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Automated Video-Based Characterization of Movement Quality in a Phase III Clinical Trial of Troriluzole in Subjects With Spinocerebellar Ataxia

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CONCLUSIONS

1. Machine learning applied to video-captured gait parameters provides an alternative quantitative approach to clinician-reported motor assessment in cerebellar ataxia
2. Using this novel method, the pose dispersion metrics showed that troriluzole improved gait performance in individuals with spinocerebellar ataxia (SCA) compared with placebo
   - Individuals treated with troriluzole exhibited significant improvement in tandem walk Pose Dispersion Index (PDI) values vs those treated with placebo (adjusted interaction coefficient, 0.58; 95% CI, 0.14 to 1.03; *P*=0.01); a similar but nonsignificant trend toward improvement in natural walk PDI values was observed with troriluzole
3. Lower baseline PDI values (i.e., less stable gait) were significantly associated with a higher risk of subsequent falls during the natural walk task (adjusted Poisson coefficient, −0.36; 95% CI, −0.70 to −0.01; *P*=0.041)

INTRODUCTION

- SCAs are autosomal-dominant, neurodegenerative diseases characterized principally by Purkinje cell death and cerebellar atrophy, resulting in progressive gait ataxia and other symptoms of cerebellar dysfunction[1]
- Traditional methods for assessing gait movement employ clinical outcome assessment measures that include structured administration and fixed clinician rating options; these may limit measurement abilities in patients with SCA, as changes in mobility can be subtle and varied[2,3]
  - Based on existing evidence,[4] we hypothesized that a machine learning analytic system may provide a novel perspective and complement traditional clinician-rated scales
- Treatment for SCA remains an unmet need, with clinical management being limited to rehabilitation and supportive measures in the absence of approved therapies[5]
- Troriluzole is a novel, third-generation tripeptide prodrug of riluzole that is under investigation for the treatment of SCA in an ongoing phase 3 clinical trial (NCT03701399); the primary outcome measure is change from baseline in the modified functional Scale for the Assessment and Rating of Ataxia (f-SARA) score[6]

References: 1. Klockgether T, et al. *Nat Rev Dis Primers*. 2019;5(1):24. **2.** Muro-de-la-Herran A, et al. *Sensors (Basel)*. 2014;14(2):3362-3394. **3.** Wade L, et al. *PeerJ*. 2022;10:e12995. **4.** Sambati L, et al. *Neurol Sci*. 2019;40(2):333-338. **5.** Ilg W, et al. *Cerebellum*. 2014;13(2):248-268. **6.** ClinicalTrials.gov. Accessed February 2, 2024. https://clinicaltrials.gov/study/NCT03701399 **7.** Cao Z, et al. *IEEE Trans Pattern Anal Mach Intell*. 2021;43(1):172-186. **8.** Andriluka M, et al. 2014 IEEE Conference on Computer Vision and Pattern Recognition, Columbus, OH, USA. 2014; 3686-3693.

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OBJECTIVE and METHODS

Objective

- To examine the effects of troriluzole vs placebo on gait quality through a novel video-based assessment of gait dispersion among individuals with SCA in a post hoc analysis of a phase 3 trial (NCT03701399)

Methods

- Eligible participants were aged 18 to 75 years with a known or suspected diagnosis of SCA 1, 2, 3, 6, 7, 8, or 10; were able to ambulate 8 meters without human assistance; and had an f-SARA total score of ≥3 and a gait subscore of ≥1. Key exclusion criteria were a score of 4 on any individual item of the f-SARA and a Mini-Mental State Examination score of <24
  - Participants were randomized 1:1 to receive troriluzole 200 mg (titrated up from 140 mg in the first 4 weeks) once daily or placebo for up to 48 weeks
  - This post hoc analysis included participants who received ≥1 dose of the randomized study medication, underwent gait assessment of the ability to complete the natural walk or tandem walk, and had paired baseline/week 48 (or early termination) efficacy measurements and videos for the natural or tandem walk that met quality control standards
- Videos were analyzed using a deep neural network architecture that tracked coordinates of key body segments and defined interpretable kinematic features of dynamic pose dispersion using the integrated PDI that reflects symmetry, balance, and stability during natural and tandem walk tasks[7,8]
- The primary endpoint was PDI values at week 48 vs screening (week 0) during a tandem walk task. The secondary endpoint was PDI values at week 48 vs screening during a natural walk task. The exploratory endpoint was the relationship between PDI value at screening and total number (count) of falls recorded during the randomization period
- The effects of troriluzole on PDI values were assessed in mixed linear models using fixed effects, subject-level grouping, and treatment group by visit week interaction, adjusting for age, sex, baseline f-SARA score, and time since diagnosis
- The association between PDI value at screening and the total number of subsequent falls was assessed using Poisson regression models, with the total number of falls during randomization as the dependent variable
- Pairwise, unadjusted comparisons between week 48 and baseline were performed using paired *t* tests; unadjusted comparisons between 2 groups were performed using, as appropriate, a chi-square test (for categorical variables), unpaired *t* tests, or Mann-Whitney *U* tests

