Background, Objective and Methods

Hereditary ATTR (hATTR) Amyloidosis with Polyneuropathy

- Inherited, rapidly progressive, life-threatening disease caused by a mutation in the transthyretin (TTR) gene that results in misfolded TTR proteins accumulating as amyloid fibrils in multiple tissues including the nerves, heart, and gastrointestinal tract
- Multi-systemic disease with heterogeneous clinical presentation including sensory and motor, autonomic (e.g., diarrhea, erectile dysfunction, hypotension), and cardiac symptoms
- Significant morbidity, disability, and mortality within 2 to 15 years of symptom onset
- Disability and loss of autonomy are major patient concerns

Rasch-built Overall Disability Scale (R-ODS)

- 24-item patient-reported outcome instrument initially designed and validated to measure the activity and social participation limitations in patients with Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, and gamopathy-related polyneuropathy
- Possibly relevant for patients with symptomatic hATTR amyloidosis with polyneuropathy

Objective

- To generate evidence of the measurement properties (reliability and internal validity) of the R-ODS in patients with symptomatic hATTR amyloidosis with polyneuropathy

Data

- 359 assessments of the R-ODS items collected in two trials investigating patisiran, an investigational RNA interference (RNAi) therapeutic in development for the treatment of polyneuropathy in patients with hATTR amyloidosis
- 225 assessments from the APOLLO Phase 3 placebo-controlled trial (baseline) (NCT01960348)
- 134 assessments from 27 patients from the Phase 2 Open-Label Extension (OLE) Study (27 at baseline, week 27, week 54 and week 81 and 26 at week 108) (NCT01961921)

Analysis

- Comprehensive cross-sectional psychometric analysis based on Rasch Measurement Theory (RMT), to emulate the psychometric methods used originally by the developers of the R-ODS
- Rasch Measurement Methods examine the extent observed data (patients' actual responses to scale items) accord with predictions of those responses from a mathematical model2

Results

Sample Description

- R-ODS assessments from 252 patients (225 from the APOLLO trial, 27 from the phase 2 study) analyzed
  - Mean age: 60 years; males: 73%
  - More than half were from Europe (56%), 19% were from Northern America, and 18% from Asia
  - Less than half of the patients (43%) had a Val30Met mutation

Cross-sectional Rasch Measurement Theory (RMT) Results

- Wide spectrum of activity and social participation limitations covered: 96% of the breadth of limitations observed in the patient sample (Figure 1)
- Possible gap for the lowest levels of limitation (i.e. the most “difficult” activities, right-hand extreme of the X axis; Figure 1)
- Appropriate response scale (no disordered thresholds) and acceptable fit for virtually all items (Figure 2)
- Good reliability indicated by Person Separation Index (0.95)
- Stable item responses between subgroups (age, gender, global region, genotype), with only a small number of items functioning differently, mostly between global regions (Figure 2)

Figure 1: Person-Item Threshold Distribution of the R-ODS in Patisiran Trials in hATTR Amyloidosis with Polyneuropathy

Figure 2: Rasch Measurement Theory (RMT) Results for R-ODS Items – Response Threshold Map, Item Fit Statistics, Differential Item Functioning

Conclusions

- The R-ODS is a reliable and valid measure of activity and social participation limitations in patients with HATTR amyloidosis with polyneuropathy
- Further research is needed to better understand longitudinal psychometric properties of the R-ODS, especially its ability to detect change in these limitations over time

References: