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Spinal Muscular Atrophy Type I: Is It Ethical to Standardize Supportive Care Intervention in Clinical Trials?

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Abstract

The natural history of spinal muscular atrophy type I (SMA-I) has changed as improved medical support has become available. With investigational drugs for spinal muscular atrophy now in clinical trials, efficient trial design focuses on enrolling recently diagnosed infants, providing best available supportive care, and minimizing subject variation. The quandary has arisen whether it is ethically appropriate to specify a predefined level of nutritional and/or ventilation support for spinal muscular atrophy type I subjects while participating in these studies. We conducted a survey at 2 spinal muscular atrophy investigator meetings involving physician investigators, clinical evaluators, and study coordinators from North America, Europe, and Asia-Pacific. Each group endorsed the concept that having a predefined degree of nutritional and ventilation support was warranted in this context. We discuss how autonomy, beneficence/non-maleficence, noncoercion, social benefit, and equipoise can be maintained when a predefined level of supportive care is proposed, for participation in a clinical trial.

Keywords

SMA, Werdnig-Hoffmann disease, clinical trial design, standard of care

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The diagnosis of classical recessively inherited proximal spinal muscular atrophy type I (SMA-I, OMIM 253300) in an infant presenting with diffuse muscle weakness and associated respiratory failure was uniformly fatal when supportive measures were not available.[1] Two advances have changed this significantly. First, clinical tools are now available for improved nutritional and ventilation support. Gastrostomy tubes are placed routinely using laparoscopic surgery, with little morbidity, and enable better nutrition. The advent of noninvasive ventilation (NIV) support for infants (bilevel positive airway pressure), tracheostomy with mechanical ventilation, and airway clearance (cough assist devices and suctioning) allow caregivers to provide care at home that previously was only possible in a hospital setting.[2] Second, discoveries in molecular genetics have provided a means to estimate the severity of the phenotype. Following the discovery in 1995 of the *SMN1* gene as the cause of spinal muscular atrophy, it was then recognized that the number of copies of the nearly identical *SMN2* gene is inversely related, in a general sense, to the severity of phenotype.[3] Knowing the SMN2 copy number in an individual patient, however, predicts the course and rate of progression to a limited extent. The association is stronger for spinal muscular atrophy type I infants with a SMN2 copy number of 2, where the descent in the survival curve is fairly linear.[4] As such, the clinician is now faced with the delicate task of explaining to parents that spinal muscular atrophy remains an incurable disease and that infants with type I face the prospect of sustained life only with aggressive nutritional and ventilation support, and/or early death. Physicians try to present the care options available to parents and help them make the "right" choice of care for their child. Patient advocacy groups have been particularly helpful in supporting families through this difficult task. Standard of care guidelines also discuss these topics.[6]

We are currently facing the possibility of a dramatic change in available therapies for spinal muscular atrophy, where targeted treatments at a molecular genetic level may alter significantly the course of this disease.[7] In clinical trials of potential therapies for spinal muscular atrophy type I, adherence to an appropriate standard of care is expected and in some cases specified as part of the study entry criteria (Table 1). Specific parameters for nutritional and ventilation support during trial participation, however, are not typically detailed. Nor are

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Table 1. Past and Current Clinical Trials in SMA Type I and Related Standard of Care Criteria.

Sponsor study start-end dates	Study name and NCT identifier	Study design	Enrollment criteria for supportive care	Participation criteria
Westat (NINDS) 1/2008-5/2009	NPTUNE 02 00439218	Phase I-IIa Open label Sodium phenylbutyrate	• Stable pulmonary care for at least 2 wk prior to enrollment • Weight $\geq$7 kg	None
Stanford University 1/2004-11/2008	00568698	Phase I/II RCT Hydroxyurea	• None	None
University of Utah 4/2008-6/2012	Carnival type I 00661453	Phase I/II Open label Valproic acid and carnitine	• None	None
University of Utah 7/2007-12/2013	STOPSMA 00528268	Phase I/II Open label Presymptomatic SMA-I Phenylbutyrate	• None	None
Ionis Pharmaceuticals 5/2013- ongoing	CS3A 01839656	Phase II, open label Intrathecal ASO SMN2 splicing modifier	• Care meets SMA SOC guidelines[5] • Weight >5%ile • Receiving adequate nutrition (with or without g-tube) and hydration • O_2 saturation >96% awake and asleep without respiratory support	Care expected to meet SOC guidelines throughout study
Ionis Pharmaceuticals 7/2014- ongoing	CS3B 02193074	Phase III, Sham-controlled RCT Intrathecal ASO SMN2 splicing modifier	• Care meets SMA SOC guidelines[5] • Weight >3%ile • Receiving adequate nutrition (with or without g-tube) and hydration • O_2 saturation >96% awake and asleep without respiratory support	Care expected to meet SOC guidelines throughout study
Biogen 5/2015- ongoing	NURTURE 02386553	Phase II Open label Presymptomatic SMA (types I, II, and III) Intrathecal ASO SMN2 splicing modifier	• O_2 saturation >96% awake and asleep without respiratory support	None
Novartis 4/2015- ongoing	02268552	Phase I/II Open label Oral small molecule *SMN2* splicing modifier	• Care meets SMA SOC guidelines[5] • Best supportive care in place and stable for at least 14 d before screening • O_2 saturation $\geq$92% awake and $\geq$90% asleep without respiratory support, or requiring oral suctioning $\geq$2 times per day	Medical care meets and is expected to continue to meet guidelines set out in the Consensus Statement for Standard of Care in SMA
Nationwide Children's Hospital/AveXis 4/2014-ongoing	02122952	Phase I Open label Systemic *SMN1* gene transfer	• Use of invasive ventilatory support (tracheotomy with positive pressure) or NIV support >16 h/d, or pulse oximetry <95% saturation • Signs of aspiration based on a swallowing test and unwilling to use an alternative method to oral feeding	None