RESULTS

Study Participants

- Of the 218 participants enrolled, 67 (30.7%) and 56 (25.7%) had videos of a tandem and natural walk attempt, respectively, both at screening and week 48; 23 of these participants had videos of both the tandem and natural walk at the 2 time points
- Baseline characteristics of participants in this post hoc analysis were generally similar to those in the overall study cohort; however, gait item scores were lower in the current analysis
- Baseline demographics, f-SARA total and gait scores, and PDI values were generally similar between treatment arms for participants included in the tandem and natural walk analyses (**Table 1**)
  - The median time since diagnosis differed between treatment arms in participants included in the tandem walk analysis

Table 1. Baseline Characteristics of Participants in the Troriluzole and Placebo Treatment Arms

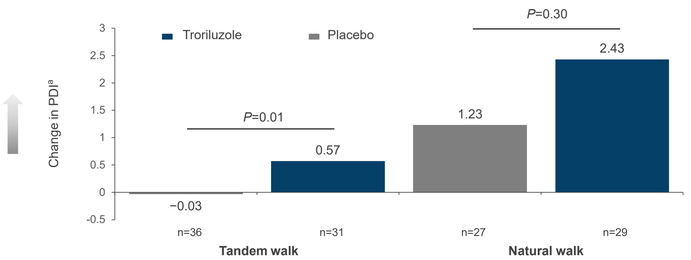
	Tandem walk				Natural walk			
	Overall N=67	Placebo n=36	Troriluzole n=31	*P* value	Overall N=56	Placebo n=27	Troriluzole n=29	*P* value
Age, mean (SD), years	45.9 (10.7)	44.5 (11.6)	47.5 (9.4)	0.258	47.3 (13.3)	47.6 (14.0)	47.0 (12.8)	0.877
Female, n (%)	34 (50.7)	18 (50.0)	16 (51.6)	1.000	37 (66.1)	18 (66.7)	19 (65.5)	1.000
Known genotype, n (%)								
SCA1	4 (6.0)	1 (2.8)	3 (9.7)		11 (19.6)	4 (14.8)	7 (24.1)	
SCA2	23 (34.3)	14 (38.9)	9 (29.0)		14 (25.0)	9 (33.3)	5 (17.2)	
SCA3	30 (44.8)	15 (41.7)	15 (48.4)		27 (48.2)	13 (48.1)	14 (48.3)	
SCA6	5 (7.5)	3 (8.3)	2 (6.5)	0.551	1 (1.8)	0	1 (3.4)	0.559
SCA7	2 (3.0)	2 (5.6)	0		1 (1.8)	0	1 (3.4)	
SCA8	1 (1.5)	0	1 (3.2)		2 (3.6)	1 (3.7)	1 (3.4)	
SCA10	2 (3.0)	1 (2.8)	1 (3.2)		0	0	0	
Baseline f-SARA								
Total score, median (IQR)	4.0 (3.0–4.5)	4.0 (3.0–4.2)	4.0 (3.0–4.5)	0.473	5.0 (4.0–6.2)	5.0 (4.0–6.0)	5.0 (4.0–7.0)	0.739
Gait item score, median (IQR)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.127	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–3.0)	0.724
Time since SCA diagnosis, median (IQR), years	2.7 (0.8–5.9)	1.7 (0.6–4.3)	3.6 (1.4–9.0)	0.040	4.7 (1.3–8.1)	4.0 (0.6–7.7)	5.0 (2.7–9.2)	0.213
PDI value, median (IQR)	1.0 (0.6–1.5)	1.3 (0.6–1.5)	0.8 (0.6–1.4)	0.352	3.0 (1.6–4.2)	2.7 (1.6–4.1)	3.3 (2.0–4.5)	0.408

f-SARA, modified functional Scale for the Assessment and Rating of Ataxia; PDI, Pose Dispersion Index; SCA, spinocerebellar ataxia.

