Validation of SCACOMS for Use in Patients With Spinocerebellar Ataxia

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BACKGROUND

- Spinocerebellar ataxia (SCA) is a group of rare neurodegenerative diseases that cause progressive cerebellar dysfunction[1]
- Clinically, patients present with motor and coordination issues, visual disturbances, and speech and swallowing difficulties[2,3]
- The development of patient-relevant SCA clinical outcome measures is important for the evaluation of disease progression and treatment efficacy in clinical trials
- The SCA composite score (SCACOMS) is a statistically derived composite measure of SCA disease progression consisting of weighted items that are most sensitive to change during early stages of disease[4]
- SCACOMS items and relative weighting include the functional Scale for the Assessment and Rating of Ataxia (f-SARA) Gait (12%), Stance (17%), Sitting (8%) and Speech (10%) items, and the Clinician Global Impression of Change (CGI) (53%)
- The content validity of SCACOMS is yet to be established

OBJECTIVE

- Conduct qualitative interviews with individuals with SCA and healthcare professionals (HCPs) with expertise in treating SCA to assess the content validity of SCACOMS as a measure of disease progression that may be used to evaluate treatment effects in clinical trials

METHODS

Qualitative interview process

- Semi-structured interviews were conducted via video call with United States-based individuals with SCA and HCPs with expertise in treating SCA between April and May 2024
- Interviews consisted of 3 parts:
  - Collection of background information
  - Concept elicitation to understand the signs, symptoms and impacts of SCA
  - SCACOMS instrument review and discussion of item contribution

SCACOMS instrument review

- The individual components of the SCACOMS instrument were evaluated for relevance in the context of predicting SCA disease progression
- The relative weighting of each SCACOMS item was ranked by perceived importance for tracking changes in SCA symptoms; items were assigned a percentage value with the total score across all items to equal 100%

Data analysis

- Interviews were audio recorded, transcribed, coded and analysed by ATLAS.Ti v23 software, following established methods[5]

RESULTS

Demographics

- Interviews were conducted with 24 individuals with SCA and 2 HCPs
- Demographics and clinical characteristics are presented in **Table 1**
  - There was a balanced distribution of males (45.8%) and females (54.2%) with SCA within the study population; SCA3 was the most common genotype (n=10; 41.7%)
  - An equal number of individuals with SCA reported having mild, moderate and severe SCA (all n=8; 33.3%)
  - Both (100.0%) HCPs were female with prior experience of using the f-SARA and CGI for assessment of SCA disease progression

Table 1. Demographics and clinical characteristics for individuals with SCA

Individuals with SCA demographics and clinical characteristics	N=24
Sex, n (%)	
Male	11 (45.8)
Female	13 (54.2)
Age in years, mean (range)	54.0 (34–75)
Age in years at diagnosis, mean (range)	44.3 (22–72)
SCA genotype, n (%)	
SCA1	6 (25.0)
SCA2	6 (25.0)
SCA3	10 (41.7)
SCA6	2 (8.3)
Self-reported SCA severity, n (%)	
Mild	8 (33.3)
Moderate	8 (33.3)
Severe	8 (33.3)

SCA, spinocerebellar ataxia.

SCACOMS items are relevant to individuals with SCA

- Individuals with SCA reported a total of 29 sign and symptom concepts related to their experience of SCA
  - Speech difficulties was the most frequently reported concept (n=19; 79.2%) (**Table 2**)
  - SCACOMS items measured all concepts reported by >50.0% of individuals with SCA
- The most frequently reported concepts by HCPs were difficulties with stance/balance issues (n=2; 100.0%) and gait/walking (n=2; 100.0%) (**Table 2**)

