RWD59

Association of Time of Loss of Ambulation with Severity of Respiratory Symptoms in Patients with nonsense mutation Duchenne Muscular Dystrophy (nmDMD)

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1. Background and objectives

DMD and ataluren

- DMD is a genetic disorder characterized by progressive muscle degeneration. Key milestones in a patient's decline include loss of ambulation (LoA) and respiratory function impairment as measured by predicted forced vital capacity (pFVC).[1]
- Ataluren is indicated for the treatment of nmDMD in ambulatory patients aged 2 years and older[2] in the European Member States and Iceland, Liechtenstein, Norway, Great Britain, Northern Ireland, Kazakhstan, Israel, Republic of Korea, Belarus, Russia, Brazil, Chile and Peru, and aged 5 years and older in the Kingdom of Saudi Arabia, and Ukraine (under special state registration).[2] In Brazil, the indication is restricted to pediatric male patients.[3]
  - The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing (see Summary of Product Characteristics for respective countries;[2] Instructions for Use – Russia[3]).
- Age at LoA (AaLoA) and respiratory symptoms for nmDMD have been compared between patients receiving ataluren plus standard of care (SoC, STRIDE registry) vs SoC alone (CINRG study).
- Recent real-world data from the STRIDE registry (2022 data cut) demonstrated a 4-year delay in LoA for ataluren-treated patients.[4]
- However, estimating treatment effects on respiratory function is challenging due to data limitations.
- There is a need to understand the relationship between LoA and respiratory outcomes.

Study objectives

- **This study aimed to assess the association between LoA and pFVC in patients with nmDMD, specifically to determine whether:**
  1. **Association between time from LoA and pFVC is independent of AaLoA;**
  2. **There is a difference in time from LoA to pFVC <50% in STRIDE (ataluren-treated) vs CINRG (SoC).**

2. Methods

Data sources

CINRG

- **C**ooperative **I**nternational **N**euromuscular **R**esearch **G**roup Duchenne Natural History Study (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 SoC (corticosteroid or palliative therapies) across 20 centers in nine countries.[5,6]

STRIDE Registry

- **S**trategic **T**argeting of **R**egistries and **I**nternational **D**atabase of **E**xcellence (NCT02369731) is an ongoing, multicenter, observational registry providing real-world evidence regarding the use of ataluren in patients with nmDMD.
- As of January 31, 2022, 307 patients across 66 centers in 14 countries had been enrolled.[4]

Study population

- Propensity score matching identified STRIDE and CINRG patients with both LoA and pFVC <50% outcomes available.
- For the present analysis, a matched dataset from the 2022 data cut was used. Propensity score matching was conducted for the following characteristics:
  - Age at first symptoms
  - Age at initiation of corticosteroid use
  - Duration of deflazacort use
  - Duration of other corticosteroid use

Analyses

Analysis 1: AaLoA and pFVC (CINRG)

- Assessed pFVC and LoA data from CINRG.
- Developed a linear mixed effects regression model in a Bayesian framework with a log link and an AaLoA covariate.
  - Inclusion of covariate generates a numerical estimate of the relationship between AaLoA and pFVC.
  - Allows prediction of pFVC using AaLoA and age.

Analysis 2: time from LoA to pFVC <50% (STRIDE & CINRG)

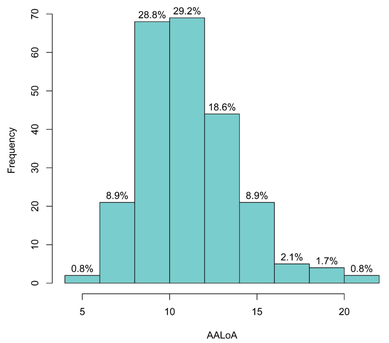
- Assessed time from LoA to pFVC <50% in STRIDE vs propensity score matched population in CINRG.[7]
- Conducted time-to-event analysis using Kaplan Meier curves.
- Calculated unstratified hazard ratio (HR) to describe the difference in time from LoA to pFVC <50% between STRIDE and CINRG.

3. Results

Analysis 1: AaLoA and pFVC (CINRG)

- An initial exploratory analysis showed that 81.8% of 236 patients who experienced LoA did so between 7.5 and 14.5 years of age. Limited data were available for patients with AaLoA outside of this range (**Figure 1**).
- **Figure 2a** shows the pFVC of all patients who lose ambulation either before or during the CINRG study. The downward trend as age increases suggests that, over time, the pFVC of these patients would decrease.
- A regression model was then fitted and stratified by AaLoA group (**Figure 2b**); predicted age at pFVC <50% for each AaLoA group is presented in **Table 1**. All 236 patients represented in **Figure 1** were used to fit the regression model.
- There is a clear relationship between AaLoA and pFVC:
  - LoA generally occurs before pFVC <50%. Of the matched CINRG population, only 5.6% of patients that lose ambulation do so after pFVC <50%.
  - Patients with later LoA are generally expected to have a higher pFVC value at all ages when compared to patients with earlier LoA.
  - The younger the AaLoA, the younger the expected age at pFVC <50%.
  - Earlier LoA is associated with earlier decline in pFVC.
- When assessing the expected decline in pFVC for the year after LoA for each AaLoA group, later AaLoA had a slower decline in pFVC after LoA (**Table 1**).

