The Patient Journey Prior to Diagnosis of Hereditary Transthyretin Amyloidosis

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INTRODUCTION/BACKGROUND

- Despite emerging treatments for hereditary transthyretin (ATTRv) amyloidosis, the disease is often misdiagnosed, with reported diagnostic delays of up to several years[1-3]
  - Due to the disease's rarity, as well as variable symptom manifestation, diagnostic delay is common and can lead to poorer outcomes and great disease burden
- Knowledge of the patient journey leading up to diagnosis may help to promote earlier intervention
- While little is known about the patient journey for other forms of amyloidosis, such as light chain (AL) and cardiac amyloidosis,[4-6] we found no real-world studies examining this journey in patients with ATTRv amyloidosis

OBJECTIVE

- To examine patient characteristics and healthcare utilization prior to ATTRv amyloidosis diagnosis

METHODS

Study design and data source

- Retrospective claims analysis of IBM® MarketScan® Commercial and Medicare Supplemental Databases* from 1/1/2011-12/31/2017

Patient identification

- Included adult patients (≥18 years of age at index) and newly diagnosed with ATTRv amyloidosis identified using a claims-based algorithm as follows:
  - Diagnosis required ≥1 medical claim with relevant amyloidosis diagnosis code (ICD-10-CM: E85.0-.4, E85.89, E85.9; excludes light chain and wild type) during identification (ID) period (1/1/16-12/31/17), and ≥1 occurrence of qualifying criteria during study period:
    - ≥15 days diflunisal use without >30-day gap OR liver transplant (patients with claim with specific codes E85.1 or E85.2 at any time did not require additional qualifier)
- Study index date was defined as the date of first claim with an amyloidosis diagnosis code in ID period
- To ensure a new diagnosis, patients with an ICD-9/10 amyloidosis code during look-back were excluded
- Patients had continuous enrollment 5 years pre-index date (look-back period)

Disease-free control group

- To serve as a reference group, an ATTRv-free cohort was created with patients without ATTRv diagnosis and matched 3:1 to ATTRv patients on age, gender, and region
- Same index and enrollment requirement as matched patients with ATTRv amyloidosis

Study measures

- Occurrence (first and any) of selected comorbidities (potential symptoms) and healthcare utilization (testing, procedures, and visits) measured during the look-back period
- Demographics, provider specialty, and Charlson comorbidity index (CCI) reported during 1 year pre-index (baseline period); CCI is a measure of 1-year mortality risk, with higher scores denoting higher risk

Statistical analysis

- Descriptive statistics generated for pre-index measures during each year of look-back period
- Plotted the cumulative probability of occurrence of selected comorbidities and testing since 5 years before the index date

*MarketScan is a trademark of IBM Corporation in the United States and other countries

RESULTS

Baseline demographics and comorbidities during 1-year pre-index period (Table 1)

- For the 141 qualifying ATTRv patients and 423 matched controls, mean (SD) age was 62.5 (14.2) years, and 53.9% were female
- Mean CCI for ATTRv patients was 2.7 (3.0) vs. 1.1 (1.9) among controls
- Primary care providers were the most common healthcare providers visited pre-index for both cohorts (46.1% and 54.4%, respectively)

