CLINICAL RESEARCH SHORT REPORT

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Evaluating longitudinal therapy effects via the North Star Ambulatory Assessment

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Abstract

Introduction/Aims: In comparative studies, treatment effects are typically evaluated at a specific time point. When data are collected periodically, an alternative, clinically meaningful approach could be used to assess the totality of treatment effects. We applied a well-developed analytical procedure for evaluating longitudinal treatment effects using North Star Ambulatory Assessment (NSAA) data for illustration.

Methods: The NSAA comprises 17 scorable items/outcomes that measure changes in motor function. Using NSAA data from the published ataluren phase 3, randomized, placebo-controlled trial (NCT01826487), cumulative counts of failures to perform each item (transition from 2/1 [able/impaired] to 0 [unable]) were collected at specified time points for each patient over 48 wk. Treatment group-wise mean cumulative item failure count curves were constructed, comparing ataluren versus placebo and deflazacort versus prednisone/prednisolone among placebo-treated patients. The steeper the curve, the worse the outcome. A clinically meaningful summary of the between-group difference was provided for each comparison.

Results: The curve was uniformly steeper for placebo than ataluren after 16 wk and for prednisone/prednisolone than deflazacort after 8 wk. The two curves in each comparison continued to diverge thereafter, indicating sustained treatment benefits over time. Using a unique analytical approach, cumulative failure rates were reduced, on average, by 27% for ataluren versus placebo (rate ratio, 0.73; 95% confidence interval [CI], 0.55–0.97; $p = .027$) and 28% for deflazacort versus prednisone/prednisolone (rate ratio, 0.72; 95% CI, 0.53–0.96; $p = .028$).

Discussion: Unlike fixed-time analyses, this analytical approach enabled demonstration of cumulative, longitudinal treatment effects over time using repeatedly measured NSAA observations.

1 | INTRODUCTION

Investigative studies typically assess efficacy and safety of new treatments by measuring changes in outcome measures at fixed time points. However, this approach does not utilize multiple outcome data, often collected repeatedly at pre-specified time points during studies, to evaluate cumulative, longitudinal treatment effects. Instead of depending on a single endpoint, the totality of evidence for treatment effects could be considered in comparative studies assessing new treatments.

Duchenne muscular dystrophy (DMD) is a progressive neuromuscular disease,[1] caused by mutations in the *DMD* gene.[2,3] Approximately 10%-15% of patients have a nonsense mutation,[4] causing an in-frame premature stop codon and formation of nonfunctional dystrophin protein.[5]

Standard of care for DMD patients includes corticosteroid treatment with deflazacort, prednisone, or prednisolone.[6] Ataluren, a mutation-specific therapy, promotes readthrough of an in-frame premature stop codon caused by a nonsense *DMD* mutation.[5,7] In the ataluren phase 3 trial (Study 020; Ataluren Confirmatory Trial in Duchenne Muscular Dystrophy [ACT DMD]; NCT01826487), patients with nonsense mutation DMD (nmDMD) receiving ataluren or placebo and corticosteroids performed the North Star Ambulatory Assessment (NSAA),[8] a validated, clinical scale comprising 17 outcomes/items with three response categories (2/1/0) that measure motor function and disease progression (Supporting Information Figure S1, which is available online).[9,10] For this progressive disease, evaluating disease burden by measuring the totality of evidence from multiple outcome data over time per patient could be highly informative. We present a unique analytical approach to assess longitudinal, cumulative treatment effects over time, using Study 020 NSAA data for patients who received ataluren versus placebo and deflazacort versus prednisone/prednisolone as illustrative examples.[8]

2 | METHODS

2.1 | Study design and patients

Study 020 was a randomized, double-blind, placebo-controlled, phase 3 trial of ataluren, consisting of 2-wk screening and 48-wk treatment (1:1 randomization, placebo:ataluren [40 mg/kg/day]).[8] Ambulatory boys aged 7–16 y with dystrophinopathy and confirmed nmDMD were enrolled between March 26, 2013 and August 26, 2014. Inclusion and exclusion criteria are reported elsewhere[8] and in the Supporting Information Appendix S1. The trial was approved by local regulatory authorities and institutional review boards of each site. Parents/guardians provided written informed consent (patients provided written assent when appropriate) before study participation.

