Crossing thresholds and changing rates of respiratory function decline are predictive of clinical outcomes in Duchenne Muscular Dystrophy (DMD)

Craig McDonald, Heather Gordish-Dressman, Milka Leinonen, Oscar H Mayer and CINRG-DNHS Investigators

1UC Davis Health, Davis, USA, 2The George Washington University School of Medicine and Health Sciences, Washington DC, USA, 3Clinical Data Science, Basel, Switzerland, 4Children’s Hospital of Philadelphia (CHOP), Philadelphia, USA

Poster presented at MDI, April 13–15, 2019, Poster: 11

Background

- Preservation of absolute FVC and FVC%p earlier in adolescence is associated with delayed pulmonary function decline, with decreased risk of pulmonary complications including the need for assisted ventilation, and crossing of the FVC <1L threshold, associated with a 4-fold increased risk of death.
- A prior study reported that falling below FVC of 1L was associated with a 5-year survival of only 8%. However, with recent improvements in standards of care, these findings are now outdated.
- Current standards of care are based on expert opinion rather than actual pulmonary data and utilize FVC%p thresholds to help guide clinical management, including the use of cough assist and nocturnal and diurnal ventilation.

No systematic analyses have assessed the impact of crossing thresholds or changing rate of respiratory function decline in Duchenne Muscular Dystrophy (DMD). These analyses demonstrate that crossing thresholds of FVC and PEF are predictive of 5-year survival and 2-year risk of assisted ventilation as a function of FVC%p (C) and PEF%p (D).

Objectives

To conduct a systematic analysis of data from CINRG-DNHS to assess:
- If falling below a 1L threshold in FVC is still predictive of 5-year survival or assisted ventilation, or if any other threshold of FVC/FVC%p or PEF/PEF%p predicts the 5-year survival or assisted ventilation.
- If rate of decline in FVC or PEF is predictive of the time to death and the initiation of assisted ventilation.

Methods

Analysis 1: Crossing thresholds of FVC or PEF
- Conducted in patients with at least one assessment at or above and one below the FVC/PEF threshold of interest. The time when the threshold was crossed is used as the baseline for the analysis.
- Thresholds were scanned in small decrements until <5 events occurred. Kaplan-Meier method was used to derive 5-year and 2-year risk estimates (and 95% CI) of disease and assisted ventilation.
- Similar analyses were conducted for FVC%p and PEF%p.

Analysis 2: Changes in rate of decline of FVC or PEF or FVC%p or PEF%p
- Conducted in patients with at least one assessment of FVC or PEF or FVC%p or PEF%p between 80 – 30% of the study. All values between 80 – 30% were used for each patient to estimate individual annual rates of decline.
- The individual rates of decline were categorized using a cut-off of 5%, the observed mean in natural history studies, as those with a more rapid decline rate (>5% per year) or less rapid rate (<5% per year). Sensitivity analyses were conducted with cut-offs at 4%, 6% and 7%.
- Time from crossing 50% of FVC or PEF or FVC%p or PEF%p for the first time was used as the baseline for the analysis and time to death or start of ventilation was estimated with Kaplan-Meier method. Sensitivity analyses were conducted with time from crossing 45%, 55% and 60% thresholds.
- The two groups (those with a more rapid rate of decline versus those with a less rapid rate) were compared with Kaplan-Meier methods. P-values were calculated with the log-rank test.

Results

- 440 patients from US, Europe, Australia and India are included in the CINRG-DNHS, 56 patients from India were excluded from this analysis because of the possibility of differing standards of care. In addition, 37 patients with no PEF or FVC data were excluded from all analyses.
- The remaining patients were used to perform the analyses as applicable (Figure 1).
- Baseline characteristics for patients with annual FVC%p and PEF%p decline <5% versus ≥5% are shown in Table 1.

Conclusions

- These analyses demonstrate that crossing thresholds of FVC and PEF are predictive of 5-year survival and 2-year risk of initiating assisted ventilation.
- Altering the rate of respiratory function decline impacted both the time to death as well as initiation of assisted ventilation, with a reduction in the rate of decline leading to a beneficial delay in both.
- Reducing the rate of respiratory function decline and delaying the time to cross clinically relevant thresholds of respiratory function is an important therapeutic goal to reduce respiratory complications and delaying time to needing assisted ventilation.

References


Conflict of interest

M. Leinonen is a part-time employee of Santhera Pharmaceuticals.

Acknowledgements

CINRG DNHS participants.