Treatment Preferences in Spinal Muscular Atrophy: A Swing Weighting Study for Caregivers of SMA Type 1 and Type 2 Patients

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Introduction

- SMA is a rare, debilitating genetic motor neuron disease, usually caused by biallelic deletion of *SMN1*[1]
  - Progressive muscle weakness, swallowing, and breathing problems occur because of the loss of motor neurons and ultimately lead to death if untreated[2]
  - Disease severity (i.e., SMA clinical type) generally correlates with variable copy number of *SMN2*— a partially functional paralog of *SMN1*[3]
- SMA is classified based on age of onset and maximum motor function achieved: very weak infants unable to sit unsupported (type 1; non-sitters), non-ambulant patients able to sit independently (type 2; sitters), ambulant patients with childhood-onset SMA (type 3), and adult-onset SMA (type 4)[4]
- SMA type 1 accounts for approximately 60% of cases and is usually fatal by 2 years of age without intervention; SMA type 2 accounts for approximately 20% of new cases[5]
- Three DMTs approved for SMA treatment in the United States in recent years answer an unmet need for treatment to help maintain or improve patients' motor function and slow disease progression; these agents have markedly improved the medical management of SMA and survival outcomes[1,6–10]
  - Nusinersen is an *SMN2*-directed antisense oligonucleotide administered via intrathecal injection every 4 months (presumably lifelong) after a series of loading doses[1,6]
  - Onasemnogene abeparvovec is a one-time gene replacement therapy that delivers a fully functional copy of the *SMN* transgene into target motor neurons via intravenous infusion[7,8]
  - Risdiplam is a once-daily, orally administered, *SMN2* gene-splicing modifier that increases functional SMN protein[9]
- Data are limited on caregiver preferences for different treatment characteristics (e.g., mode of delivery or potential effectiveness and/or safety outcomes) that may inform choice of DMT.[11–13] Such information is useful for informing treatment choices and facilitating shared decision-making between patients (or their caregivers) and HCPs.

Objective

- We sought to examine preferences for caregivers of patients in the United States affected by SMA type 1 (non-sitters) or 2 (sitters) and preferences for different SMA DMT attributes

Methods

- An online, interviewer–assisted, cross-sectional preference survey using swing weighting methodology was conducted with caregivers of patients with SMA types 1 or 2 to estimate their preference of DMTs for SMA for the children in their care
  - Swing weighting methodology estimates weights in a multi-attribute utility function, whereby an improvement from the worst value to the best value on each criterion is described as a "swing"
  - Swing weighting surveys are divided into the following phases:
    - Ranking of levels where no prespecified ranking was available: for attributes levels that were non-numerical, and we believed did not have an ordinal ranking (i.e., burden of treatment administration, access to treatment, and facility where treatment is available), determine caregiver preference for best and worst attribute levels and determine the swing for each caregiver
    - Ranking of attributes: determine where the respondent ranks the improvements in each attribute (from the worst to best level, or the swing) in the order of importance
    - Rating of attributes: caregivers were then asked to assign points between 0 (worst level) and 100 (best level) to each attribute they had ranked in the previous step. Their most preferred attribute was given 100 points, and participants were asked to score the other attributes compared with their most preferred attribute in a pairwise fashion
    - Rating of mid-levels: participants were then asked to score the intermediate levels of the attributes again and were reminded that 0 was the score allocated to the worst level and 100 to the best level
  - The attributes and levels included in the study (**Table 1**) were derived from a targeted literature review and qualitative interviews with caregivers and HCPs conducted in an earlier phase of this study[14]
  - The levels of the attributes were selected by researchers based on the interview results and results of clinical studies at the time of the study development, representing credible values of each attribute that can be experienced by the target population
  - A pilot of the swing weighting survey was completed with caregivers to confirm the choice of attributes and levels and to ensure respondents' understanding of the swing weighting exercise
- The results of the swing weighting exercise were used to estimate the relative value of four hypothetical SMA DMT scenarios (see Results for scenarios), allowing estimation of the perceived value to caregiver for new treatment administration modalities and description of the subsequent treatment impact

