CO160

Relationship between loss of ambulation (LoA), disease burden, and physical functioning among boys with Duchenne muscular dystrophy (DMD)

Heather Gordish-Dressman, PhD[1]; Rongrong Zhang, MSc[2]; Rhiannon Kamstra, MSc[3]; Christian Werner, MD[4]; Emelline Liu, MD MSHS[5]; Kathryn Morrison, PhD[3]; Ioannis Tomazos, PhD MBA[5]

[1] Children's National Hospital, Washington, DC, USA; [2] PTC Therapeutics Sweden AB, Askim, Sweden; [3] Precision Analytics Inc., Montreal, QC, Canada; [4] PTC Therapeutics Inc, Germany GmbH; [5] PTC Therapeutics Inc, South Plainfield, NJ, USA

Background & Objectives:

- Duchenne muscular dystrophy (DMD) is an X-linked disease affecting the dystrophin protein found in muscles.[1]
- Individuals with DMD often begin to show symptoms of muscle weakness and delays in or inability to achieve physical developmental milestones as young children.[1]
- DMD progression is marked by progressive loss of lower and upper extremity strength and function, pulmonary and cardiac impairment, eventually requiring ventilation and feeding tubes, and then death in young adulthood.[1]
- While progression of DMD through clinical milestones is well documented, few studies explore how loss of ambulation (LoA) is associated with other outcomes in DMD. This is particularly important as, for example, progression of disease-related milestones has been shown to differ with age at LoA (AaLoA).[2]
- Moreover, existing studies tend to be short-term and focused on clinical endpoints; broader examinations of patient burden of disease and health-related quality of life (HRQoL) are lacking.

This study sought to:

1. Characterize changes in disease burden and physical functioning before and following LoA among boys with DMD, and
2. Compare these changes by AaLoA.

Methods:

Data source & study population

- CINRG DNHS (**C**ooperative **I**nternational **N**euromuscular **R**esearch **G**roup **D**uchenne **N**atural **H**istory **S**tudy, NCT00468832) was a prospective, longitudinal study in which patients with DMD were followed up between 2006 and 2016.
  - In total, 440 patients with DMD received standard of care (corticosteroid or palliative therapies) across 20 centers in nine countries.[2,3]
- In the present observational study, boys who experienced LoA during follow-up or 6 months prior to enrollment were identified from the CINRG DNHS.

Analyses

- Individuals who had available AaLoA data and visits within 5 years prior to or following LoA were analyzed, and categorized into three AaLoA groups:
  - <10 years
  - 10-13 years
  - >13 years.
- Clinical outcomes assessments included:
  - **LoA** defined as self/parent-reported full-time wheelchair use. Counts and proportion of patients who used a wheelchair/walker daily and less than daily were calculated at 6-month intervals.
  - **Disease burden** measured with Major Adverse Dystrophinopathy Events (MADE) scores. The MADE score was developed by clinical experts to capture disease burden across body systems and severities, and comprises cardiac, myopathy, nutrition status, and respiratory domains. Higher scores indicate greater burden (max: 92).[4]
  - **Physical function** measured by Quantitative Muscle Testing (QMT), which captures small variations in muscle strength and enables testing of individual muscle groups.[5] Grip strength scores were assessed in this study, with available mean grip score representing the maximum value of the two attempts on the dominant side.

Results:

Patient Characteristics

- Among 165 patients with LoA data, mean (standard deviation [SD]) age at enrollment was 11.0 (3.6) years (**Table 1**)
  - AaLoA <10 years: n=45
  - AaLoA 10-13 years: n=88
  - AaLoA >13 years: n=32.
- Patients were primarily enrolled from the United States (US, 38%) and non-US Americas (27%).
- At enrollment, 42% of patients were non-ambulatory. According to AaLoA group, 51% of patients with AaLoA <10 years, 42% of patients with AaLoA 10-13 years, and 28% of patients with AaLoA >13 years were non-ambulatory at enrollment.
- The majority (88%) of patients had never used walkers at the time of enrollment.
- Mean (SD) MADE scores at enrollment were as follows among the 3 AaLoA categories:
  - <10 years: 9.3 (6.8)
  - 10-13 years: 8.7 (6.9)
  - >13 years: 8.9 (6.2)

Table 1. Baseline characteristics[1] of boys and young men enrolled in the CINRG DNHS who had available AaLoA data and visits within 5 years prior to or following LoA (n = 165 out of 440 participants)

Description	Overall n=165	AaLoA		
		< 10 years n=45	10 - 13 years n=88	> 13 years n=32
Age, years				
Mean (SD)	11.0 (3.6)	9.0 (2.6)	10.7 (3.2)	14.3 (3.5)
Region, n (%)				
US	63 (38.2%)	27 (60.0%)	30 (34.1%)	6 (18.8%)
Americas (non-US)	45 (27.3%)	2 (4.4%)	25 (28.4%)	18 (56.2%)
Europe	22 (13.3%)	1 (2.2%)	13 (14.8%)	8 (25.0%)
Australia	8 (4.8%)	2 (4.4%)	6 (6.8%)	0 (0.0%)
India	27 (16.4%)	13 (28.9%)	14 (15.9%)	0 (0.0%)
Weight, kg				
Mean (SD)	37.4 (17.1)	34.1 (15.9)	36.3 (16.6)	44.8 (18.2)
Calculated height, cm				
Mean (SD)	137.1 (17.5)[a]	131.5 (15.5)[b]	136.3 (17.8)	147.0 (15.5)
Ambulatory status, n (%)				
Non-ambulatory	69 (41.8%)	23 (51.1%)	37 (42.0%)	9 (28.1%)
Walker use, n (%)				
Occasionally	1 (0.6%)	0 (0.0%)	1 (1.1%)	0 (0.0%)
Previously but discontinued	18 (11.0%)	6 (13.6%)	8 (9.1%)	4 (12.5%)
Never use	145 (88.4%)	38 (86.4%)	79 (89.8%)	28 (87.5%)
Wheelchair use, n (%)				
Not used	68 (41.2%)	20 (44.4%)	37 (42.0%)	11 (34.4%)
Less than once per week	7 (4.2%)	0 (0.0%)	3 (3.4%)	4 (12.5%)
Once per week	2 (1.2%)	0 (0.0%)	2 (2.3%)	0 (0.0%)
3-5 times per week	3 (1.8%)	1 (2.2%)	1 (1.1%)	1 (3.1%)
Daily (part-time)	16 (9.7%)	1 (2.2%)	8 (9.1%)	7 (21.9%)
Daily (full-time)	69 (41.8%)	23 (51.1%)	37 (42.0%)	9 (28.1%)
Overall MADE score, max. 92 points				
Mean (SD)	8.9 (6.7)	9.3 (6.8)	8.7 (6.9)	8.9 (6.2)

