6%)

Note: Data presented as n (proportion %) unless specified otherwise.

[*]n=3 missing.

Table 2: Caregivers' experiences with nusinersen

	Time point			
	At baseline (*n*=47)	**6 m (*n*=38)**	**12 m (*n*=40)**	**18 m (*n*=37)**
Positive experience of nusinersen	44 (96%)	37 (97%)	39 (100%)*	37 (100%)
Ever considered terminating the treatment with nusinersen	2 (5%)	2 (5%)	1 (3%)	2 (5%)**
Would advise other families to start treatment with nusinersen	45 (96%)	37 (100%)*	40 (100%)	36 (97%)*

Note: Data presented as n (proportion %).

** n=1 missing. **n=2 patients switched to risdiplam.*

Figures

Figure 1: Wordcloud illustration of parents' thoughts about nusinersen

Note: The wordcloud was textmined using replies to the open text question "What are your thoughts about the impact of nusinersen on your child with SMA?"

Figure 2: Wordcloud illustration of parents' thoughts about the future

Note: The wordcloud was textmined using replies to the open text question "What are your thoughts about the future for your child and family?"