2.2 | Study assessments

Patients were assessed using the NSAA at screening, baseline and every 8 wk until treatment end between March 26, 2013 and August 20, 2015.[8]

2.3 | Statistical analyses

2.3.1 | Analysis populations

Patients in the intent-to-treat (ITT) population included all randomized patients with a valid baseline and at least one valid, post-baseline 6-min walk distance (6MWD) value.

2.3.2 | Cumulative loss of function of NSAA items

This analysis used data representing cumulative failure to perform NSAA items in patients at multiple time points (six visits) over 48 wk. Failure to perform an item was defined as a score transition from 2 or 1 to 0 at evaluation. For individual patients, we show examples of the cumulative number of failures across all 17 items over 48 weeks in Supporting Information Figure S2. Only post-baseline failures were considered in the present analysis. For each treatment group, we then constructed the mean of all such patients' individual curves, reflecting the average cumulative number of failures over time (Figures 1 and 2). The higher the curve, the worse the study treatment effect. To quantify the group difference, we assumed that the ratio of two corresponding underlying group-wise curves was constant over time, and used the Lin, Wei, Yang and Ying (LWYY) analytic method[11] to estimate this constant ratio. This summary measure can also be interpreted as the ratio of the intensities of occurrences of failures over time. Originally used to analyze multiple failure-time data for the same failure type, the LWYY method has been utilized in cardiovascular and sickle cell anemia studies,[12,13] in both cases demonstrating cumulative treatment benefits over time. The LWYY method has not yet been applied to studies of progressive neuromuscular diseases, for which the method could provide unique insights into disease burden and response to treatment by assessing the totality of multiple clinical outcomes over time.

Here, the procedure was generalized to handle different failure types. This methodology assumes that the ratio of the two group-wise curves is constant over time and estimates this ratio.
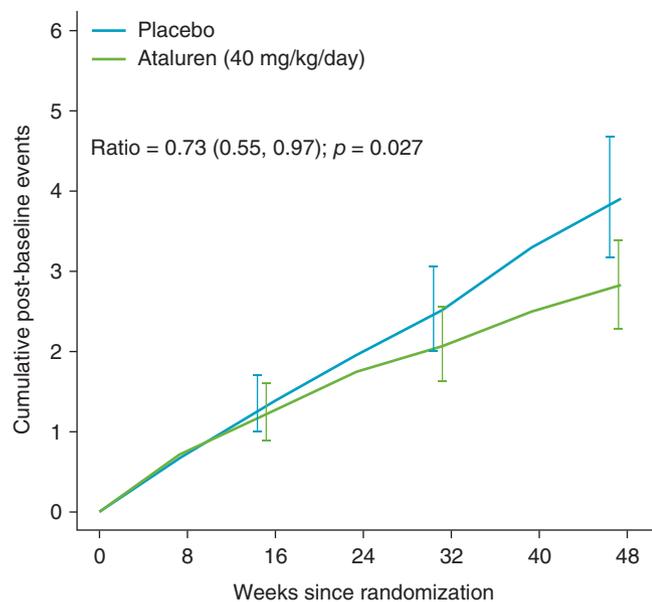
FIGURE 1 Group-wise mean cumulative counts of lost NSAA functions (failures) at each visit over 48 wk for patients in study 020 receiving placebo (n = 114) or ataluren (40 mg/kg/day; n = 114) in the overall ITT population. Error bars represent the 95% pointwise confidence intervals
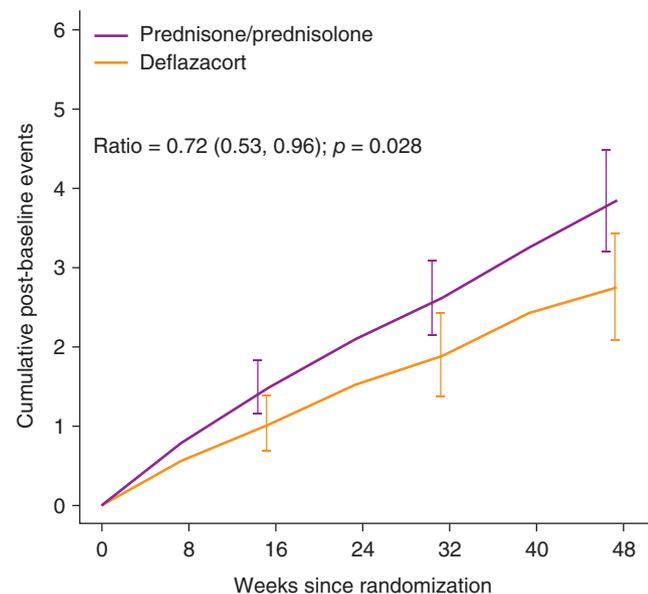
FIGURE 2 Group-wise mean cumulative counts of lost NSAA functions (failures) at each visit over 48 wk for patients in study 020 receiving placebo and prednisone/prednisolone (n = 61) or placebo and deflazacort (n = 53) in the overall ITT population. Error bars represent the 95% pointwise CI

