TITLE: SUITABILITY OF NATURAL HISTORY DATA FOR EXTERNAL CONTROLS IN DUCHENNE MUSCULAR DYSTROPHY

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ABSTRACT

OBJECTIVES: Use of natural history (NH) controls in DMD drug evaluations is of high interest; however, the heterogeneity among patients or outcome assessments could potentially bias comparisons between NH and clinical trials, especially for performance-based outcomes. As a follow-up to our previous work using the 6-minute walk distance (6MWD), we aimed to assess this concern by comparing outcomes between NH data sources and clinical trial placebo arms using the NSAA.

METHODS: Placebo arm data from phase III trials of tadalafil and ataluren in DMD was used. NH data came from PRO-DMD-01 (provided by CureDuchenne) and UZ Leuven. Sensitivity analyses incorporated data from Cincinnati Children's Hospital Medical Center (CCHMC) and the NorthStar UK Clinical Network (NSUK). Change in NSAA total score over ~48-week intervals was studied in boys aged 6-18 years with NSAA >12 at baseline.

RESULTS: Multivariable regression was used to compare NSAA changes between NH and placebo arms adjusting for baseline prognostic factors. Primary analyses included 187 intervals (187 patients) from placebo arms, and 317 intervals (180 patients) from NH data. The unadjusted difference in mean ~48-week change in NSAA between NH and placebo was -1.36 (p=0.001). Adjusting for baseline characteristics (age, baseline NSAA, steroid use, timed function tests, height, weight and BMI) decreased the difference to -0.04 units (p=0.9). Results were similar in sensitivity analyses incorporating the CCHMC (unadjusted: -1.67; p <0.001, adjusted: -0.19; p=0.6) and NSUK databases (unadjusted: -1.14; p=0.004, adjusted: -0.28; p=0.5). Without adjustment for baseline prognostic factors, changes in NSAA total score differed slightly between NH and placebo. After adjustment, no significant differences between NH and placebo were observed for this outcome.

CONCLUSIONS: These findings align with our previous research using 6MWD, and further demonstrate the suitability of NH controls for providing interpretative context, or potentially augmenting or replacing placebo arms, in DMD drug evaluations.

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