Correlation Between Volume- and Flow-Related Pulmonary Function Outcomes in Patients with DMD

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Background

In DMD, progressive loss of respiratory function leads to restrictive pulmonary disease and a steady decline in pulmonary function over time.[1–4] Serial assessment of respiratory function is a critical element of recommended routine monitoring for patients with DMD, as it may enable early identification and treatment of respiratory complications.[5,6] Historically, expiratory volume-related respiratory function outcomes, such as percent predicted measures of Forced Vital Capacity (FVC%p) and Forced Expiratory Volume in 1 second (FEV1%p) were used to monitor disease progression. Maximum Inspiratory Pressures (MIPs) and Maximum Expiratory Pressures (MEPs) are used to measure respiratory muscle strength early in the course of DMD disease.[7,8]

Idebenone (Raxone®) is in development as a treatment to help manage the pulmonary aspects of DMD.[9-13] Idebenone is formulated as an oral tablet and in clinical trials in DMD, is administered as 300 mg three times daily (with meals). Idebenone is a short-chain benzoquinone, capable of stimulating mitochondrial electron flux and cellular energy production, resulting in increased ATP production and decreased reactive oxygen species (ROS).[7] In the Phase 3 DELOS trial, idebenone significantly reduced the loss of respiratory function.[11]

Objectives

- To demonstrate that the flow-related outcome of percent predicted Peak Expiratory Flow (PEF%p) is a reliable alternative measure suitable for routine monitoring of progressive respiratory function decline in DMD.[10]

Methods

- In the Phase 3, placebo-controlled trial (DELOS) in 64 patients with DMD 10-18 years of age, the effect of long-term (52-week) treatment with idebenone on pulmonary function (as measured by PEF, FEV1, and FVC) was evaluated.[11] Study participants stopped using glucocorticoids (GCs) at least 12 months prior to study enrollment and did not use concomitant GCs during the trial.
- The results from this trial were compared to outcomes assessed for patients enrolled in the Duchene Natural History Study (DNHS) performed by the Cooperative International Neuromuscular Research Group (CINRG).

Results

- The within-subject coefficients of variation (CV) for measures taken on average 16.7 days (SD 12.4) apart were lowest and similar for PEF%p and FVC%p, indicating that these parameters have a similar degree of within-subject variability and can be reliably assessed in 10-18 year old DMD patients **(Table 1)**[10]
- In the baseline of the DELOS trial, PEF%p, FVC%p and FEV1%p correlated well with each other (Spearman's rho: PEF%p-FVC%p: 0.54; PEF%p-FEV1%p: 0.72; FVC%p-FEV1%p: 0.91) **(Figure 1)**[10]
- The changes from baseline to the last visit in the placebo group (N=33) were most similar for PEF%p and FVC%p and also closely correlated (Spearman's rho: PEF%p-FVC%p: 0.60; PEF%p-FEV1%p: 0.79; FVC%p-FEV1%p: 0.73) **(Table 2)**[10]
- These findings are supported by data from the CINRG DNHS, representing the natural course of the disease
  - Across all patients at baseline there was a linear relationship between FVC%p and PEF%p (Pearson r= 0.8507).

Table 1. PEF and FVC can be measured reliably in patients with DMD[10]

	Parameter	Within-subject CV (%)
Variability between Screening and Baseline	PEF%p	6.97
	FVC%p	6.69
	FEV1%p	11.11
	MIP%p	18.00
	MEP%p	15.73