If this assumption is not plausible, the resulting estimate reflects an averaged ratio between the two curves over time. The lower the ratio, the greater the treatment effect. If a patient discontinued (placebo = 3 [deflazacort = 2; prednisone/prednisolone = 1]; ataluren = 4), the cumulative failure number was censored upon discontinuation.

3 | RESULTS

3.1 | ACT DMD study population

Of 230 patients (placebo = 115; ataluren = 115; as-treated population), 228 were included in the ITT population (placebo = 114; ataluren = 114).[8] Of 114 placebo-treated patients, 53 were receiving deflazacort and 61 prednisone/prednisolone.[14] Baseline demographics and patient characteristics were comparable between groups (Supporting Information Appendix S1).[8,14] The proportion of patients able to perform each NSAA item at baseline was similar between placebo and ataluren groups and between deflazacort and prednisone/prednisolone groups of the placebo arm (ITT population).[8] Mean (SD) total NSAA scores at baseline were 21.9 (8.0) and 22.2 (7.8) for placebo and ataluren groups, respectively, and 23.0 (9.0) and 20.9 (7.0) for deflazacort and prednisone/prednisolone groups, respectively.[8,14]

3.2 | Cumulative counts of lost NSAA functions at each visit over 48 weeks

Every patient in the ITT population (n = 228) was assessed for each NSAA item (placebo, 1938 items [deflazacort, 901 items; prednisone/prednisolone, 1037 items]; ataluren, 1938 items).[8] Curves for the group-wise mean cumulative number of failures over 48 wk for placebo and ataluren groups are shown in (Figure 1). The placebo curve was steeper than that for ataluren after week 16 and continued to diverge until the end of treatment. The LWYY method was utilized to quantify the difference between the two group-wise curves (i.e., the treatment effect).[11] The mean cumulative NSAA failure count at week 48 was 3.90 and 2.82 for placebo and ataluren groups, respectively. Over the study, a reduction of 27% in the mean cumulative failure rate was observed in ataluren-treated versus placebo-treated patients (rate ratio, 0.73; 95% confidence interval [CI], 0.55–0.97; p = .027).

Cumulative curves for placebo-treated patients who received deflazacort or prednisone/prednisolone revealed a steeper curve for prednisone/prednisolone than for deflazacort, beginning at week 8, after which the curves continued to diverge (Figure 2). The LWYY method demonstrated that the mean cumulative NSAA failure count at week 48 was 2.75 and 3.84 for deflazacort and prednisone/prednisolone, respectively. The mean cumulative failure rate reduced by 28% in deflazacort-treated versus prednisone/prednisolone-treated patients over the study (rate ratio, 0.72; 95% CI, 0.53–0.96; p = .028). Although cumulative failure rate ratios at individual time points may not significantly differ between treatments (group-wise 95% confidence intervals overlap in the figures), the LWYY procedure considers all time points to demonstrate the totality of treatment effects.