Table 1. Baseline demographics and comorbidities during 1-year pre-index period

	Newly Diagnosed ATTRv Patients N=141	Matched Controls[a] N=423
Age, years, mean (SD)	62.5 (14.3)	62.5 (14.2)
18-34, n (%)	6 (4.3)	18 (4.3)
35-54	27 (19.1)	81 (19.1)
55-64	52 (36.9)	156 (36.9)
65+	56 (39.7)	168 (39.7)
Female, n (%)	76 (53.9)	228 (53.9)
Region, n (%)		
Midwest	26 (18.4)	78 (18.4)
Northeast	47 (33.3)	141 (33.3)
South	55 (39.0)	165 (39.0)
West	13 (9.2)	39 (9.2)
Insurance type, n (%)[b]		
PPO/POS	99 (70.2)	239 (56.5)
HMO/EPO	8 (5.7)	30 (7.1)
CDHP/HDHP	14 (9.9)	72 (17.0)
Comprehensive	20 (14.2)	80 (18.9)
Charlson comorbidity index, mean (SD)	2.7 (3.0)	1.1 (1.9)
Number of chronic conditions, mean (SD)	5.1 (2.7)	3.2 (2.3)
Usual provider specialty, n (%)		
Primary Care	65 (46.1)	230 (54.4)
Cardiologist	5 (3.5)	10 (2.4)
Dermatologist	4 (2.8)	16 (3.8)
Gastroenterologist	6 (4.3)	6 (1.4)
Neurologist	6 (4.3)	2 (0.5)
Rheumatologist	5 (3.5)	6 (1.4)
Other[c]/Unknown	50 (35.5)	153 (36.2)

[a]Matched with age, gender, and region.
[b]Two matched controls had missing/unknown insurance type.
[c]Includes podiatrists and individual specialties with count <5.

Comorbidities and healthcare utilization during 5-year look-back period

- Selected comorbidities, testing, and visits were common among ATTRv patients during the look-back period with higher relative frequencies compared to controls:
  - Cardiovascular, gastrointestinal, metabolic, musculoskeletal, nervous system, and ocular conditions were all more common among ATTRv patients vs. controls (**Table 2 in Supplement; see QR code**)
  - Cardiac testing (81.6% vs. 65.7%), blood/urine testing (34.8% vs. 9.5%), biopsy/genetic testing (34.8% vs. 20.8%), and pyrophosphate imaging (2.1% vs. 0%) (results not shown)
  - ED visits (60.3% vs. 47.0%) and hospitalization (47.5% vs. 24.3%) (results not shown)
- First occurrence of comorbidities and diagnostic testing was often low during the look-back period until a gradual rise in the year before index diagnosis (**Figures 1, 2**)

Scan QR code for Table 2

Figure 1. First observed evidence of comorbidities during the 5 years prior to diagnosis

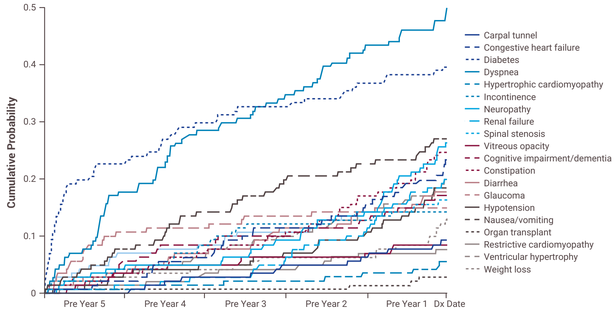
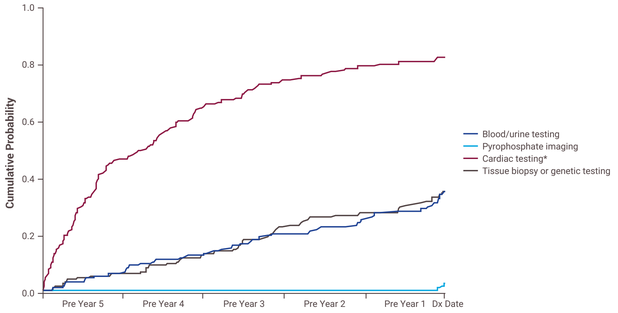


Figure 2. First observed evidence of diagnostic testing during the 5 years prior to diagnosis



*Cardiac magnetic resonance imaging, electrocardiography, and echocardiogram.

CONCLUSIONS

- **Patients with ATTRv amyloidosis experience substantial comorbidity, testing, and hospitalization prior to diagnosis**
- **Occurrence of potential markers of disease is most common in the year before diagnosis, but does happen, less frequently, in earlier years suggesting potential opportunities for early diagnosis**
- **This study has potential limitations:**
  - **As the look-back period was only 5 years prior to diagnosis, existing comorbidities (and other outcomes) may have been misclassified as first occurring during that period**
  - **Results may not be generalizable to patients without continuous enrollment in a healthcare plan or to those with other types of insurance coverage**

DISCLOSURES

MVL and MP are employees of Akcea Therapeutics. SRR, EC, and MHT are employees of Partnership for Health Analytic Research, LLC, which was paid by Akcea to perform this research.

