Relationship Between Quantitative Strength Changes and Functional Outcomes in the Phase 2 FORTITUDE-ALS Trial

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INTRODUCTION

- In amyotrophic lateral sclerosis (ALS), physical function and the patient's quality of life (QoL) are well established outcome measures
  - The ALS Functional Rating Scale-Revised (ALSFRS-R) is the standard assessment of physical function, while the patient's subjective perception of their well-being is assessed using the 5-item ALS Assessment Questionnaire (ALSAQ-5), a self-reported QoL scale
  - Muscle strength loss is intrinsic to decline in function but the specific relationships of strength in individual muscles or muscle groups to functional state or QoL has not been well described
- *Reldesemtiv*, a fast skeletal troponin activator, selectively activates the fast skeletal muscle troponin complex by increasing its sensitivity to calcium; in preclinical studies this increases muscle force in response to neural input and delays the onset and magnitude of muscle fatigue
- **FORTITUDE-ALS** was a 12-week, Phase 2, double-blind trial of *reldesemtiv* in 458 patients with ALS (diagnosis ≤ 24 months), who were randomized to 1 of 3 *reldesemtiv* doses or placebo
  - Outcome measures included slow vital capacity (SVC), ALSFRS-R, quantitative muscle strength testing utilizing hand-held dynamometry (HHD), and the ALSAQ-5
  - Although the primary analysis of SVC was not statistically significant, effect sizes were generally regarded as clinically important,[1] and a post hoc analysis also showed that *reldesemtiv* also reduced the need for durable medical equipment[2]

OBJECTIVES

- To evaluate the relationship between individual or grouped muscle strength and:
  - The fine and gross motor domains of the ALSFRS-R
  - Items 1 and 2 of the ALSAQ-5

METHODS

- This post hoc analysis of the FORTITUDE-ALS trial (NCT03160898) included all patients in the full analysis set
- Outcome measures were performed at Screening, Day 1, Weeks 2, 4, 8, 12, and follow-up
- Strength was measured with HHD in 3 upper extremity muscles (first dorsal interosseous, wrist extensors, and elbow flexors) and 3 lower extremity muscles (ankle dorsiflexors, quadriceps, and hip flexors); mean strength of each muscle measured bilaterally was used for analysis
- HHD scores for individual muscles and combined muscle groups were correlated with:
  - Functional status, based on scores of the ALSFRS-R fine motor domain and gross motor domain; lower scores reflect reduced physical function
  - QoL, based on Questions 1 and 2 of the ALSAQ-5; higher ALSAQ-5 scores reflect worse QoL
- Correlation was assessed using Spearman's rank correlation coefficient, defining scores <0.3 as very weak correlation, 0.3–0.49 as weak, 0.5–0.69 as moderate, 0.7–0.8 as strong, and >0.8 as very strong

RESULTS

Figure 1. Correlation of HHD and ALSFRS-R domains

Muscle	Strength, lbs, mean (SD)	Fine Motor Domain (mean ± SD score 7.7 ± 3.0) Includes handwriting, cutting food and handling utensils, dressing and hygiene: Spearman's correlation coefficient (95% CI)	Gross Motor Domain (mean ± SD score 7.1 ± 3.1) Includes turning in bed and adjusting bedclothes, walking, climbing stairs: Spearman's correlation coefficient (95% CI)
Upper extremity	45.9 (29.5)	0.706 (0.686, 0.725)	0.309 (0.274, 0.344)
First dorsal interosseous	4.0 (3.8)	0.686 (0.665, 0.706)	0.260 (0.224, 0.296)
Wrist extension	16.1 (11.5)	0.697 (0.677, 0.717)	0.293 (0.257, 0.328)
Elbow flexion	25.7 (16.6)	0.633 (0.609, 0.656)	0.293 (0.257, 0.328)
Lower extremity	99.0 (52.0)	0.119 (0.080, 0.157)	0.617 (0.592, 0.640)
Hip flexion	31.4 (17.4)	0.136 (0.097, 0.174)	0.608 (0.583, 0.632)
Knee extension	41.2 (20.5)	0.095 (0.056, 0.133)	0.484 (0.453, 0.513)
Ankle dorsiflexion	26.3 (20.3)	0.111 (0.073, 0.150)	0.601 (0.575, 0.625)

ALSFRS-R, ALS Functional Rating Scale-Revised; CI, confidence interval; HHD, hand-held dynamometry; lbs, pounds; SD, standard deviation

Figure 2. Correlation of HHD and ALSAQ-5 items

Muscle	Strength, lbs, mean (SD)	ALSAQ-5 Item 1 (mean score 41.4 ± 35.0) Patients answer the question: I have found it difficult to stand up: Spearman's correlation coefficient (95% CI)	ALSAQ-5 Item 2 (mean score 49.9 ± 33.6) Patients answer the question: I have had difficulty using my arms and hands: Spearman's correlation coefficient (95% CI)
Upper extremity	45.9 (29.5)	-0.259 (-0.295, -0.223)	-0.661 (-0.682, -0.639)
First dorsal interosseous	4.0 (3.8)	-0.240 (-0.276, -0.203)	-0.605 (-0.629, -0.579)
Wrist extension	16.1 (11.5)	-0.242 (-0.278, -0.205)	-0.640 (-0.663, -0.617)
Elbow flexion	25.7 (16.6)	-0.247 (-0.283, -0.210)	-0.609 (-0.633, -0.584)
Lower extremity	99.0 (52.0)	-0.548 (-0.575, -0.520)	0.017 (-0.022, 0.056)
Hip flexion	31.4 (17.4)	-0.536 (-0.563, -0.508)	-0.010 (-0.049, 0.029)
Knee extension	41.2 (20.5)	-0.448 (-0.479, -0.417)	0.013 (-0.026, 0.052)
Ankle dorsiflexion	26.3 (20.3)	-0.517 (-0.545, -0.488)	0.028 (-0.011, 0.067)

ALSAQ-5, 5-item ALS Assessment Questionnaire; CI, confidence interval; HHD, hand-held dynamometry; lbs, pounds; SD, standard deviation

CONCLUSIONS

- In this study, upper extremity muscle strength (individually and summed), as measured by HHD testing, demonstrated:
  - Moderate to strong positive correlation with the ALSFRS-R fine motor domain
  - Moderate inverse correlation with ALSAQ-5 Item 2 (higher ALSAQ-5 scores reflect increasing difficulty)
- Lower extremity strength (individually and summed) generally showed:
  - Moderate correlation with the ALSFRS-R gross motor domain
  - Moderate inverse correlation with ALSAQ-5 Item 1
- In general, summed relationships were stronger than those seen with individual muscles

Summary

- These findings suggest that beyond being an objective quantitative measure of ALS progression, extremity muscle HHD testing is moderately to strongly related to function established through associated domains of the ALSFRS-R and to the associated items on the ALSAQ-5, a disease-specific QoL scale

References

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