Abbreviations: NCT, Clinicaltrials.gov NCT Identifier Number; NIV, noninvasive ventilation; RCT, randomized controlled trial; SOC, standard of care; SMA-I, spinal muscular atrophy type I.

there guidelines for the provision of such support should a predefined threshold be reached during participation in the study. For example, if an enrolled subject were to falter in weight gain and become malnourished, there is no provision for protocol-driven supplemental nutrition. Enhanced nutritional support remains an option for the caregiver in discussion with the treating physician, who may or may not be the site investigator for the study.[8,9,10] Practice standards also vary within and among countries.[9,11,12] When to consider initiation of ventilation support may be even more vexing for the clinician and parents.[13] As such, these issues may directly affect the time to the clinical endpoints of death or permanent ventilation support and motor function that are used in spinal muscular atrophy type I clinical studies.[14] To further explore these issues, the objective of this study was to examine expert opinion on the ethics of specifying the provision of nutritional and/or ventilation support during participation in a clinical trial of an investigational product to treat infants with spinal muscular atrophy type I.

Methods

Personal observations (R.S.F.) from participation in an earlier open-label study in infantile-onset spinal muscular atrophy were the basis for the hypothesis that unstructured supportive care in a clinical trial increases the variability in the outcome measures. Two questions were then developed to test this hypothesis among an experienced group of clinicians, clinical evaluators, and study coordinators.

A survey was conducted of participants at 2 different investigator meetings for a phase III randomized clinical trial in infants with spinal muscular atrophy type I, one representing North America (July 2014, United States and Canada) and the other representing Europe and the Asia Pacific region (October 2014, Europe, Australia, Asia ["Europe–Asia Pacific"]). The combined group included physicians, physical therapists, and study coordinators, but excluded any employees of the sponsors or the contract research organizations.

Participants were asked to submit yes/no responses to 2 questions on an anonymous survey form:

> Do you *personally* believe that it is ethically acceptable to require parents of spinal muscular atrophy type I subjects enrolled in a therapeutic clinical trial to:
>
> a. Have supplemental nutritional support provided if a predefined weight target is not maintained?
>
> Yes___ No__ Uncertain___
>
> b. Initiate ventilation support once insufficient cough or hypoventilation has been identified?
>
> Yes___ No__ Uncertain___

Instructions provided to the participants made it clear that predefined guidelines would be established to identify if and when an enrolled subject met one of these criteria. In neither instance was the type of supportive care specified, for example, nasogastric tube, gastrostomy tube, cough assist, noninvasive ventilation (bilevel positive airway pressure), tracheostomy, and/or mechanical ventilation. Nor was it prespecified whether parental failure to accept these guidelines and interventions would affect further participation of their child in the proposed study.

Table 2. Results of the Survey.

	Yes (%)	No or uncertain	Total respondents
Nutritional support			
Physicians			
North America	17 (85)	3	20
Europe–Asia Pacific	20 (91)	2	22
Total	37 (88)	5	42
	$P = .66$		
Total group			
North America	36 (77)	11	47
Europe–Asia Pacific	39 (91)	4	43
Total	75 (83)	15	90
	$P = .09$		
Ventilation support			
Physicians			
North America	13 (65)	7	20
Europe–Asia Pacific	14 (64)	8	22
Total	27 (64)	15	42
	$P = 1.0$		
Total group			
North America	28 (57)	21	49
Europe–Asia Pacific	27 (63)	16	43
Total	55 (60)	37	92
	$P = .67$		

Data analysis was performed using Fisher exact test, with $P < .05$ to indicate a significant difference between responses from the North American and Europe–Asia Pacific groups of responders.