Figure 1. Frequency of AaLoA in CINRG (N=236)



AaLoA, age at loss of ambulation; CINRG, Cooperative International Neuromuscular Research Group

Figure 2a. Raw pFVC data of patients with LoA from CINRG

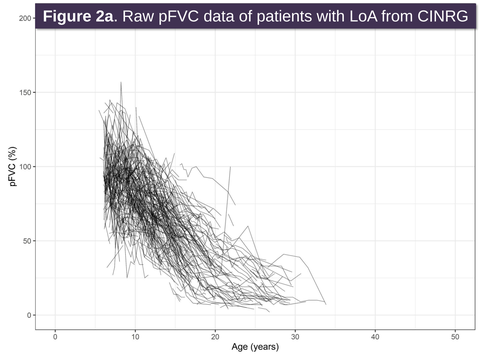
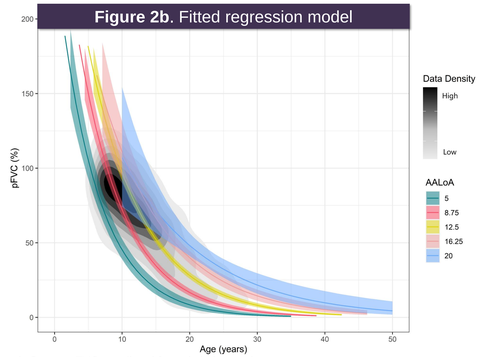


Figure 2b. Fitted regression model



AaLoA, age at loss of ambulation; CINRG, Cooperative International Neuromuscular Research Group; pFVC, predicted forced vital capacity

Table 1. Age at pFVC <50% and rate of decline in pFVC at LoA, by AaLoA group

AaLoA group, years	Predicted age at pFVC <50% (CrI)	Expected decline in pFVC in the year following AaLoA
5	9.4 (8.6, 10.3)	-16.6
8.75	12.5 (12.0, 13.0)	-12.1
12.5	15.4 (14.9, 15.8)	-8.6
16.25	17.8 (16.9, 18.7)	-5.9
20	19.5 (17.1, 21.5)	-3.9

AaLoA, age at loss of ambulation; CrI, credible interval; pFVC, predicted forced vital capacity

Analysis 2: time from LoA to pFVC <50% (STRIDE & CINRG)

- As shown in **Table 2,** 39.5% of patients receiving ataluren (15/38 patients in STRIDE) and 55.1% of those receiving SoC (38/69 patients in CINRG) reached pFVC <50%.
- Time to pFVC <50% after LoA was not significantly different between CINRG and STRIDE (HR [95% confidence interval, CI]: 1.01 [0.55-1.85]).

Table 2. Number of patients reaching pFVC <50% and time from LoA to pFVC <50% in STRIDE and CINRG

Outcome	STRIDE (ataluren + SoC) N = 38	CINRG (SoC) N = 69
N (%) reaching pFVC <50%	15 (39.5)	38 (55.1)
N (%) censored	23 (60.5)	31 (44.9)
Median (95% CI) years from LoA to pFVC <50%	4.91 (3.92 to 7.33)	4.60 (3.72 to 5.83)
HR (95% CI)	-	1.01 (0.55 to 1.85)

CI, confidence interval; CINRG, Cooperative International Neuromuscular Research Group; HR, hazard ratio; LoA, loss of ambulation; pFVC, predicted forced vital capacity; SoC, standard of care; STRIDE, Strategic Targeting of Registries and International Database of Excellence

4. DISCUSSION

- The results of the present study show that delay in LoA is associated with delayed respiratory decline at any age.
- Limitations in the data should be noted; while this study focused on averages within the data, there may be substantial variation between individual patients.
- Low patient numbers in the analyses may impact the generalizability of findings; moreover, the analysis of time from LoA to pFVC <50% was not sufficiently powered to estimate any additional clinically important improvements.
- Notably, previous research has shown that median (95% CI) AaLoA was statistically significantly higher among patients in the STRIDE registry (17.0 [15.0, NA] years) than in CINRG (13.0 [12.0, 14.0] years; p<0.0001).[7] Given that patients in STRIDE receive ataluren plus SoC, while those in CINRG receive SoC only, the previous work demonstrated that ataluren delays LoA.[7]

5. CONCLUSION

- **The results from this study, in context with previous work, suggest that delay in LoA due to ataluren will lead to comparable delay in the decline of respiratory outcomes.**

References

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Disclosures

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