Notes: [1]Assessed at enrollment, [a]n=163; [b]n=43
Abbreviations: AaLoA: age at loss of ambulation; CINRG DNHS: Cooperative International Neuromuscular Research Group Duchenne Natural History Study; LoA: loss of ambulation; MADE: major adverse dystrophinopathy event; SD: standard deviation.

Figure 1. Percentage of observations with walker/wheelchair use during the ambulatory period

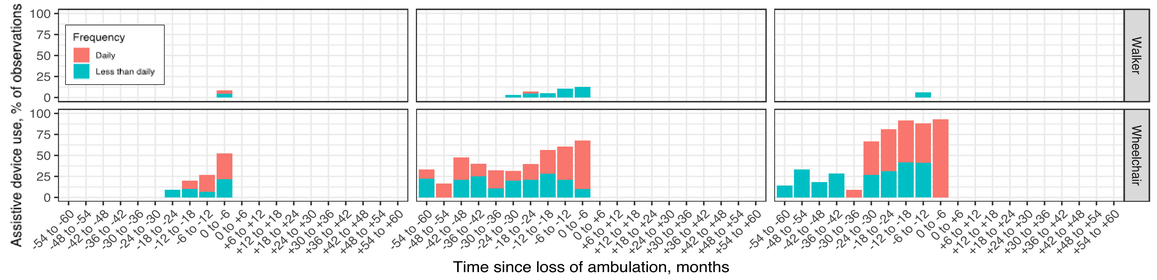

Figure 2. MADE score distribution across 6-month intervals before and after reported LoA, stratified by AaLoA

Figure 3. QMT grip score distribution across 6-month intervals before and after reported LoA, stratified by AaLoA

Abbreviations: AaLoA, age at loss of ambulation; LoA: loss of ambulation; MADE: major adverse dystrophinopathy event

Abbreviations: AaLoA, age at loss of ambulation; LoA: loss of ambulation; QMT, quantitative muscle testing

Clinical Outcomes

Assistive device use

- Among those with AaLoA <10 years, wheelchair use was observed from 2 years before LoA, progressing to >50% having wheelchair use, including daily use, ≤6 months pre-LoA (**Figure 1**).
- Among those with AaLoA >13 years, wheelchair use started 5 years before LoA, progressing to >90% having daily wheelchair use ≤6 months pre-LoA (**Figure 1**).

Disease burden

- Across AaLoA groups, MADE scores increased over time, particularly around 2 years before LoA (**Figure 2**). Burden, as measured by MADE scores, was markedly higher while patients were non-ambulatory compared to when they were ambulatory, although statistical testing for significance was not conducted.
- Burden at the time of LoA was generally higher with later AaLoA (**Figure 2**). Mean (SD) MADE scores were:
  - <10 years: 14.1 (6.9)
  - 10-13 years: 15.8 (7.0)
  - >13 years: 17.4 (5.8).

Physical functioning

- QMT grip strength score peaked 2-3 years pre-LoA, then decreased over time, across all groups (**Figure 3**).
- At the time of LoA, grip strength was greater among patients with later LoA. Mean (SD) QMT grip strength scores were:
  - <10 years: 10.4 (3.7)
  - 10-13 years: 12.2 (4.7)
  - >13 years: 16.2 (7.0).

Discussion:

- This analysis of data from a prospective, longitudinal study in DMD demonstrated that LoA represents an important marker of disease burden and physical functioning, in a gradual course of progressive decline.
- Patients with earlier AaLoA progressed to full-time wheelchair use faster from initiation of wheelchair use.
- A later AaLoA may suggest a later declination in grip strength, for example by better adaptation through a later ambulatory stage involving wheelchair use.
- **Limitations:**
  - As non-ambulatory status was defined as full-time wheelchair use, lack of access to wheelchairs may have influenced classification of non-ambulatory status, particularly in low income or developing settings. Patients unable to walk may have been misclassified as ambulatory, and the true need of assistive device use may be underestimated.
  - There is a possibility of bias related to the exclusion of patients with missing LoA information.
  - Standard care varied across sites, including use of steroids and cardiac testing. In particular, cardiac test results likely underestimate the prevalence of reduced cardiac function, which is a component of the MADE score.

Conclusions:

Observed trends from this analysis of longitudinal data suggest that therapies that slow progression to LoA may also address the worsening burden and functioning in DMD regardless of timing of LoA.

References:

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CONTACT INFORMATION: ytomazos@ptcbio.com

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