Table 1. Treatment attributes and levels used in the swing weighting exercise

Attributes	Levels	Levels' development source
Ability to sit without support after 1 year of treatment	30% of patients	FIREFISH Part 2 (NCT02913482)
	45% of patients	45% was chosen as a mid-value between the upper bounds' levels (30% and 60%)
	60% of patients	STR1VE US (NCT03306277)
Need for permanent ventilation after 1 year of treatment[a]	40% of patients	ENDEAR (NCT02193074)
	25% of patients	25% was chosen as a mid-value between the upper bounds' levels (10% and 40%)
	10% of patients	STR1VE US (NCT03306277)
Ability to feed orally after 1 year of treatment[b]	40% of patients	STR1VE US (NCT03306277)
	60% of patients	60% was chosen as a mid-value between the upper bounds' levels (40% and 80%)
	80% of patients	FIREFISH Part 2 (NCT02913482)
Burden of treatment administration[c]	Six spinal injections first year, three in every following year (continuously)	Nusinersen
	One-time spinal injection for lifetime	Hypothetical
	One-time intravenous infusion for lifetime	Onasemnogene abeparvovec
	Daily oral solution (continuously)	Risdiplam
Risk of severe adverse events within 1 year after treatment initiation[d]	50%	Hypothetical
	25%	FIRESFISH Part 2 (NCT02913482)
	10%	STR1VE-US (NCT03306277)
Access to treatment[e]	Treatment is covered and available after 1-week financing procedure	Based on literature review and interviews with caregivers and HCPs
	Treatment is covered and available after 4-week financing procedure	
	Treatment is not covered, available immediately after agreeing to an arrangement to pay within 1 year	
	Treatment is not covered, available immediately after agreeing to an arrangement to pay within 5 years	
Type of facility in which the treatment is available[f]	Any neurologic department or office that offers SMA care (usually closer to patient's home)	Based on literature review and interviews with caregivers and HCPs
	Highly specialized neuromuscular facility (usually farther from patient's home)	

HCP, health care provider; SMA, spinal muscular atrophy.
[a]Refers to the percentage of patients who start the treatment at diagnosis and spend more than 16 hours a day on ventilatory support after 1 year of treatment.
[b]Refers to the percentage of patients who start the treatment at diagnosis and are able to eat at least some part of their food (liquid or solid) orally (by mouth) after 1 year of treatment.
[c]Refers to the invasiveness and the frequency of the treatment administration but also to the laboratory tests required to qualify for and monitor the treatment.
[d]Refers to adverse events requiring hospitalization or effects that are life-threatening or result in persistent or substantial disability.
[e]Total cost of treatment for 5 years can be upward of $2 million. Treatment may be covered by insurance, public health plan, or patient support program, possibly requiring applicable copayments and possibly delayed because of administrative tasks to determine if coverage is possible. If cost is not reimbursed, patient's family must cover via a 1- or 5-year payment arrangement.
[f]Visit(s) related to qualification for the treatment and its administration as well as monitoring the possible treatment's adverse events may be done in any medical facility offering care for SMA patients or only in more specialized facilities offering multidisciplinary care, which are usually fewer and scarcer.

Results

Demographics

- Twenty caregivers participated in the study; 80% were female, and mean age was 38 (SD: 7; range: 27–53) years
- A total of 45% of caregivers were full-time caregivers; 60% relied on Medicaid for health insurance for their children with SMA and 20% had employment-based private health insurance; and two caregivers (10%) cared for more than one child with SMA
- All of the children with SMA (10 each males and females) for which the caregivers cared were receiving at least one DMT for SMA; 75% had SMA type 1, and 80% did not require ventilation
- The most advanced motor milestones currently achieved by children being cared for by the caregiver study group was standing with support (35%), followed by sitting independently >10 seconds (20%), head control (15%), and walking without support (15%)

Ranking of levels with no clear prespecified logical ordering

- **Table 2** describes the ranking of the levels for the attributes that did not have a definite best to worst scaling
- For treatment administration "a one-time intravenous infusion for lifetime" was ranked as the best swing with "six spinal injections first year, three in every following year" the least preferred

