

Validation of a prognostic score for changes in six-minute walk distance (6MWD) in patients with Duchenne muscular dystrophy (DMD)

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Drug efficacy trials in DMD have been clouded by variation in rates of change in ambulatory function. We previously reported a prognostic score that explained 60% of variation in 1-year 6MWD changes, and significantly improved upon prognosis from baseline age, 6MWD and steroid use by also incorporating timed function tests, height and weight. This score was developed using natural history data from Universitaire ziekenhuizen Leuven. Here we report the validation of this score using 48-week placebo arm data from the Phase 3 clinical trial of tadalafil in DMD. Among patients with a calculable baseline prognostic score (n=104), mean (SD) annualized change from baseline in 6MWD was -50.1 (93.9) meters. Grouping patients by prognostic scores, 42% were predicted to have “fast decline”, 41% “moderate decline”, 14% to be “stable” and 3% “improving.” Mean (SD) annualized changes in 6MWD in these groups were -91.1 (99.4), -39.3 (79.3), 19.0 (59.5) and 48.6 (24.7) meters, respectively. No significant differences were observed vs. corresponding mean changes in updated Leuven data (n=181 non-overlapping ~1-year intervals): -107.3 (93.2), -35.9 (47.3), -1.6 (48.8) and 43.2 (54.4) meters, all $p > 0.05$, though SDs were higher for some groups on placebo. Mean reduction in 6MWD was numerically greater on the placebo arm compared to Leuven (difference = -15.2 meters, $p=0.21$), even after adjusting for baseline age, 6MWD and steroid use (difference = -16.6 meters, $p=0.14$). However, the difference between placebo and natural history became negligible after adjusting only for baseline prognostic score (difference = 0.5 meters, $p=0.96$). We conclude that a prognostic score developed using natural history data from a single center performed well when applied to placebo arm data from a clinical trial. These findings further support the potential for composite prognostic scores to inform DMD clinical trials, adjusted comparisons to natural history and clinical practice.

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