Table 2. SCA concepts most frequently reported by individuals with SCA and HCPs

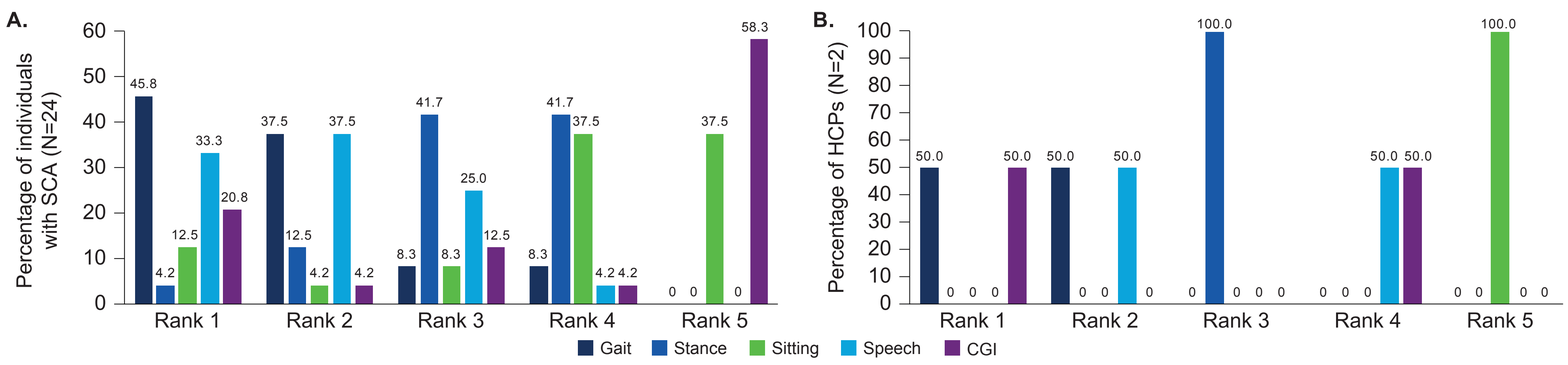
SCA sign or symptom concept	Frequency of report by individuals with SCA (N=24), n (%)[a]	Frequency of report by HCPs (N=2), n (%)
Speech difficulties	19 (79.2)	1 (50.0)
Stance/balance issues	18 (75.0)	2 (100.0)
Gait/walking difficulties	16 (66.7)	2 (100.0)
Swallowing issues	9 (37.5)	0
Weakness	9 (37.5)	0

[a]Concepts reported by >2 individuals with SCA. HCP, healthcare professional; SCA, spinocerebellar ataxia.

Gait was ranked as one of the most important SCACOMS items for assessing SCA disease progression

- Almost half of the individuals with SCA (n=11; 45.8%) ranked Gait as the most important item for assessing disease progression; CGI was ranked as least important (n=14; 58.3%) (**Figure 1A**)
- HCPs ranked Gait as the most (n=1; 50.0%) and second most (n=1; 50.0%) important item. The Sitting item was ranked as the least important by both HCPs (n=2; 100.0%) (**Figure 1B**)

Figure 1. Ranking of importance of SCACOMS items by individuals with SCA[a] (A) and HCPs (B)

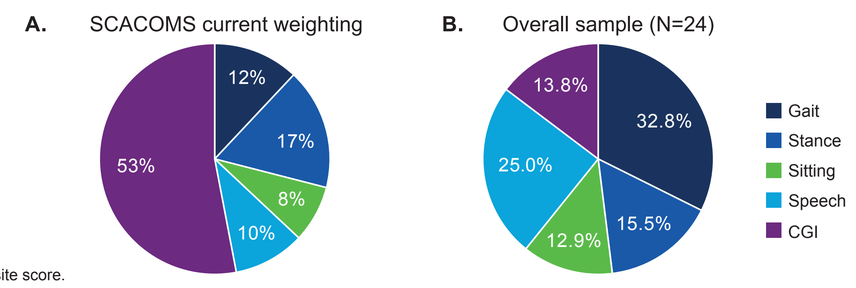


[a]One individual with SCA ranked all 5 SCACOMS items as equally most important (Rank 1).
CGI, Clinician Global Impression of Change; HCP, healthcare professional; SCA, spinocerebellar ataxia; SCACOMS, SCA composite score.

Relative weighting of SCACOMS items reveals that Gait was the most important item to individuals with SCA independent of their disease severity

- Weighting of SCACOMS items was derived using natural history cohorts and partial least squares regression, with CGI displaying the highest sensitivity to change with SCA disease progression (relative SCACOMS item weight contribution of approximately 33–50%)
  - The resulting relative weights of SCACOMS items are shown in **Figure 2A**
- When considering relative weighting of SCACOMS items, individuals with SCA assigned the highest weight to the Gait item (mean [SD], 32.8% [13.24]) and the lowest weight to the Sitting item (12.9% [7.98]) (**Figure 2B**)
- Relative weights of SCACOMS items were similar independent of SCA disease severity
  - All severity groups assigned the highest weight to the Gait item (mean range: 29.0–37.0%) and the lowest weight to the Sitting item (mean range: 12.0–13.0%)
  - Those with moderate and severe SCA were more likely to assign a higher weight to CGI (mean range: 17.0–19.0%) than those with mild SCA (mean: 9.0%) at the expense of the Gait item