Table 2. Ranking of levels

Ranking	Treatment administration	Treatment access	Treatment location
1	One-time intravenous infusion for lifetime, n=16 (80%)	Treatment is covered and available after 1-week financing procedure, n=19 (99%)	Any neurologic department or office that offers SMA care (usually closer to patient's home), n=12 (60%)
2	One-time spinal injection for lifetime, n=15 (40%)	Treatment is covered and available after 4-week financing procedure, n=15 (75%)	Highly specialized neuromuscular facility (usually farther from patient's home), n=8 (40%)
3	Daily oral solution (continuously), n=11 (55%)	Treatment is not covered, available immediately after agreeing to an arrangement to pay within 5 years, n=13 (65%)	
4	Six spinal injections first year, three in every following year (continuously), n=12 (60%)	Treatment is not covered, available immediately after agreeing to an arrangement to pay within 1 year, n=13 (65%)	

%=percentage of participants ranking the level in that position.; n=number of participants ranking the level in that position; SMA, spinal muscular atrophy.

Ranking of attributes

- The first ranked swing attribute most frequently chosen by respondents as their most preferred change was the swing from 50% to 10% in risk of severe adverse events (**Table 3**)
  - This was chosen as the first ranked swing attribute by 30% of the sample
  - Reduction in ventilation needs attribute swing from 40% to 10% of patients was chosen by 35% of the respondents as their second most important consideration

Table 3. Attribute ranking

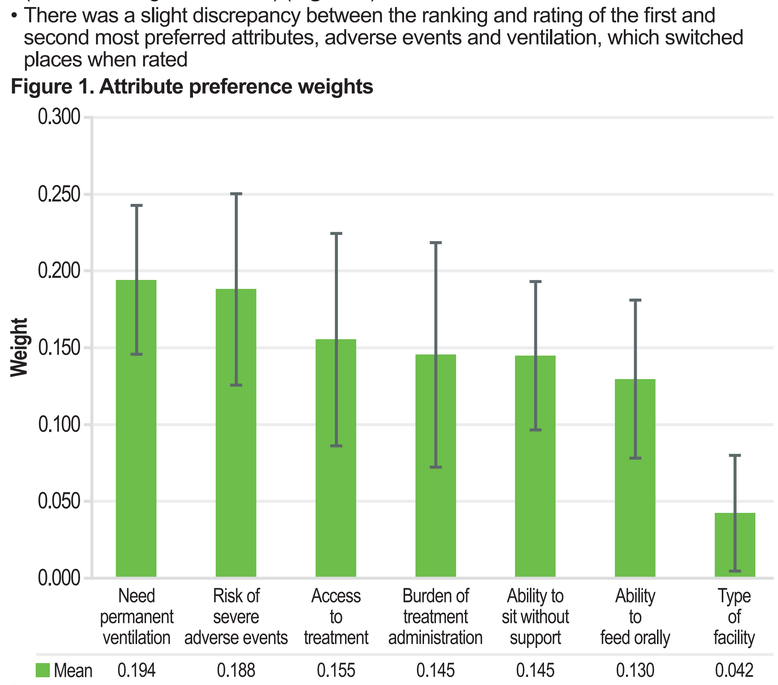
Ranking	Attribute and associated level	n (%)[a]
1	**Attribute:** Risk of severe adverse events within 1 year after treatment initiation Attribute level swing: 50% of patients → 10% of patients	6 (30)
2	**Attribute:** Need permanent ventilation after 1 year of treatment Attribute level swing: 40% of patients → 10% of patients	7 (35)
3	**Attribute:** Access to treatment Attribute level swing: (Varied) worst level → best level	6 (30)
4[b]	**Attribute:** Burden of treatment administration Attribute level swing: (Varied) worst level → best level	5 (25)
	Attribute: Ability to sit without support after 1 year of treatment Attribute level swing: 30% of patients → 60% of patients	5 (25)
6	**Attribute:** Ability to feed orally after 1 year of treatment Attribute level swing: 40% of patients → 60% of patients	9 (45)
7	**Attribute:** Type of facility in which the treatment is available Attribute level swing: Worst level → best level	17 (85)

%=percentage of participants ranking the attribute in that position; n=number of participants ranking the attribute in that position.
[a]Ranking based on frequency.
[b]Level 5 ranking does not exist because two attributes were equally ranked in the fourth position.

