4TH INTERNATIONAL ATTR Amyloidosis meeting

November, 2-3 2023
Madrid

Baseline Characteristics of Patients with ATTR Amyloidosis Enrolled into the ConTTRibute Registry

Michael Polydefkis[1], Luca Leonardi[2], Andoni Echaniz-Laguna[3], Julian D. Gillmore[4], Fabian Knebel[5], Davide Pareyson[6], Brian Drachman[7], Hans Nienhuis[8], Guilhem Solé[9], Juliette Svahn[10], Shaun Bender[11], Colleen Moffitt[11], Catherine Summers[11], Kelley Capocelli[11], Mathew S. Maurer[12]

[1]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]Department of Neuroscience, Mental Health and Sensory Organs, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy; [3]Department of Neurology, Assistance Publique Hôpitaux de Paris, CHU de Bicêtre, Le Kremlin-Bicêtre, France; [4]National Amyloidosis Centre, University College London, Division of Medicine, Royal Free Hospital, London, UK; [5]Charité University Hospital, Berlin, Germany; [6]Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [7]Penn Presbyterian Medical Center, Philadelphia, PA, USA; [8]Amyloidosis Center of Expertise, University Medical Center Groningen, Groningen, The Netherlands; [9]Department of Neurology and Neuromuscular Diseases, CHU Bordeaux, University of Bordeaux, Bordeaux, France; [10]Service de Neurologie, Hôpital Pierre Wertheimer, Bron, France; [11]Alnylam Pharmaceuticals, Cambridge, MA, USA; [12]Columbia University Irving Medical Center, New York, NY, USA.

Conclusions

- **Of participants with diagnosed transthyretin-mediated (ATTR) amyloidosis, those with hereditary (ATTRv; v for variant) amyloidosis were younger at both symptom onset and diagnosis compared with those with wild-type ATTR (ATTRwt) amyloidosis**
- **A relatively high proportion of participants (~25%) with ATTR amyloidosis presented with a mixed phenotype of polyneuropathy and cardiomyopathy at diagnosis; this was consistent for both participants with ATTRv and those with ATTRwt amyloidosis**
- **At enrollment, approximately 30% of participants assessed for polyneuropathy had a polyneuropathy disability (PND) score ≥II, and approximately 45% assessed for cardiomyopathy had a New York Heart Association (NYHA) class ≥II**
- **Approximately two-thirds of all participants were either currently receiving, or had previously received, ATTR amyloidosis treatment at enrollment**

Background and Rationale

ATTR amyloidosis

- ATTR amyloidosis is a progressive and fatal disease caused by accumulation of transthyretin (TTR) amyloid fibrils in multiple tissues and organs, including the peripheral nerves and heart[1–3]
- There are two types of ATTR amyloidosis: ATTRwt and ATTRv amyloidosis[4,5]
- Over 130 pathogenic *TTR* variants have been identified in ATTRv amyloidosis, and identification of *TTR* variant carriers can enable regular follow-up and timely diagnosis upon emergence of symptomatic disease[6,7]
- Several therapies have been approved for the treatment of the clinical manifestations of ATTR amyloidosis, including tafamidis for cardiomyopathy in patients with ATTRv or ATTRw amyloidosis, and patisiran, vutrisiran, and inotersen for polyneuropathy in patients with ATTRv amyloidosis[8–15]

The ConTTRibute Registry

- This prospective, global, multicenter, long-term observational study (NCT04561518) is designed to document the clinical outcomes of patients with ATTR amyloidosis, and asymptomatic carriers of *TTR* variants
- The aims of the study are to describe:
  - Epidemiologic and clinical characteristics, natural history, and real-world clinical management of patients with ATTR amyloidosis
  - Disease emergence/progression in asymptomatic carriers of a known disease-causing *TTR* variant
  - The safety and effectiveness of patisiran in the real-world clinical setting

Objective

- Describe the baseline characteristics of patients with ATTR amyloidosis and asymptomatic carriers of *TTR* variants who were enrolled into ConTTRibute

Methods

- Eligible patients include those with ATTRv amyloidosis, ATTRwt amyloidosis, and asymptomatic carriers of *TTR* variants, regardless of treatment **(Figure 1)**
  - Enrollment is currently ongoing
- No visits or examinations, laboratory tests, or procedures are mandated as part of the study
  - Data are collected after each patient visit as part of routine clinical care
- Baseline characteristics and assessments presented here were collected at enrollment into ConTTRibute

Figure 1. Study design

Patient population

- Confirmed diagnosis of ATTR amyloidosis (ATTRv or ATTRwt) regardless of treatment
- Documented known disease-causing TTR variant, for asymptomatic carriers
- No current enrollment in a clinical trial for any investigational agent
- Patient consent per local regulations or ethics committee