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ABBREVIATIONS

ATTRv: hereditary transthyretin; CDHP/HDHP: consumer directed health plan/high deductible health plan; EPO: exclusive provider organization; HMO: health maintenance organization; PPO/POS: preferred provider organizations/point of service; SD: standard deviation.

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Table 2. Selected comorbidities during the 5 years prior to ATTRv diagnosis

	Newly Diagnosed ATTRv Patients N=141	Matched Controls[a] N=423	Newly Diagnosed ATTRv Patients N=141	Matched Controls[a] N=423	Newly Diagnosed ATTRv Patients N=141	Matched Controls[a] N=423	Newly Diagnosed ATTRv Patients N=141	Matched Controls[a] N=423
Nervous system and metabolic								
	Cognitive impairment		Neuropathy		Incontinence		Diabetes	
N (%)	24 (17.0)	39 (9.2)	37 (26.2)	25 (5.9)	20 (14.2)	23 (5.4)	56 (39.7)	107 (25.3)
First evidence occurred, n (%)								
No evidence	117 (83.0)	384 (90.8)	104 (73.8)	398 (94.1)	121 (85.8)	400 (94.6)	85 (60.3)	316 (74.7)
Pre Y1	6 (4.3)	8 (1.9)	17 (12.1)	7 (1.7)	2 (1.4)	2 (0.5)	4 (2.8)	8 (1.9)
Pre Y2	4 (2.8)	6 (1.4)	7 (5.0)	4 (0.9)	1 (0.7)	4 (0.9)	6 (4.3)	12 (2.8)
Pre Y3	2 (1.4)	8 (1.9)	6 (4.3)	4 (0.9)	5 (3.5)	2 (0.5)	4 (2.8)	3 (0.7)
Pre Y4	4 (2.8)	6 (1.4)	1 (0.7)	3 (0.7)	6 (4.3)	7 (1.7)	10 (7.1)	16 (3.8)
Pre Y5	8 (5.7)	11 (2.6)	6 (4.3)	7 (1.7)	6 (4.3)	8 (1.9)	32 (22.7)	68 (16.1)
Ocular and severe organ dysfunction or failure								
	Glaucoma		Vitreous opacity		Renal failure		Organ transplant	
N (%)	21 (14.9)	53 (12.5)	12 (8.5)	18 (4.3)	28 (19.9)	24 (5.7)	4 (2.8)	0 (0.0)
First evidence occurred, n (%)								
No evidence	120 (85.1)	370 (87.5)	129 (91.5)	405 (95.7)	113 (80.1)	399 (94.3)	137 (97.2)	423 (100.0)
Pre Y1	1 (0.7)	0 (0)	2 (1.4)	3 (0.7)	13 (9.2)	4 (0.9)	2 (1.4)	0 (0)
Pre Y2	1 (0.7)	1 (0.2)	2 (1.4)	4 (0.9)	6 (4.3)	6 (1.4)	1 (0.7)	0 (0)
Pre Y3	3 (2.1)	9 (2.1)	4 (2.8)	2 (0.5)	2 (1.4)	3 (0.7)	0 (0)	0 (0)
Pre Y4	1 (0.7)	10 (2.4)	2 (1.4)	3 (0.7)	2 (1.4)	3 (0.7)	1 (0.7)	0 (0)
Pre Y5	15 (10.6)	33 (7.8)	2 (1.4)	6 (1.4)	5 (3.5)	8 (1.9)	0 (0)	0 (0)
Gastrointestinal								