Attribute scoring analysis

- The reduction in the need for permanent ventilation ranked first, with an estimated mean weight of 0.194 (SD: 0.5; range: 0.07–0.26), and the reduction in the risk of severe adverse events ranked second, with estimated mean weight of 0.188 (SD: 0.06; range: 0.08–0.32) (**Figure 1**)
- There was a slight discrepancy between the ranking and rating of the first and second most preferred attributes, adverse events and ventilation, which switched places when rated

Figure 1. Attribute preference weights



Error bars represent standard deviation values.

Mid-level scoring analysis

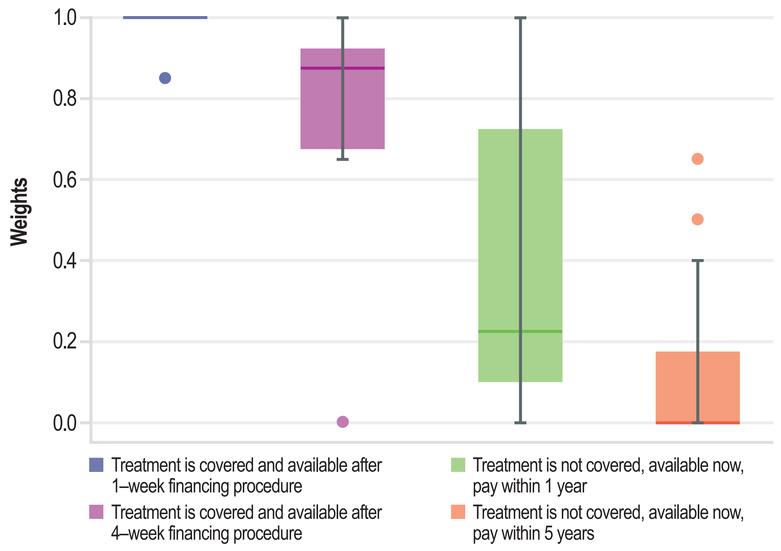
- Caregivers were asked to value the mid-levels of treatment administration and access to treatment
- For this valuation, "best level" and "worst level" of these attributes were not fixed at 1 and 0. This allowed for a more detailed and precise estimation of the level weights, as the best and worst levels are defined for each participant separately, according to their own ranking of levels
- For treatment burden, the most preferred level was the one-time intravenous with no anesthesia option (**Table 4**)
- For access to treatment, treatment that was "covered" was preferred over "not covered" despite "not covered" getting immediate access (**Figure 2**)

Table 4. Mid-levels preference weight of burden of treatment administration

Treatment burden	Mean	SD
One-time intravenous infusion for lifetime (3 hours in medical center; blood test is needed before treatment administration and every 2 weeks for the next 3 months)	0.87	0.28
One-time spinal injection for lifetime (under local anesthesia; 3–6 hours in medical center; headache and infection at injection site; a blood test is needed before treatment administration and every 2 weeks for the next 3 months)	0.72	0.27
Daily oral solution (administered either in the feeding tube or by mouth; no laboratory tests are needed)	0.52	0.40
Six spinal injections first year, three in every following year (under local anesthesia; 3–6 hours in medical center; headache and infection at injection site; blood and urine tests are needed before each treatment administration)	0.37	0.47

SD, standard deviation.