Change in PDI Values

- Over 48 weeks, participants who received troriluzole exhibited a significant increase in PDI values for the tandem walk task vs those who received placebo (adjusted interaction coefficient, 0.58; 95% CI, 0.14 to 1.03; *P*=0.01), indicating an improvement in gait performance (**Figure 1; Table 2**)
  - This improvement was independent of age, sex, baseline f-SARA score, and/or years since diagnosis
- For the natural walk task, troriluzole led to a numerical increase in PDI values vs placebo (adjusted interaction coefficient, 1.20; 95% CI, −1.07 to 3.46; *P*=0.30) (**Figure 1; Table 2**)
- Results for individual patients on the tandem and natural walk tasks are shown in **Figure 2**

Figure 1. Change in PDI Values During a Tandem Walk Task and a Natural Walk Task at Week 48



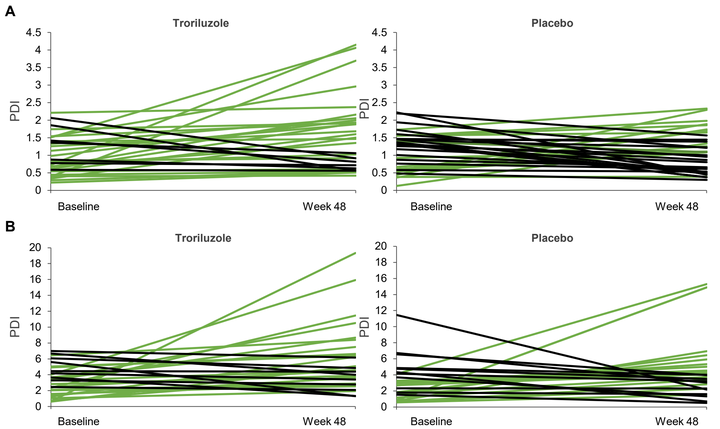
PDI, Pose Dispersion Index.
[a]Positive change in PDI values indicates improvement in gait performance.

Table 2. Adjusted Mixed Linear Model of PDI During a Tandem and Natural Walk Task

	Coefficient	SE	z	*P*>|z|	95% CI
Tandem walk					
Intercept	0.752	0.395	1.902	0.057	−0.023 to 1.526
Arm (troriluzole or placebo)	−0.092	0.172	−0.539	0.590	−0.429 to 0.244
Visit (week 0 or week 48)	−0.022	0.155	−0.140	0.889	−0.326 to 0.282
Arm × visit interaction	0.584	0.228	2.561	0.010	0.137 to 1.031
Sex	0.208	0.135	1.539	0.124	−0.057 to 0.473
Baseline f-SARA score	0.039	0.057	0.691	0.490	−0.072 to 0.151
Age in years	0.004	0.006	0.633	0.527	−0.008 to 0.016
Years since diagnosis	−0.016	0.012	−1.309	0.190	−0.040 to 0.008
Individual participant	0.041	0.099	–	–	–
Natural walk					
Intercept	0.197	1.533	0.129	0.898	−2.807 to 3.202
Arm (troriluzole or placebo)	0.345	0.824	0.419	0.676	−1.270 to 1.960
Visit (week 0 or week 48)	2.425	0.802	3.023	0.002	0.853 to 3.997
Arm × visit interaction	1.198	1.155	1.037	0.300	−1.067 to 3.462
Sex	0.045	0.615	0.073	0.942	−1.160 to 1.249
Baseline f-SARA score	0.307	0.162	1.896	0.058	−0.010 to 0.625
Age in years	0.045	0.022	2.008	0.045	0.001 to 0.089
Years since diagnosis	−0.104	0.064	−1.613	0.107	−0.230 to 0.022
Individual participant	0.000	0.501	–	–	–

f-SARA, modified functional Scale for the Assessment and Rating of Ataxia; PDI, Pose Dispersion Index.

Figure 2. Change in PDI Values in Individual Patients During a Tandem Walk Task (A) and Natural Walk Task (B) From Baseline Through Week 48



Association Between PDI Values and Number of Falls

- Lower baseline PDI values (i.e., less stable gait) were associated with higher risk of subsequent falls during the randomized phase (**Table 3**)
  - This was statistically significant for the natural walk–derived PDI values (adjusted Poisson coefficient, −0.36; 95% CI, −0.70 to −0.01; *P*=0.041) but not the tandem walk–derived PDI values (*P*=0.231)
  - These associations were independent of age, sex, baseline f-SARA scores, time since diagnosis, and treatment group

Table 3. Per-Unit Increase in PDI Values in Adjusted Poisson Regression Models[a] of Fall Counts During Weeks 0 Through 48

	Coefficient	SE	z	*P*>|z|	95% CI
Natural walk (n=56)	−0.3555	0.174	−2.039	0.041	−0.697 to −0.014
Tandem walk (n=67)	−0.7442	0.622	−1.197	0.231	−1.963 to 0.475

f-SARA, modified functional Scale for the Assessment and Rating of Ataxia; PDI, Pose Dispersion Index.
[a]All models further adjusted for age, sex, baseline f-SARA score, time since diagnosis, and treatment arm, with an offset term for each participant's follow-up time.