Figure 2. Current weighting of SCACOMS items (A) and assigned mean relative weighting of items by individuals with SCA (B)

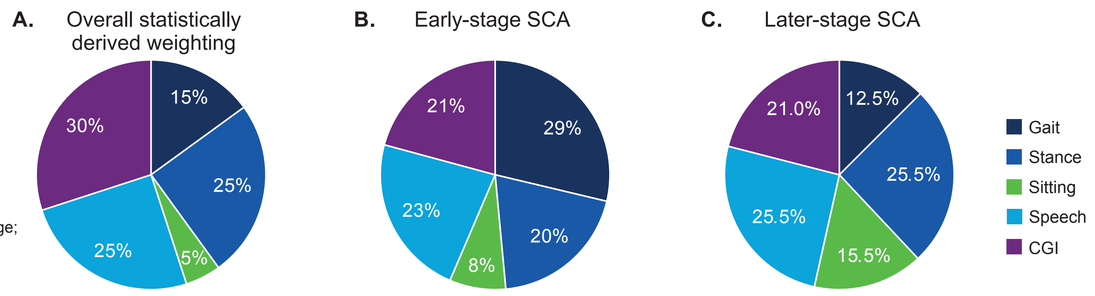


CGI, Clinician Global Impression of Change; SCA, spinocerebellar ataxia; SCACOMS, SCA composite score.

HCPs varied the relative weighting of SCACOMS items dependent on disease severity

- The overall statistically derived weighting of SCACOMS items assigned by HCPs is shown in **Figure 3A**
  - CGI was assigned the highest weight (30.0%), and Sitting was assigned the lowest weight (5.0%)
- HCPs assigned varying relative weights to SCACOMS items dependent on SCA disease severity
  - For early-stage SCA, HCPs assigned more weight to the Gait item (mean, 29.0%) than for later-stage disease (mean, 12.5%) (**Figure 3B and C**)
  - For later-stage SCA, the Sitting item was assigned more weight (mean, 15.5%) compared with early-stage disease (mean, 8.0%) (**Figure 3B and C**)

Figure 3. Statistically derived relative weighting of SCACOMS items by HCPs (A) and assigned relative mean weighting of items stratified by SCA disease severity (B and C)



CGI, Clinician Global Impression of Change; HCP, healthcare professional; SCA, spinocerebellar ataxia; SCACOMS, SCA composite score.

Agreement with current SCACOMS weighting varied among participants

- Most individuals with SCA (n=10; 41.6%) strongly disagreed with the current SCACOMS weighting and indicated that the weight of the CGI item was too high
  - Most of these individuals considered assessment of individual symptoms directly to be more important than the clinician perspective
  - Some individuals with SCA (n=5; 20.8%) generally agreed with the overall SCACOMS weighting and acknowledged the importance of the CGI item for clinician assessment
- One HCP (n=1; 50.0%) disagreed with the CGI weighting, suggesting that it should be reduced; the other HCP (n=1; 50.0%) agreed with the current weighting

CONCLUSIONS

- SCACOMS is a valid and relevant measure in the context of assessing SCA disease progression, particularly early-stage disease
- When developing composite measures based on sensitivity to detect disease progression, patient and HCP input is critical to validate item selection and respective weights
- The weightings of individual SCACOMS items may warrant adjustment to better reflect their importance to individuals with SCA

DISCLOSURES: MH, KR, NS, RD, KJ, MJ and CB are employees of Parexel International and have been compensated as consultants by Biohaven Pharmaceuticals Inc. **LA-W** received consultancy fees from Parexel International for this study. **JS** received compensation from Biohaven Pharmaceuticals Inc. for this study, serves on the editorial board for *The Cerebellum*, and has received research support from Biohaven Pharmaceuticals Inc. and the National Ataxia Foundation. **MP, MW-B, VC** and **GL** are employed by and hold stock/stock options in Biohaven Pharmaceuticals Inc.

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