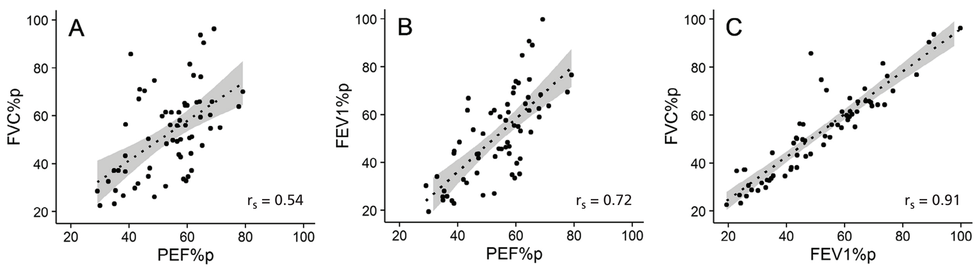
CV: coefficient of variation

Table 2. Yearly rate of natural history change in respiratory function outcomes (Placebo-DELOS patients)[10]

Pulmonary function parameter	All placebo (N = 33)	GC use status (prior GC-use)	
		No (N = 14)	Yes (N = 19)
PEF%p	-8.9 (2.0) (-13.0, -4.7) $p = 0.0001$	-10.2 (3.5) (-17.7, -2.7) $p = 0.0120$	-7.8 (2.7) (-13.5, -2.2) $p = 0.0090$
FVC%p	-8.7 (1.1) (-11.0, -6.5) $p < 0.0001$	-8.6 (2.1) (-13.1, -4.1) $p = 0.0014$	-8.7 (1.3) (-11.4, -5.9) $p < 0.0001$
FEV1%p	-10.2 (2.0) (-14.2, -6.2) $p < 0.0001$	-12.2 (3.6) (-20.1, -4.2) $p = 0.0059$	-8.7 (1.9) (-12.7, -4.7) $p = 0.0003$
MIP%p	-4.5 (1.3) (-7.2, -1.8) $p = 0.0017$	-5.8 (2.1) (-10.4, -1.3) $p = 0.0164$	-3.8 (1.8) (-7.5, -0.0) $p = 0.0492$
MEP%p	-2.8 (1.1) (-5.1, -0.5) $p = 0.0188$	-2.0 (1.9) (-6.1, 2.1) $p = 0.3017$	-3.2 (1.5) (-6.4, -0.05) $p = 0.0466$

P-values denote statistically significant decline at week 52 from baseline for Placebo-DELOS patients

Figure 1. Baseline correlation between dynamic pulmonary function test outcomes*[10]



*Baseline correlation between dynamic pulmonary function test outcomes. Individual patient data are represented by dots (with regression line); shaded area: 95% confidence interval band.

Conclusion

Results from the DELOS and the CINRG-DNHS studies indicate that the flow-related PEF%p is a sensitive measure of respiratory function change in DMD patients in the respiratory function decline phase (10-18 years), and closely correlated to changes observed for volume-related respiratory function outcomes (FVC%p and FEV1%p).[10]

References

1. McDonald CM, et al. *Am J Phys Med Rehabil*, 1995;74:S70-92.
2. Gozal D. *Pediatr Pulmonol*, 2000;29:141-50.
3. Simonds AK. *Semin Respir Crit Care Med*, 2002;23:231-8.
4. Bourke SC. *Clin Med (Lond)*, 2014;14:72-5.
5. Birnkrant DJ, et al. *Pediatr Pulmonol*, 2010;45:739-48.
6. Finder JD, et al. *Am J Respir Crit Care Med*, 2004;170:456-65.
7. Bushby K, et al. *Lancet Neurol*, 2010;9:177-89.
8. Suarez AA, et al. *Am J Phys Med Rehabil*, 2002;81:506-11.
9. Buyse GM, et al. *Neuromuscul Disord*, 2011;21:396-405.
10. Meier T, et al. *Neuromuscul Disord*, 2017;27:307-314.
11. Buyse GM, et al. *Lancet*, 2015;385:1748-57.
12. McDonald CM, et al. *Neuromuscul Disord*, 2016;26:473-80.
13. Buyse GM, et al. *Pediatr Pulmonol*, 2017;52:508-15.

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Conflict of interest

O. H. Mayer, E. Henricson, C. McDonald and G. Buyse are paid consultants for Santhera and also participated in prior/current studies with idebenone in DMD; G Buyse is co-inventor of relevant patent applications.

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