	Diarrhea		Constipation		Nausea/vomiting		Weight loss	
N (%)	25 (17.7)	47 (11.1)	35 (24.8)	49 (11.6)	38 (27.0)	55 (13.0)	19 (13.5)	30 (7.1)
First evidence occurred, n (%)								
No evidence	116 (82.3)	376 (88.9)	106 (75.2)	374 (88.4)	103 (73.0)	368 (87.0)	122 (86.5)	393 (92.9)
Pre Y1	5 (3.5)	8 (1.9)	11 (7.8)	11 (2.6)	6 (4.3)	5 (1.2)	10 (7.1)	5 (1.2)
Pre Y2	4 (2.8)	11 (2.6)	9 (6.4)	14 (3.3)	4 (2.8)	15 (3.5)	0 (0)	7 (1.7)
Pre Y3	6 (4.3)	11 (2.6)	5 (3.5)	5 (1.2)	8 (5.7)	17 (4.0)	3 (2.1)	6 (1.4)
Pre Y4	5 (3.5)	6 (1.4)	5 (3.5)	11 (2.6)	9 (6.4)	8 (1.9)	2 (1.4)	6 (1.4)
Pre Y5	5 (3.5)	11 (2.6)	5 (3.5)	8 (1.9)	11 (7.8)	10 (2.4)	4 (2.8)	6 (1.4)
Musculoskeletal and cardiovascular								
	Spinal stenosis		Carpal tunnel		Congestive heart failure		Hypotension	
N (%)	23 (16.3)	43 (10.2)	13 (9.2)	28 (6.6)	33 (23.4)	25 (5.9)	26 (18.4)	26 (6.1)
First evidence occurred, n (%)								
No evidence	118 (83.7)	380 (89.8)	128 (90.8)	395 (93.4)	108 (76.6)	398 (94.1)	115 (81.6)	397 (93.9)
Pre Y1	3 (2.1)	16 (3.8)	4 (2.8)	4 (0.9)	11 (7.8)	6 (1.4)	11 (7.8)	6 (1.4)
Pre Y2	5 (3.5)	6 (1.4)	2 (1.4)	6 (1.4)	6 (4.3)	3 (0.7)	5 (3.5)	6 (1.4)
Pre Y3	3 (2.1)	6 (1.4)	3 (2.1)	2 (0.5)	7 (5.0)	3 (0.7)	3 (2.1)	5 (1.2)
Pre Y4	2 (1.4)	8 (1.9)	4 (2.8)	8 (1.9)	6 (4.3)	4 (0.9)	2 (1.4)	4 (0.9)
Pre Y5	10 (7.1)	7 (1.7)	0 (0)	8 (1.9)	3 (2.1)	9 (2.1)	5 (3.5)	5 (1.2)
Cardiovascular (continued)								
	Dyspnea		Ventricular hypertrophy		Hypertrophic cardiomyopathy		Restrictive cardiomyopathy	
N (%)	70 (49.6)	109 (25.8)	28 (19.9)	24 (5.7)	8 (5.7)	2 (0.5)	11 (7.8)	8 (1.9)
First evidence occurred, n (%)								
No evidence	71 (50.4)	314 (74.2)	113 (80.1)	399 (94.3)	133 (94.3)	421 (99.5)	130 (92.2)	415 (98.1)
Pre Y1	9 (6.4)	15 (3.5)	8 (5.7)	6 (1.4)	3 (2.1)	1 (0.2)	1 (0.7)	0 (0)
Pre Y2	12 (8.5)	15 (3.5)	6 (4.3)	6 (1.4)	2 (1.4)	0 (0)	4 (2.8)	0 (0)
Pre Y3	9 (6.4)	21 (5.0)	5 (3.5)	6 (1.4)	1 (0.7)	1 (0.2)	1 (0.7)	2 (0.5)
Pre Y4	15 (10.6)	16 (3.8)	4 (2.8)	1 (0.2)	1 (0.7)	0 (0)	3 (2.1)	0 (0)
Pre Y5	25 (17.7)	42 (9.9)	5 (3.5)	5 (3.5)	1 (0.7)	0 (0)	2 (1.4)	6 (1.4)

ATTRv: hereditary transthyretin.

[a]Matched with age, gender, and region.