Impact of Hereditary Transthyretin-Mediated Amyloidosis on Use of Health Care Services: An Analysis of the APOLLO Study

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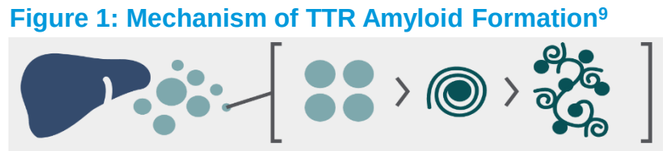
Background and Rationale

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, life-threatening, multi-systemic disease caused by mutations in the TTR gene resulting in debilitating morbidity and high mortality
  - Mutations lead to destabilization of tetrameric TTR proteins, subsequent dissociation and misfolding; misfolded proteins self-assemble into oligomers, forming amyloid fibrils and plaques in the extracellular space of various tissues, including the peripheral nervous system, heart, gastrointestinal tract, and other organs leading to cellular injury and organ dysfunction[1] (Figure 1)
  - Cardinal manifestations are polyneuropathy and cardiomyopathy
  - Median survival of 4.7 years following diagnosis and further reduced to 3.4 years for those with cardiomyopathy[2-5]
- Familial amyloidotic polyneuropathy (FAP) stage has been used to stage disability in ambulation associated with hATTR amyloidosis[6]; in the APOLLO study, patients' FAP Stages at baseline were based on physician assessments
- Health care utilization has been used in other diseases to measure disease burden, but there has been limited data published among patients with hATTR amyloidosis[7,8]

Figure 1: Mechanism of TTR Amyloid Formation[9]



Objective

- To estimate utilization of various health care services from one of the largest available datasets of patients with hATTR amyloidosis

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 focused on utilization of health care services, patient-reported need for mobility assistance devices, and ability to perform activities of daily living in the year prior to enrollment (Figure 2)

Statistical Analysis

- Descriptive statistics are presented as percentages for categorical variables and means and standard deviations for continuous variables
- Wilcoxon two-sample and chi-squared tests were performed to test differences across disease stages, as measured by 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

Figure 2: APOLLO Pharmacoeconomics Questionnaire

Self-administered questionnaire with a 12-month recall period

Collected information on a variety of elements related to disease burden:

Health resource utilization	• Outpatient general practitioner & specialists visits • Hospitalizations • Emergency room visits
Patient Productivity	• Ability to work and care for personal needs • Missed work days
Caregiver Productivity	• Ability to hold a paying job • Missed work days
Need for government compensation	• Receipt of government compensation due to illness

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% were FAP Stage 1, 2, or 3, respectively (Figure 3)

Figure 3: 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 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)

Health Care Utilization

- Patients averaged 7.6 visits to general practitioners (once every 7 weeks) and 8.8 visits to specialists (once every 6 weeks) in the year prior to enrollment (Figure 4)
- Approximately 23% of patients had at least one emergency room visit in the year prior to enrollment
- 28% of patients reported at least one overnight hospitalization
- Across disease stages (i.e., FAP Stage 1 and 2) 53% of patients required at least one device to assist with mobility including: 1 cane (31.3%), 2 canes/walker (22.8%), and/or a wheelchair (11.6%)

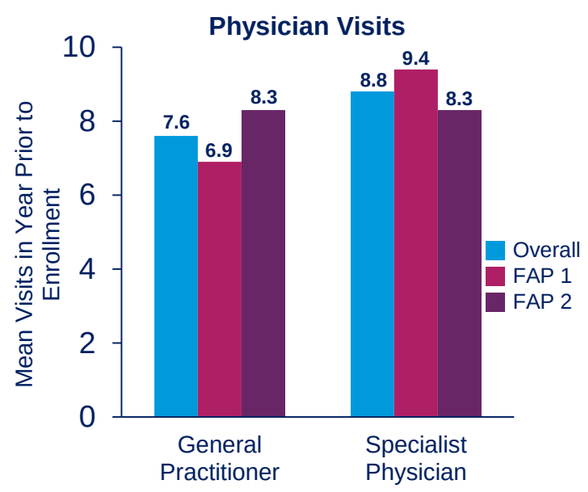
Figure 4: Health Care Utilization in the Year Prior to Enrollment

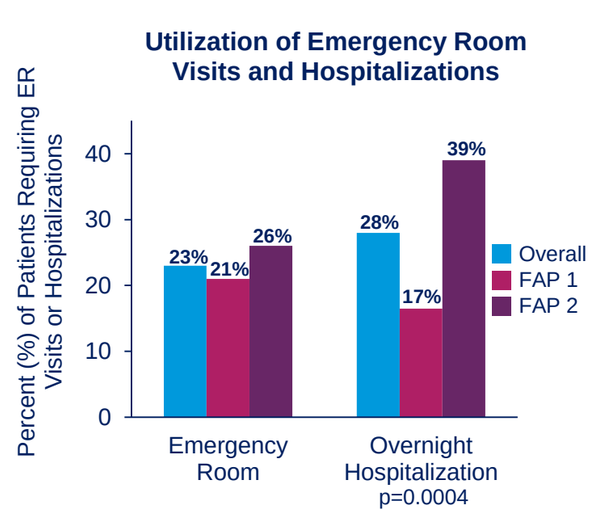
Service	Utilization
Outpatient Services	
General practitioner visits, Mean (SD)	7.6 (11.2)
Specialist physician visits, Mean (SD)	8.8 (10.3)
Emergency room visits	
N (%)	47 (23.2)
Mean visits/year (SD)	0.4 (1.2)
Overnight Hospitalizations	
N (%)	62 (28.1)
Mean hospitalizations/year (SD)	0.5 (1.0)
Items to Help Walk or Stand (%)	
Required at least one assistive device	53
1 Cane	31.3
2 Canes/walker	22.8
Wheelchair	11.6

