Patient and caregiver preferences for treatment attributes in Type 2 and non-ambulatory Type 3 spinal muscular atrophy: a pan-European stated preference survey

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Introduction

- Spinal muscular atrophy (SMA) is a rare neuromuscular disease resulting in progressive skeletal muscle weakness and atrophy.[1]
- SMA is classified into types based on age at onset and highest motor milestone achieved.
- Three treatments for SMA are approved in Europe for the use in (some) patients with Types 2 and 3 SMA
  - Nusinersen (SPINRAZA®)
  - Onasemnogene abeparvovec (ZOLGENSMA®)
  - Risdiplam (EVRYSDI®)
- The present study objective was to evaluate patient and caregiver preferences for treatment attributes in Type 2 and non-ambulatory Type 3 SMA across five European countries in a stated preference survey using a discrete-choice experiment (DCE).

Methods

Attribute development and DCE design

- Attribute selection and attribute descriptions were informed by an earlier DCE study. [2] The study design was updated to include treatment attributes reflecting key treatment characteristics for onasemnogene abeparvovec [3,4] and to reflect the most recent available data on nusinersen and risdiplam.[5,6]
- The design included main effects for the 5 attributes, each with 3 categorical attribute levels (Table 1), and 4 interactions. Interactions were included to examine if evidence in Type 2 and/or 3 SMA (vs. Type 1 SMA only) affected strength of preference for treatments with stable or better motor/breathing functions.
- A D-efficient design with 30 choice questions divided into 2 blocks of 15 choice sets was generated using NGene software version 1.2.1.

Sample and procedure

- Adult patients and caregivers of patients with Type 2 and non-ambulatory Type 3 SMA were included in the study.
- Patient associations in Portugal, the Netherlands, Finland, Ireland and Belgium shared details of the study with their communities via e-mail and social media channels.
- The sample included sixty-five adult patients (n=42) and caregivers of patients (n=23) from Portugal (n=18), the Netherlands (n=17), Finland (n=12), Ireland (n=11) and Belgium (n=7).
- Participants completed a version of the online survey in their local language.
- The DCE survey also contained four brief multiple-choice questions aimed at assessing survey participants' understanding of the text describing the treatment attributes.
- Data collection took place between September 2020 and March 2021.
- This study was reviewed and exempted by the Western Institutional Review Board (WIRB) on 19 August 2020 (2639333-44664387). All participants gave informed consent prior to taking part in the study.

Analysis

- Sample characteristics were analysed using descriptive statistics.
- Conditional logit models with clustering by respondent were used to estimate strength of preference for each attribute. A model with main effects for all treatment attributes and pre-specified interaction terms was first tested, showing non-significant interaction effects. Interaction terms were removed from the final model.
- A sensitivity analysis explored whether the direction, the relative order, and magnitude of estimated coefficients in the conditional logit model with clustering were impacted by excluding participants who had incorrectly answered ≥2 of 4 comprehension questions.

Table 1: Overview of selected attributes and attribute levels

	Level 1 *Reference category*	Level 2	Level 3
Motor function	Motor function will be worse by one level in a year's time [a]	Motor function will be the same as the current level of function in a year's time [a]	Motor function will be better by one level in a year's time [a]
Breathing function	Breathing function will get worse in a year's time	Breathing function will be the same in a year's time	Breathing function will get better in a year's time
Treatment administration	Treatment is taken by an oral liquid daily or by gastric tube at home	Injection into the spine at the lower back in hospital every four months	Once-only injection into a vein in hospital with daily oral tablets for two months
Treatment risks and side effects	A 17% (1 in 6) risk of diarrhea and rash	Most patients will have fever, headache, vomiting and/or body pain for 1–2 days every four months	A 10% (1 in 10) risk of liver injury. Fatigue, headache and nausea for two months
Treatment evidence	Effectiveness has been demonstrated in patients with Types 1, 2 and 3 SMA	Effectiveness has been demonstrated in patients with Types 1 and 2 SMA	Effectiveness has been demonstrated in patients with Type 1 SMA

[a] Current level of motor function as indicated by participant (see Table 2 for motor function levels)

Results

- Summary patient clinical and demographic characteristics are shown in Table 2.
- All treatment attributes were statistically significant, meaning that each was important to patients and caregivers (Figure 1).
- Participants placed most value on maintaining or improving motor function, followed by breathing function.
- Participants preferred to avoid intrathecal injections compared with daily oral therapy.
- Participants placed significant value on the avoidance of liver injury risk. Fatigue, headache and nausea vs. diarrhoea and rash were equally valued.
- Our sample of patients with Types 2 and 3 SMA and caregivers preferred treatments with proven evidence of effectiveness in Types 1, 2 or 3 SMA compared with treatments tested in Type 1 SMA only.
- In the subgroup who had answered 3 out of 4 comprehension questions correctly, participants were also less likely to choose treatments with a one-off injection with daily tablets for 2 months (vs. daily oral treatment).