Using a different analytical procedure, the rate ratios of the concurrent failure number at each time point decreased from 1.05 to 0.54 for ataluren versus placebo and from 0.71 to 0.55 for deflazacort versus prednisone/prednisolone from visit one to six

(Supporting Information Tables S1 and S2). The mean of these ratios over time was 0.72 and 0.71 respectively, suggesting robust long-term treatment benefits.

4 | DISCUSSION

The LWYY approach investigated here expands on published fixed-time analyses as a new clinically meaningful approach to evaluating NSAA data in clinical trials. A previous ACT DMD post hoc single time point analysis showed that patients receiving ataluren experienced a 31% reduced risk of loss of function, measured by the ability to perform each NSAA item (ataluren-treated patients lost 12.9% of functions; placebo-treated patients lost 18.8% of functions; risk ratio, 0.687; 95% CI, 0.516–0.914; $P = .010$), compared with placebo after 48 weeks.[8] Here, we show that the cumulative NSAA item failure rate was significantly reduced by 27% in ataluren-treated compared with placebo-treated patients. We also analyzed data from placebo-treated patients who received deflazacort or prednisone/prednisolone: the number of cumulative NSAA item failures was significantly reduced by 28% in patients receiving deflazacort relative to patients receiving prednisone/prednisolone. The methodology presented here demonstrates broad utility and practical use in enabling the observation of cumulative treatment effects, using NSAA data from DMD patients as illustrative examples.

The typical methodology for assessing treatment effects in investigative studies involves measuring changes in outcome measures from one fixed time point to another, usually from baseline to study end. The unique approach presented here answers a different clinical question by investigating the longitudinal profile of the treatment effect over time, rather than evaluating the effect at a single, fixed time point only. For progressive diseases like DMD, evaluating the totality of evidence from multiple outcome data over time using this approach complements traditional fixed time point analyses and offers clinically meaningful insights into disease burden and the temporal nature of treatment effects.

Work is in progress to develop an appropriate method to analyze cumulative gain of function in young DMD patients in whom maturational improvements may mask treatment effects.

4.1 | Conclusions

Analyses of temporal data using the approach presented here demonstrated longitudinal, cumulative treatment effects over time, measured by the NSAA. This method could shape the design of future clinical studies, as well as clinically meaningful outcome measures, for patients with progressive neuromuscular disorders such as DMD.

CONFLICT OF INTEREST

Craig M. McDonald has acted as a consultant on clinical trials of DMD for Astellas, Capricor, Catabasis, Edgewise Therapeutics, Epirium Bio (formerly Cardero Therapeutics), FibroGen, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals and Sarepta Therapeutics. He has received research support for clinical trials from Capricor, Catabasis, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals and Sarepta Therapeutics. Lee-Jen Wei has acted as a consultant for Johnson and Johnson, Merck and co., Pfizer, PTC Therapeutics and Sarepta Therapeutics. Kevin M. Flanigan has acted as a consultant for Apic Bio, Audentes Therapeutics, Dynacure, Italfarmaco, Marathon Pharmaceuticals, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics, Tivorsan Pharmaceuticals, and 4D Molecular Therapeutics; has been a clinical trial investigator for Abeona Therapeutics, Akashi Therapeutics BioMarin and Sarepta Therapeutics; has received grants from Beauhawks Foundation and CureDuchenne; and has received royalty payment from Audentes Therapeutics. Gary Elfring and Panayiota Trifillis are employees of PTC Therapeutics. Francesco Muntoni has received consulting fees from AveXis, Biogen, Dyne Therapeutics, Capricor, Catabasis, Novartis, Pfizer, PTC Therapeutics, Roche, Santhera Pharmaceuticals, Sarepta Therapeutics and Wave Therapeutics, and is supported by the National Institute of Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. Medical writing and editorial support were funded by PTC Therapeutics Ltd.

ETHICAL APPROVAL

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

APPENDIX A.

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