Impact of Hereditary Transthyretin-Mediated Amyloidosis on Daily Living and Work Productivity: Baseline Results from APOLLO

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Background and Rationale

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, life-threatening disease caused by a mutation in the transthyretin (TTR) gene that results in misfolded TTR proteins, which accumulate as amyloid deposits leading to significant morbidity and disability
- Multi-systemic amyloid accumulation often leads to dysfunction in multiple organs, including the peripheral nervous system, heart, gastrointestinal tract, and kidneys[1]
- Accumulation of fibrils in nerves can lead to manifestations of polyneuropathy, including peripheral neuropathy, autonomic dysfunction, and motor weakness causing fine and gross motor impairments
- Activity and participation abilities have been studied using the Rasch-built Overall Disability Scale (R-ODS) in hATTR amyloidosis with polyneuropathy and in other neuropathic conditions[2-3]

Objective

- To describe impairments in activities daily living and work productivity loss among patients with hATTR amyloidosis and their caregivers, using one of the largest available datasets of patients with this disease

Methods

Phase 3 Study Design

- APOLLO was a multicenter, international, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy
- Each patient was asked to complete a questionnaire at baseline ascertaining levels of disability, social and functional limitations, patient and caregiver work loss, and receipt of government financial support due to their illness in the year prior to enrollment
- At baseline, R-ODS was administered to patients to measure activity and social participation limitations; R-ODS contains 24 patient-ranked items on a three-point scale (0, 1, 2) with total scores ranging from 0 to 48 points; lower scores correspond to higher degrees of limitation

Statistical Analysis

- Descriptive statistics, including percentages for categorical variables and means and standard deviations for continuous variables, are presented
- Wilcoxon two-sample and chi-squared tests were performed to test differences across disease stages, as measured by familial amyloidotic polyneuropathy (FAP) Stage
  - Analyses were limited to patients with FAP Stage 1 and FAP Stage 2 disease due to limited sample size of patients with FAP Stage 3

Results

Baseline Demographics

- Median age of APOLLO enrollees (N=225) was 62 years (range 24-83 years); 74% were male, 43% were genotype V30M, and 46%, 53%, and 0.4% of FAP Stage 1, 2, or 3, respectively (Figure 1)

Figure 1: Baseline Demographics of APOLLO Enrollees, by FAP Stage*

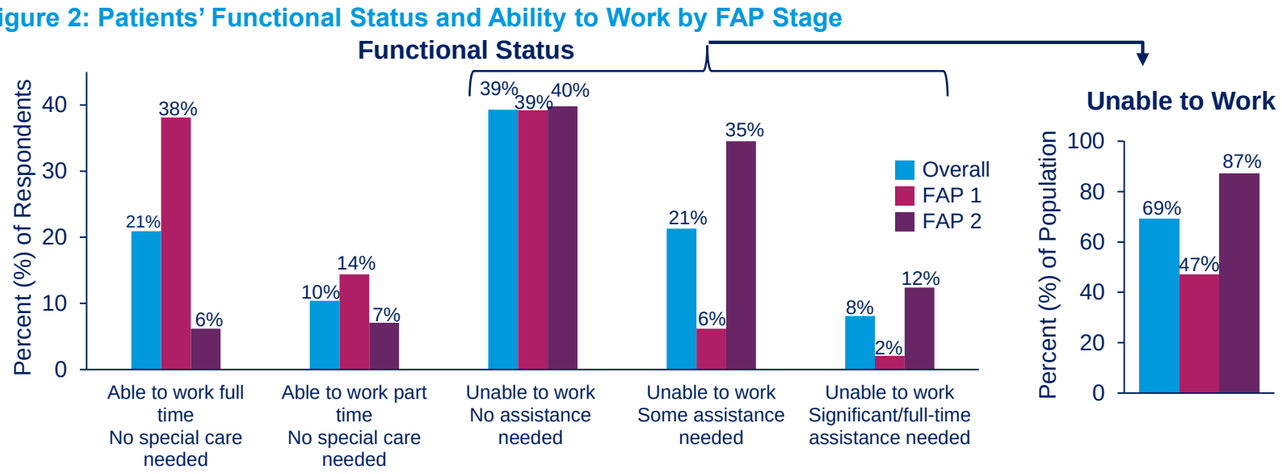
	Overall Cohort	Subgroup Analysis	
Characteristic	**APOLLO Population (N=225)**	**FAP Stage 1 (N=104)**	**FAP Stage 2 (N=120)**
Median Age, years (range)	62 (24, 83)	60 (24,80)	65 (34, 83)
Gender, males	167 (74.2)	76 (73.1)	90 (75.0)
Region~			
North America	47 (20.9)	23 (22.1)	24 (20.0)
Western Europe	98 (43.6)	43 (41.3)	54 (45.0)
Rest of World	80 (35.6)	38 (36.5)	42 (35.0)
hATTR Diagnosis			
Years since hATTR diagnosis, mean (min, max)	2.5 (0.0, 21.0)	2.6 (0.0, 21.0)	2.4 (0.0, 16.5)
TTR Genotype			
V30M	96 (42.7)	44 (42.3)	51 (42.5)
nonV30M‡	129 (57.3)	60 (57.7)	69 (57.5)
NIS			
Mean (min, max)	59.3 (6.0, 141.6)	34.4 (6.0, 115.3)	80.7 (19.5, 141.6)
<50	97 (43.1)	82 (78.8)	15 (12.5)
≥50 - <100	96 (42.7)	20 (19.2)	75 (62.5)
≥100	32 (14.2)	2 (1.9)	30 (25.0)
Cardiac Subpopulation**			
NYHA Class I	50 (39.7)	27 (49.1)	23 (32.4)
NYHA Class II	76 (60.3)	28 (50.9)	48 (67.6)