Figure 1: Estimated patient and caregiver preference weights (model beta coefficients) for SMA treatment attributes

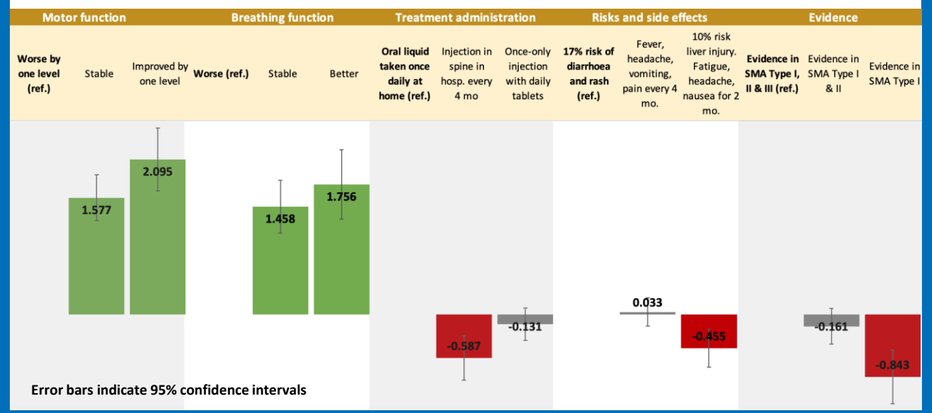

Table 2: Patient clinical and demographic characteristics

Patient Characteristics		Total N=65	Patients self-reported N=42	Caregivers proxy-reported N=23
Age	Mean (SD)	31.1 (18.0)	41.7 (12.2)	11.8 (8.4)
	Min – Max	1 – 62	20 – 62	1 – 44
Gender	Male n (%)	29 (45%)	19 (45%)	10 (43%)
Reported SMA type	Type 2	43 (66%)	23 (55%)	20 (87%)
	Type 3	21 (32%)	18 (43%)	3 (13%)
	Don't know	1 (2%)	1 (2%)	0
Motor function	Cannot sit	4 (6%)	2 (5%)	2 (9%)
	Sit with some support	20 (31%)	13 (31%)	7 (30%)
	Sit independently for few secs.	12 (18%)	8 (19%)	4 (17%)
	Sit independently for longer	22 (34%)	14 (33%)	8 (35%)
	Stand with assistance	2 (3%)	2 (5%)	0
	Walk with assistance	3 (5%)	1 (2%)	2 (9%)
	Walk independently for few steps (<10 meters)	2 (3%)	2 (5%)	0
Breathing function	Mech. support >16 hours per day	2 (3%)	2 (5%)	0
	Mech. support <16 hours per day	9 (14%)	7 (17%)	2 (9%)
	No mechanical support	54 (83%)	33 (79%)	21 (91%)
SMA treatment	Nusinersen	26 (40%)	10 (24%)	16 (70%)
	Onasemnogene abeparvovec	0	0	0
	Surgery	28 (43%)	19 (45%)	9 (39%)
	Other	6 (9%)	5 (12%)	1 (4%)
	None	18 (28%)	13 (31%)	5 (22%)

Conclusions

Adult patients and caregivers of patients with Type 2 and non-ambulatory Type 3 SMA place substantial value on accessing effective therapies to relieve the burden of their condition.

Specifically, patients and caregivers placed great value on motor function, followed by breathing function, with considerable value placed on improvement as well as stabilisation of function.

Patients and caregivers also made choices to avoid intrathecal injections, treatments described as involving risk of liver injury in combination with fatigue, headache and nausea, and treatments with demonstrated effectiveness in Type 1 SMA only.

The pooled study data from five small- and medium-sized European countries could inform national decision making in this rare disease.

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