Role of the Funding Source

There were no funded sponsors for this study. The 2 surveys were conducted at the Ionis Pharmaceuticals–sponsored investigator meeting for a phase III study (ClinicalTrials.gov Identifier: NCT02193074). Ionis had no role in the study design, collection, analysis, or interpretation of the data. Dr Bishop was an employee of Ionis Phamaceuticals at the time the surveys were conducted and was independent of the sponsor during the data analysis and interpretation.

Results

Table 2 lists the results of the survey. Overall participation in this survey among those who attended these investigator meetings (N = 92) was more than 83% for physicians and 64% for study coordinators. Attendance by clinical evaluators (physical therapists) was optional for this session and their attendance was not confirmed with a sign-in sheet, as it was for the physicians and clinical evaluators. A minimum participation rate for the clinical evaluators was 58% North American and 41% for Europe–Asia Pacific.

Physicians who were already engaged in a clinical trial of spinal muscular atrophy type I were strongly in favor of requiring nutritional support (North American 85%; Europe–Asia Pacific 91%, $P = .65$) and noninvasive ventilation support (North American 65%, Europe–Asia Pacific 64%, $P = 1.0$)

during participation in an investigational study. Responses were similar between the North American and Europe–Asia Pacific investigator groups. Clinical evaluators and study coordinators also favored these supportive measures but to a lesser extent. Overall, 83% of responders favored nutritional support and 60% favored ventilation support, with no significant differences between Europe–Asia Pacific and North American responders (nutrition, $P = .09$, ventilation, $P = .67$).

Discussion

Data from these surveys of expert opinion support the concept of protocol-driven interventions for nutritional and ventilatory support in an intervention clinical trial in infants with spinal muscular atrophy type I, should a predefined threshold be reached. There was a larger consensus for nutritional support than for support of hypoventilation.

There are several limitations to this study. First, the participants were recruited from a sponsor's investigational meeting. As such, those who chose to respond to this survey were experienced in clinical trials but also had the potential for contextual bias. Second, it was not defined in the survey instructions whether failure to follow proposed nutritional and/or ventilation support requirements would negatively impact the study design or analysis, or the subject's ability to continue in the study. Third, input from the patient and caregiver was not included. This was by design, as the aim of this study was to focus upon expert opinion of clinicians experienced in spinal muscular atrophy and clinical trials. Additional study is necessary to ascertain caregiver perspectives and combine those with the perspective gained from this study.

It is important to recognize that the protocol-driven emphasis for instituting nutritional and/or ventilation support, as proposed here, does not undermine the parents' role in providing initial and continuing permission for an infant to be enrolled in the study. At study screening and enrollment, and during the conduct of the clinical trial, the study investigator needs to address these topics with parents and ensure that continued study participation is in the infant's best interest. Although the decision may be difficult, a parent who a priori would decide against such supportive care in the future should not be enrolled in the study. Many parents may be uncertain, as could be expected, and enrolling their children in the study would be reasonable. In these cases, a subsequent decision not to pursue supportive care must be respected.

There are at least 2 reasons why an investigator might encourage parents to agree to additional supportive care should it became clinically necessary. First, participants who falter early in the course of the study due to progression of disease and do not receive supportive care, may add significant variability to the primary endpoint of the study. Protein-calorie malnutrition during infancy has profound effects on the developing nervous system.[8] Inadvertent cachexia also hastens muscle wasting. Experience in treating infants with spinal muscular atrophy has demonstrated that malnourished infants falter more readily and have earlier and more severe morbidity and mortality.[2,9,10] However, if a parent believes that such supportive care is not in the infant's best interest, the parent's decision should be respected regardless of concerns about the scientific validity of the study. Second, the risks of administering the investigational product must be justified by the potential for clinical benefit (which is one of the criteria for the intervention to be approvable under the additional safeguards for children enrolled in clinical investigations under the United States' Food and Drug Administration policy 21 CFR 50.52).[15] In order for an infant with spinal muscular atrophy type I to potentially benefit from an experimental intervention, especially where such benefit may be delayed from the time of administration, it can be argued that maintaining good general health is a necessity. Without optimal supportive care, the infant may succumb to malnutrition-related issues or from complications of poor airway clearance and hypoventilation prior to the possibility of any clinical benefit being realized. Some caregivers may enroll their infant with spinal muscular atrophy type I into an investigational study, exposing the infant to additional risks (ie, from the investigational product, frequent study visits, travel, etc), while expressing their preference for a palliative care approach for the management of spinal muscular atrophy–related nutrition and ventilatory support. This approach may place the infant at risk from an investigational product, while undermining interpretability of the clinical data, should the infant's general health deteriorate from chronic malnutrition or hypoventilation or acutely from a respiratory infection. The investigator must be cautious not to imply that the investigational product will have a clinical benefit, as this is not known (it may even be harmful), and may reinforce the misconception that the purpose of being in the clinical trial is therapeutic rather than to gain scientific knowledge.[16]