Data collection of key assessments during follow-up

- ATTR amyloidosis signs and symptoms
- ATTR amyloidosis pharmacologic treatments
- HCP-assessed polyneuropathy (PND score, FAP stage, NIS)
- HCP-assessed cardiomyopathy (NYHA class)
- Patient reported outcomes (Norfolk QOL-DN, KCCQ, R-ODS)
- Safety assessments

Results

Demographics

- From November 2020 through August 2023, 828 participants were enrolled from 10 countries
- Of these 828 participants, 386 had ATTRv amyloidosis, 315 had ATTRwt amyloidosis, and 127 were asymptomatic carriers
- Most participants were recruited in the US (441 [53.3%]); the remainder were recruited in Europe and Brazil **(Table 1)**
- Most participants were white (639 [77.2%]), and male (567 [68.5%]) **(Table 1)**
  - Among those who had ATTRv amyloidosis, 77 (19.9%) were Black or African American compared with 8.4% across those with ATTRwt amyloidosis and asymptomatic carriers
- Participants with ATTRv amyloidosis were mostly under 70 years of age (60.1%) whereas those with ATTRwt amyloidosis were mostly over 70 years of age (92.1%)

Table 1. Demographics of ConTTRibute registry participants

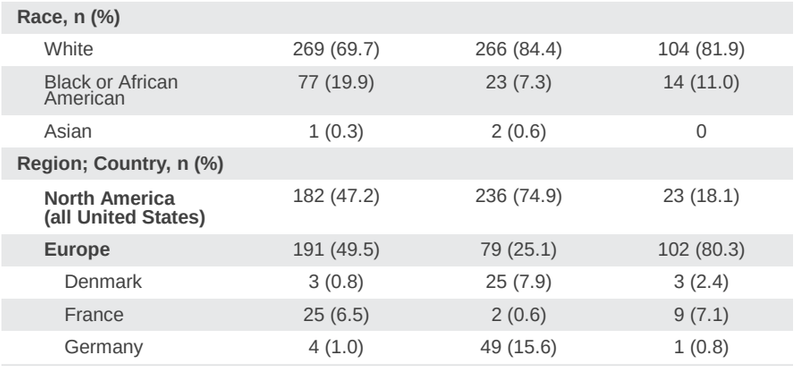
Parameter	ATTRv amyloidosis (n=386)	ATTRwt amyloidosis (n=315)	Asymptomatic carrier (n=127)
Sex, n (%)			
Male	232 (60.1)	282 (89.5)	53 (41.7)
Age, n (%)			
<70	232 (60.1)	25 (7.9)	116 (91.3)
Race, n (%)			
White	269 (69.7)	266 (84.4)	104 (81.9)
Black or African American	77 (19.9)	23 (7.3)	14 (11.0)
Asian	1 (0.3)	2 (0.6)	0
Region; Country, n (%)			
North America (all United States)	182 (47.2)	236 (74.9)	23 (18.1)
Europe	191 (49.5)	79 (25.1)	102 (80.3)
Denmark	3 (0.8)	25 (7.9)	3 (2.4)
France	25 (6.5)	2 (0.6)	9 (7.1)
Germany	4 (1.0)	49 (15.6)	1 (0.8)
Israel	6 (1.6)	2 (0.6)	8 (6.3)
Italy	21 (5.4)	0	7 (5.5)
Netherlands	19 (4.9)	0	16 (12.6)
Portugal	42 (10.9)	0	4 (3.1)
Spain	71 (18.4)	1 (0.3)	54 (42.5)
Latin America (all Brazil)	13 (3.4)	0	2 (1.6)

ATTRv genotype

- The most frequent *TTR* variant among participants with ATTRv amyloidosis and asymptomatic carriers was V30M/V50M (256 [50.2%]) **(Figure 2A)**
  - The distribution of variants was similar between groups
- The V122I/V142I *TTR* variant was the most prevalent variant in the US (48.3%), whereas in Europe the most prevalent variant was V30M/V50M (78.4%) **(Figure 2B)**

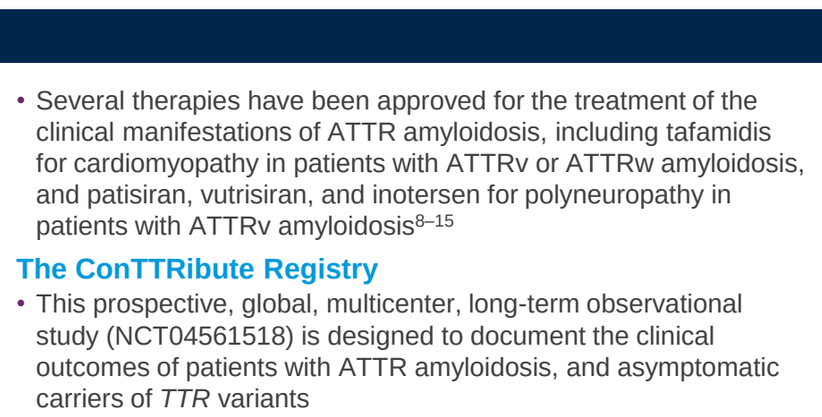
Figure 2. *TTR* variants of ConTTRibute registry participants

A. *TTR* variants of participants with ATTRv amyloidosis and asymptomatic carriers



[a]Not reported: n=2. [b]Not reported: n=1.

