Disease Burden in Patients with Spinal Muscular Atrophy (SMA) Treated with Survival Motor Neuron (SMN)-Targeted Therapies: A Targeted Literature Review

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Background/Introduction

- Spinal muscular atrophy (SMA), a genetic neuromuscular disease, is characterized by the loss of motor neurons in the spinal cord and brain stem, which results in progressive muscle weakness and atrophy of the voluntary muscles of the limbs and trunk[1,2]
- Approved SMA treatments include 3 survival motor neuron (SMN)-targeted therapies that improve survival and motor function[2]
- This targeted literature review and gap analysis provides an overview of the current publications (abstracts, articles, published reviews) on the clinical burden and treatment landscape for SMA

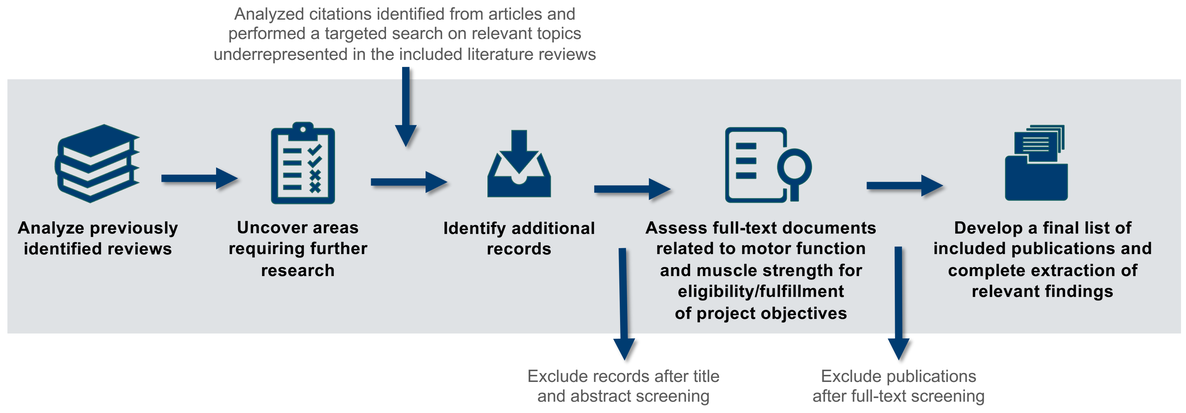
Objective

- To understand the ongoing burden of SMA in patients who are treated with SMN-targeted therapies (i.e., nusinersen, risdiplam, and onasemnogene abeparvovec) via a review of current literature

Methods

- A literature review was conducted in PubMed®, Embase®, and Northern Light® databases to identify SLRs on the topics of disease burden, clinical benefit, economic benefit, improvements in quality of life and daily activities, and epidemiology in SMA from from 2011 to 2023 (**Figure 1**)
- A targeted literature search on identified underrepresented topics was performed with key search parameters:
  - Population: SMA
  - Treatment type: All
  - Publication date: 2019–2023
  - Geographic region: All regions
  - Language: English
- An assessment of unmet needs related to motor function and muscle strength was conducted based on identified literature to characterize the disease burden and remaining unmet needs of SMA in patients treated with SMN-targeted therapies

Figure 1. Targeted Literature Review Methodology



Results

- From 14 SLRs, 42 of 500 publications were included in the assessment

Unmet need associated with clinical disease burden

- Despite treatment, improvement varied for adults and pediatric patients with either type 2 or 3 SMA, treated with nusinersen over a 10-14 month period, with an HFMSE change ranging from −1 to +6 points[3]
- Patients and caregivers desire not only meaningful improvement, but also continued development of nuance-sensitive scales (**Table 1**)
- Unmet need remains for short- and long-term improvement in and/or sustainment of muscle strength and motor function, as well as fatigability
  - Current data on increased motor strength and its impact on motor function are limited (1 publication)