Figure 2. Box plot detailing the weight distribution associated with each level of the access to treatment attribute



Valuing caregivers' treatment scenario preference framework for SMA

- To compare preferences for different hypothetical treatment profiles, a value matrix was created, pairing the attributes and levels in each profile with the corresponding utility values (in parentheses) as per swing weighting study (**Table 5**)
- Based on the preferences of caregivers in our study, a positive utility was estimated for all hypothetical SMA therapies
- The results of this study indicated that Treatment A with a value of 4.87 was preferred over Treatment D (4.72), Treatment C (2.62), and Treatment B (0.37) – the only difference between Treatment scenarios A and D being a one-time intravenous infusion vs. a one-time spinal injection

Table 5. Matrix detailing the characteristics of the hypothetical treatment scenarios and corresponding utility values

Treatment scenario	Administrative burden	Ventilation	Ability to feed orally	Ability to sit without support	Risk of severe adverse events	Total score
Treatment A[a]	One-time intravenous infusion for lifetime **(0.87)**	10% of patients will spend more than 16 hours a day on a ventilatory support after 1 year of treatment **(1)**	80% of patients will be able to eat at least some part of their food orally (by mouth) after 1 year of treatment **(1)**	60% of patients will be able to sit without support after 1 year of treatment **(1)**	10% of patients will experience severe adverse events within a year after treatment initiation **(1)**	**4.87**
Treatment B[b]	Six spinal injections first year, three in every following year (continuously) **(0.37)**	40% of patients will spend more than 16 hours a day on a ventilatory support after 1 year of treatment **(0)**	40% of patients will be able to eat at least some part of their food orally (by mouth) after 1 year of treatment **(0)**	30% of patients will be able to sit without support after 1 year of treatment **(0)**	50% of patients will experience severe adverse events within a year after treatment initiation **(0)**	**0.37**
Treatment C[c]	Daily oral solution **(0.52)**	25% of patients will spend more than 16 hours a day on a ventilatory support after 1 year of treatment **(0.5)**	60% of patients will be able to eat at least some part of their food orally (by mouth) after 1 year of treatment **(0.5)**	45% of patients will be able to sit without support after 1 year of treatment **(0.5)**	25% of patients will experience severe adverse events within a year after treatment initiation **(0.6)**	**2.62**
Treatment D[d]	One-time spinal injection **(0.72)**	10% of patients will spend more than 16 hours a day on a ventilatory support after 1 year of treatment **(1)**	80% of patients will be able to eat at least some part of their food orally (by mouth) after 1 year of treatment **(1)**	60% of patients will be able to sit without support after 1 year of treatment **(1)**	10% of patients will experience severe adverse events within a year after treatment initiation **(1)**	**4.72**

[a]Best treatment as described by the perceived "best" levels according to caregivers' preferences in the swing weighting study.
[b]Worst treatment as described by the perceived "worst" levels according to caregivers' preferences in the swing weighting study.
[c]Average treatment as described as those levels that were perceived "middle" levels according to caregivers' preferences in the swing weighting study.
[d]A mirror of Treatment A with just the inclusion of a change in treatment administration.

Limitations

- Current results reflect responses from a small number of caregivers, thus limiting the ability to explore variation in preferences between caregivers, especially for those who care for an individual with type 1 versus type 2 SMA
- Recruitment of caregivers from a patient group may bias the results of the study because caregivers involved with these patient organizations tend to be highly engaged with their care, which may not reflect the general SMA caregiver population
- Given the limited number of treatments available for SMA, caregivers could have associated treatment attributes to actual approved treatments rather than the hypothetical reference treatment described in the survey, which may have influenced treatment preference choices

Conclusions

- Results of this survey suggest that the attributes with the greatest influence on treatment preference were decrements in permanent ventilation needs and reduction of the risk of severe adverse events
- Both the quantitative and qualitative components of the study found that one-time intravenous infusion was preferred to all other administration options
- The valuation of the hypothetical treatments identified the burden of treatment administration as the driving force in the ranking of treatments
- The results of this study can be used to provide important contextual information for HCPs and caregivers of patients living with SMA

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Abbreviations
DMT, disease-modifying treatment; HCP, health care provider; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival motor neuron; *SMN1*, *survival motor neuron 1* gene; *SMN2*, *survival motor neuron 2* gene; US, United States.

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