*Unless otherwise indicated, all values represent the number of patients (%); patient with FAP Stage 3 (n = 1) not included in subgroup analysis
~North America: USA, CAN; **Western Europe**: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; **Rest of world**: *Asia*: JPN, KOR, TWN, *Eastern Europe*: BGR, CYP, TUR; *Central & South America:* MEX, ARG, BRA
‡Represents 38 different TTR mutations
**Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement at baseline without confounding medical conditions (i.e., patients with baseline left ventricular [LV] wall thickness ≥ 13 mm and no aortic valve disease or hypertension in medical history)

Ability to Function

- 69% of patients reported being unable to work (Figure 2)
- Ability to work and requirement for assistance to live independently was associated with FAP Stage, increasing from 47% unable to work to 87% between FAP Stage 1 and 2

Figure 2: Patients' Functional Status and Ability to Work by FAP Stage



Work Attendance and Need for Government Compensation

- Patients reported an average of 39 work days lost in the year prior to enrollment (Figure 3)
  - Lost workdays numerically increased from 24 to 63 days in FAP Stage 1 vs 2 (p=0.061)
- 24% of patients received government compensation due to their illness (Figure 4)
  - Need for government compensation increased from 18% to 30% in FAP Stage 1 vs 2 (p=0.03)

Figure 3: Patients' Work Loss

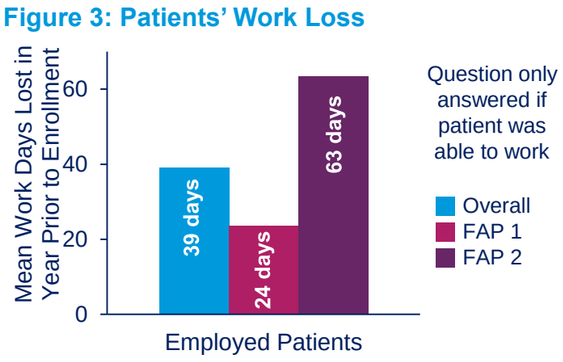
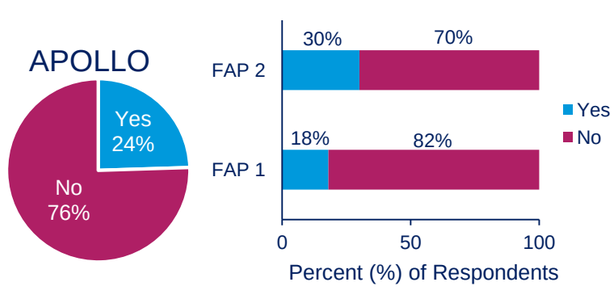