Unmet need associated with activities of daily living and quality of life

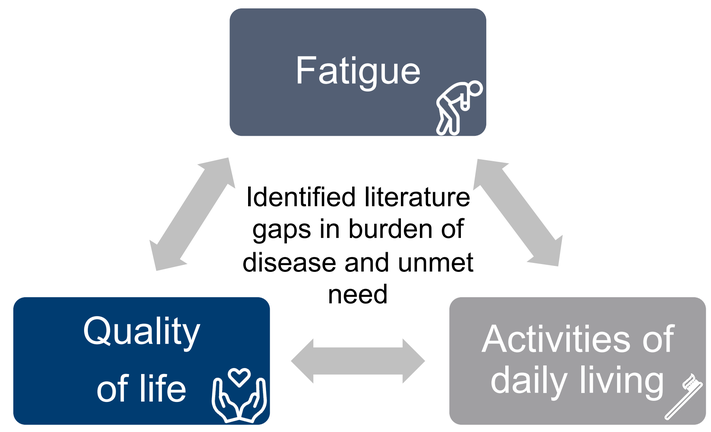
- SMA is associated with the following burdens, as shown by qualitative and quantitative research:
  - Mobility/walking
  - Breathing difficulties/choking/swallowing
  - Activities of daily living: personal hygiene, grooming, dressing, toileting, feeding, transferring, and ambulating
- Patients believe that, although HFMSE and Revised Upper Limb Module (RULM) items are appropriate, they are not sufficiently sensitive to capture small changes that they observe after initiation of SMN-targeted therapies[4]

Table 1. Assessments Used to Assess Motor Function in Patients with SMA

	Description	Clinical Utility
Motor function scales		
Hammersmith Functional Motor Scale–Expanded (HFMSE)[5-7]	13 clinically relevant items validated from the Gross Motor Function Measure (GMFM) related to lying/rolling, crawling, crawling/kneeling, standing, and walking/running/jumping	Motor function
Revised Upper Limb Module (RULM)[8]	20-item assessment of upper limb functions that relate to everyday life (e.g., placing hands from lap, pressing a button, picking up a token) in nonambulatory patients with SMA	Upper limb motor function
World Health Organization (WHO) motor development milestones[9]	6 gross motor milestones are assessed (walking alone, standing alone, walking with assistance, hands and knees crawling, standing with assistance, sitting without support)	Motor development
Motor Function Measure (MFM)[10,11]	32 items are assessed across 3 dimensions (standing position and transfers, axial and proximal motor function, distal motor function)	Motor function
Timed tests		
6-Minute Walk Test (6-MWT)[12]	Participants are instructed to walk as fast as possible along a 25-meter course on a flat linoleum surface, turn around a marker cone, and return in the opposite direction (the loop is repeated as often as possible for 6 minutes)[13]	Endurance
10-Meter Walk/Run Test (10-MWRT)[14]	Assesses walking speed in meters per second over a short distance	Walking speed Functional mobility
Rise From Floor[15]	Measures the time taken to rise from supine to standing	Clinical progression, risk of future nonambulation
Muscle strength assessments		
Medical Research Council (MRC) Scale for Muscle Strength[16]	Muscle function is measured and rated from 0 (patient cannot activate the muscle) to 5 (full strength)	Muscle strength
Manual Muscle Testing (MMT)[17]	Used to evaluate muscle deterioration or function using MRC scoring system	Muscle strength

- The literature reports that clinicians, patients, and caregivers emphasize the importance of small improvements, including what may appear to the general population as too small to be beneficial[4]
- Patients noted that trials should assess changes in abilities related to independence through everyday examples: opening doors, combing hair, turning book pages, holding a drink, etc[4]
- Relevant reviews and associated publications highlight the need for improvements in daily activities (7 publications), fatigue (4 publications), and quality of life (14 publications) within SMA (**Figure 3**)

Figure 3. Identified SMA Literature Gaps



Conclusions

- Despite advancements in SMA treatment, there are significant unmet medical needs including addressing muscle weakness, fatigue, and improvement of daily activities
- Current published literature likely underestimates the true burden of SMA in terms of impact of the disease on functional status, activities of daily living, and health-related quality of life
- Data are warranted to further describe activities of daily living, fatigue, and quality of life in patients with SMA

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