Health Care Utilization by FAP Stage

- Number of general practitioner visits was 6.9 vs 8.3 for FAP Stage 1 vs 2 patients (p=0.36); number of specialist visits was 9.4 vs 8.3 for FAP Stage 1 and 2 patients (p=0.25) (Figure 5)
- 21% of FAP Stage 1 patients reported emergency room visits vs 26% with FAP Stage 2 (p=0.42)
- Percentage of patients with an overnight hospitalization more than doubled between FAP Stage 1 and 2 (17% vs 39%, p=0.0004)

Figure 5: General Practitioner and Specialist Visits in the Year Prior to Enrollment

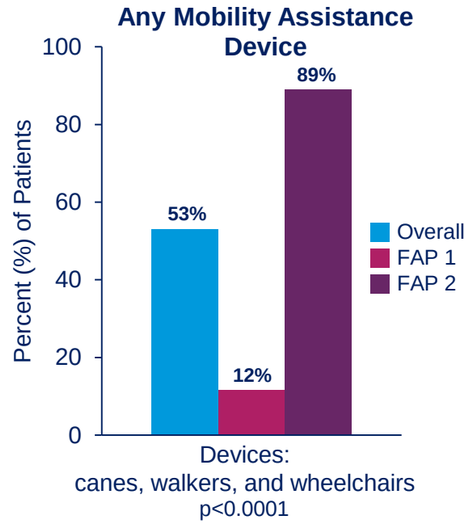


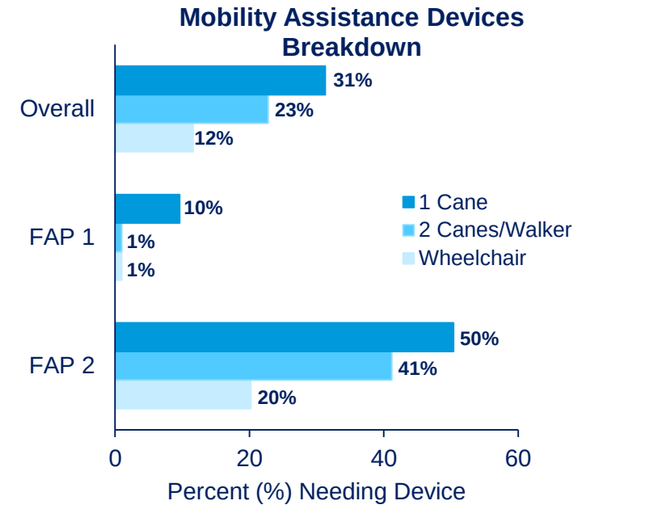


Patient-Reported Utilization of Mobility Assistance Devices by FAP Stage

- Need for mobility assistance devices was higher in FAP Stage 1 than FAP Stage 2 (12% vs 89%, p<0.0001) (Figure 6)
- 10% of FAP Stage 1 patients reported the use of 1 cane vs 50% of those with FAP Stage 2 (p<0.0001); 1% vs 41% used 2 canes/walker in FAP Stage 1 vs 2 (p<0.0001)
- Wheelchairs were utilized by 1% with FAP Stage 1 vs 20% of patients with FAP Stage 2 (p<0.0001)

Figure 6: Patient-Reported Need for Assistance Devices at Baseline





Summary

- Patients with hATTR amyloidosis report substantial levels of medical management at even early stages of disease as evidenced by high utilization of general practitioner and specialists visits, emergency room visits, hospitalizations, and mobility assistance devices
- Approximately 1 in 4 patients report emergency room visits or overnight hospitalizations; twice as many patients with FAP Stage 2 vs FAP Stage 1 reported overnight hospitalization stays
- Magnitude of use of mobility assistance devices highlights the debilitating nature of hATTR amyloidosis, as evidenced by the utilization of additional assistance devices (e.g., walker, wheelchair) at even early disease stages
- Considerable unmet need for therapeutic options to address this disabling and progressively burdensome disease

FAP, familial amyloidotic polyneuropathy; mNIS+7, modified neuropathy impairment score + 7; NYHA, New York Heart Association; R-ODS, Rasch-built Overall Disability Scale

References: 1. Hou X, Aguilar MI, Small DH. FEBS J. 2007;274(7):1637-50. 2. Swiecicki PL, Zhen DB, Mauermann ML, et al. Amyloid. 2015;22(2):123-31. 3. Plante-Bordeneuve V, Said G. Lancet Neurol. 2011;10(12):1086-97. 4. Gertz MA, Kyle RA, Thibodeau SN. Mayo Clin Proc. 1992;67(5):428-40. 5. Sattianayagam PT, Hahn AF, Whelan CJ, et al. Eur Heart J. 2012;33(9):1120-7. 6. Coutinho P, da Silva AM, Lima JL, et al. Amyloid and amyloidosis: proceedings of the Third International Symposium on Amyloidosis, Povoa de Varzim, Portugal, 23-28 September 1979. Amsterdam: Excerpta Medica; 1980:88-98. 7. BURQOL RD. Social economic burden and health-related quality of life in patients with rare diseases in Europe. Available at: http://www.burqol-rd.com/. Accessed January 22, 2018. 8. Stewart M, Loftus J, Lenderking WR, et al. Value and Health. 2013;A386;PSY49. 9. Adapted from: Conceição I, González-Duarte A, Obici L, et al. J Peripher Nerv Syst. 2016;21(1):5-9.