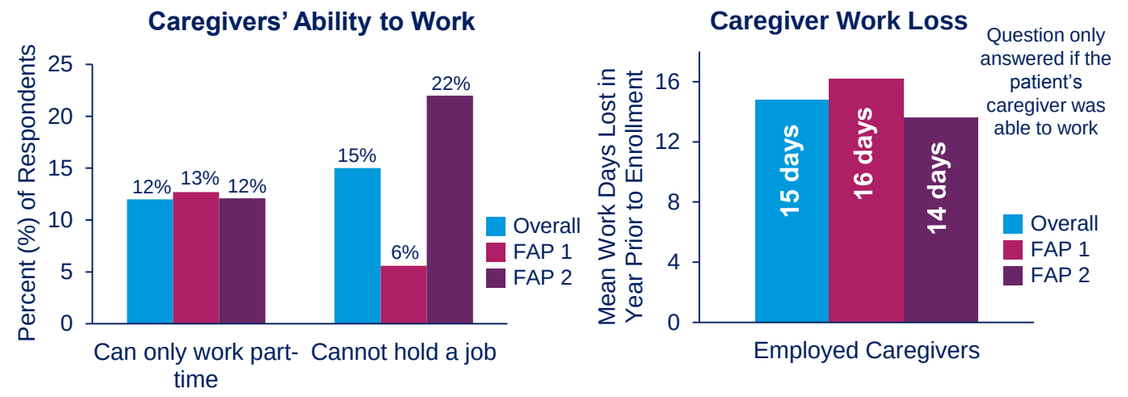
Figure 4: Need for Government Compensation



Caregiver Ability to Work and Work Attendance

- 12% of caregivers reported limiting work to part-time due to patients' hATTR amyloidosis symptoms (Figure 5)
  - 13% limited to part-time work vs 12% for those caring for a patient with FAP Stage 1 vs 2, respectively
- 15% of caregivers could not hold paying jobs due to patients' hATTR amyloidosis symptoms
  - Inability to hold a paying job rose from 6% to 22% for those caring for a patient with FAP Stage 1 disease vs FAP Stage 2 (p<0.0001)
- Caregivers lost about 3 work weeks/year across FAP Stage 1 and 2 (p=0.22)

