Prognostic factors for changes in 4-stair climb ability in patients with Duchenne muscular dystrophy (DMD)

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Background: The timed 4-stair climb (4SC) is used to assess ambulatory function in patients with DMD and as an endpoint in clinical trials. This study identified prognostic factors for changes in 4SC velocity, developed a composite prognostic score, assessed consistency across data sources and quantified impacts on trial sample size and power.

Methods: Boys with DMD receiving care at UZ Leuven in Belgium, Cincinnati Children's Hospital and Medical Center (CCHMC), or those who received placebo in the phase 3 DMD trial of tadalafil, were studied. Annualized change in 4SC velocity was studied over ~1-year intervals (8-16 months follow-up; required to have 4SC < 12 seconds at baseline) and related to candidate prognostic factors using multivariable regression. Simulations were used to quantify impacts on trial design.

Results: Mean (SD) changes from baseline in 4SC velocity in Leuven, CCHMC and the tadalafil trial placebo arm were -0.06 (0.65), -0.12 (0.56) and -0.18 (0.41) stairs/second (n=235, 543 and 82), respectively. Prognostic models incorporating baseline age, 4SC and duration of steroid use explained only a small portion of variability in 4SC outcomes (R^2: 8% to 17%). Adding baseline walking and rising ability significantly increased explained variation (R^2: 29% to 36%). In a randomized trial with equal allocation to treatment and placebo arms, baseline adjustment for such a prognostic score would enable a treatment effect of 0.25 stairs/second to be detected with 100-120 total patients, compared to170-190 patients without use of the prognostic score (at 80% power).

Conclusion: Combining multiple measures of ambulatory function more than doubled prognostic accuracy for 1-year changes in 4SC velocity. This finding was consistent across data sources, and with previous studies of prognostic factors for change in 6-minute walk distance in DMD. Clinical trials incorporating a validated prognostic score could reduce sample size requirements by approximately 40%.

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