It will be important to predefine criteria for when to initiate additional supportive care. For example, if an infant has not gained weight over 4 weeks, in the absence of an acute illness or postoperatively, then the infant would be considered at risk for malnutrition. One would not wait until weight loss is evident. A predefined protocol for supplemental feeding would then be initiated. None of the interventions considered would go beyond current treatment strategies commonly in use and supported by the SMA Standard of Care guidelines.[17] A current effort to update these guidelines includes patient/caregiver input and gives pharmaceutical companies an opportunity to comment.[18]

There may be several challenges that arise in implementing this approach. The study investigator may not be the treating clinician for the infant, as often a spinal muscular atrophy type 1 infant travels to a specialty investigational center to participate in a clinical study. In this case, implementation of care mandated within a study protocol would require agreement and coordination from the infant's treating physician and treatment team, treating hospital/institution, and, in some regions, the family's insurance carrier. This situation increases the complexity enormously, especially as care for spinal muscular atrophy infants varies widely, despite published guidelines and the efforts of advocacy groups to facilitate implementation. In

our experience (R.S.F., K.M.B.), despite these guidelines, provision of these specialty consultative services and necessary equipment are sometimes resisted by providers and insurance companies in the United States. Because of the rapidly progressive nature of spinal muscular atrophy type I disease and the observation that type I infants usually exhibit fairly advanced motor system degeneration by the time of diagnosis, most clinical studies in spinal muscular atrophy type I aim to enroll infants relatively early in the disease (ie, before 6 or 7 months of age). Often parents of infants enrolled in clinical trials are still trying to deal with the diagnosis itself and may not be prepared to accept the need for additional nutritional and ventilatory support. In addition, enrolling in a clinical trial may be accompanied by overly hopeful expectations of therapeutic benefit. Combined, these factors often may work against implementation of supportive care.

To not provide adequate care in the context of a clinical trial, especially regarding nutritional status and the avoidance/treatment of malnutrition, would be unethical. In effect, this approach negates any opportunity for enrollment of infants whose parents wish to pursue a palliative care course. Given the advanced nature of symptomatic spinal muscular atrophy type I disease and the time likely required for SMN upregulation to result in a clinical benefit on motor function, provision of supportive care may be necessary to adequately assess a meaningful clinical endpoint in a clinical trial. In addition, standardization of clinical care may minimize the impact of variability in other clinical factors that may otherwise impact on the outcome variable, for example, malnutrition[2,9,10] and country-specific factors.[9,11,12] Generally speaking, reducing variance among participants (interindividual variability) in a clinical trial reduces type 2 error and permits a smaller sample size. Absent protocol-driven standardization of supportive care, the clinical trial may be unable to assess the impact of the study intervention, or the sample size necessary to overcome this variability may render a trial difficult or infeasible.

Conclusions

Clinical trials in spinal muscular atrophy type I should be properly designed to obtain the necessary data to evaluate whether the drug is both safe and effective. To do so, it is important to minimize confounding factors that add variability to the clinical data and to optimize the opportunity to assess the clinical impact of the investigational drug. Providing ''best available supportive care'' should reduce sources of variability in a clinical trial. For spinal muscular atrophy type I, ensuring satisfactory nutrition, airway clearance, and ventilation during the study may be fundamental to achieving these goals. Within this context, we believe it is ethically appropriate to have clearly defined criteria that are specified in the protocol, requiring, for example, supplemental nutrition and/or noninvasive ventilation for airway and ventilatory support, as a condition for enrollment in an investigational study in spinal muscular atrophy type I. Although parents retain the right to refuse such treatment at any time in the future, initial enrollment would be predicated on the understanding that such support would be expected if clinically indicated.

Author Contributions

RSF designed the study, conducted the surveys, analyzed the data, and wrote the first draft of the manuscript. KMB assisted in the design and conduct of the study, data analysis, and contributed to writing the manuscript. RMN contributed to the data analysis and writing of the manuscript.

Author Note

The views expressed in this article are those of the authors and do not reflect the policies of the Food and Drug Administration or the Department of Health and Human Services.

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