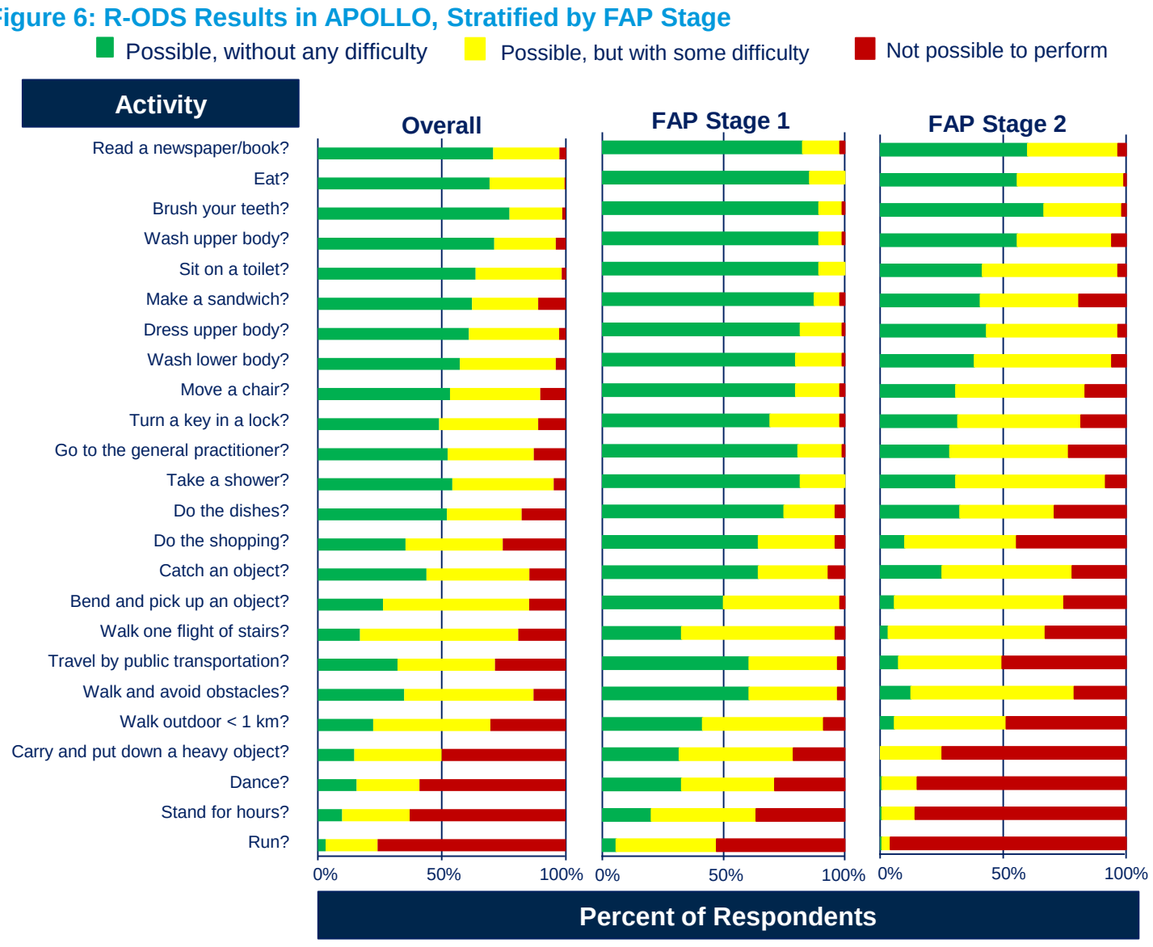
Figure 5: Impact of hATTR Amyloidosis on Caregivers' Ability to Work



Activity and Participation Abilities as Measured by the R-ODS

- Patients reported some difficulty performing lower intensity tasks, such as reading a newspaper or book (27%) and eating (30%); majority were unable to perform more difficult tasks, such as dancing (59%), standing for a long period of time (i.e., hours) (63%), or running (76%) (Figure 6)
  - Number of tasks and activities that ≥ 50% of patients were unable to perform increased between FAP Stage 1 and FAP Stage 2
    - FAP Stage 1: 53% unable to run
    - FAP Stage 2: 50% unable to travel by public transportation, carry and put down a heavy object (75%), dance (85%), stand for hours (86%), and run (96%)

Figure 6: R-ODS Results in APOLLO, Stratified by FAP Stage



Summary

- Patients with hATTR amyloidosis report high levels of disability, impacting activity and social participation; levels of disability worsen by FAP Stage
- Symptoms of hATTR amyloidosis limit the ability of patients and their caregivers to function and work
- hATTR amyloidosis represents a significant burden to society, since about 1 in 4 patients require government compensation due to disease; this proportion increases to about 1 in 3 among patients with FAP Stage 2 disease
- Safe and effective therapeutic options are needed to address this highly disabling and progressively burdensome disease

FAP, familial amyloidotic polyneuropathy; mNIS+7, modified neuropathy impairment score + 7; NYHA, New York Heart Association; PND, polyneuropathy disability; R-ODS, Rasch-built Overall Disabiity Scale; mBMI, modified body mass index; COMPASS-31, Composite Autonomic Symptom Score-31; NSAID, nonsteroidal anti-inflammtory drug; RNAi, RNA interfernce; WT, wild type

References: 1. Conceição I, González-Duarte A, Obici L, et al. J Peripher Nerv Syst. 2016;21(1): 5-9. 2. van Nes SI, Vanhoutte EK, van Doorn PA, et al. Neurology. 2011;76(4):337-45. 3. Pruppers MH, Merkies IS, Faber CG, et al. J Peripher Nerv Syst. 2015;20(3):319-27.