B. Distribution by region of *TTR* variants of participants with ATTRv amyloidosis and asymptomatic carriers

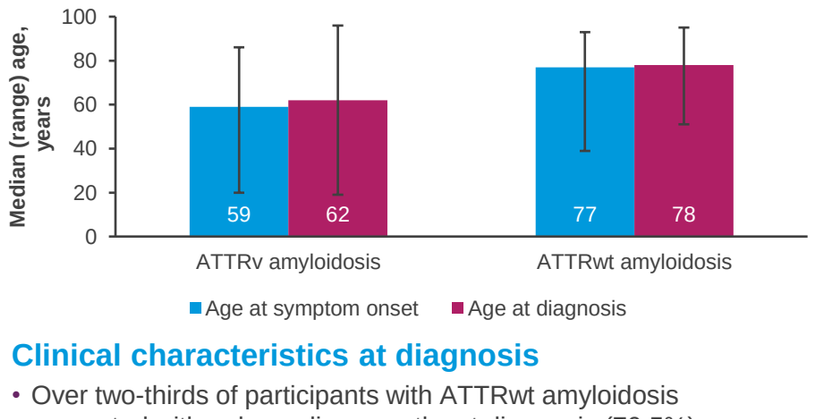


[a]Not reported: n=2. [b]Not reported: n=1. [c]Not reported: n=0.

Age at symptom onset and diagnosis

- Participants with ATTRv amyloidosis were younger than those with ATTRwt amyloidosis at both symptom onset (median [range] age 59 [20, 86] vs 77 [39, 93] years) and diagnosis (median [range] age 62 [19, 89] vs 78 [44, 95] years) **(Figure 3)**
- Difference between median symptom onset age and median diagnosis age was 3 years (ATTRv amyloidosis) and 1 year (ATTRwt amyloidosis) **(Figure 3)**

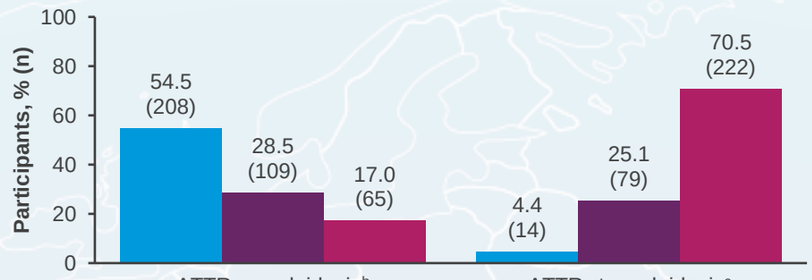
Figure 3. Age at symptom onset and diagnosis



Clinical characteristics at diagnosis

- Over two-thirds of participants with ATTRwt amyloidosis presented with only cardiomyopathy at diagnosis (70.5%) **(Figure 4)**
- A greater proportion of participants with ATTRv amyloidosis presented with only polyneuropathy (54.5%) at diagnosis than those with ATTRwt amyloidosis (4.4%) **(Figure 4)**
  - Of participants with ATTRwt amyloidosis presenting with polyneuropathy or mixed phenotype at diagnosis (93 [29.5%]) who were assessed for polyneuropathy at enrollment, 9 had PND scores ≥II, and 6 had familial amyloid polyneuropathy (FAP) stages ≥II
- Similar proportions of those with ATTRv amyloidosis and those with ATTRwt amyloidosis (28.2% and 25.1%, respectively) presented with a mixed phenotype of both polyneuropathy and cardiomyopathy

Figure 4. Clinical characteristics of participants with ATTRv and ATTRwt amyloidosis at diagnosis[a]



[a]Phenotype at diagnosis reported by investigators. [b]Not reported: n=4. [c]Not reported: n=0.

Baseline assessments of polyneuropathy and cardiomyopathy

- Overall, at enrollment 371 (44.8%) participants were assessed for PND score, 359 (43.4%) for FAP stage, and 720 (87.0%) for NYHA class
- A greater proportion of participants with available data and ATTRv amyloidosis had a PND score of ≥II (108 [44.6%]) or FAP stage ≥II (66 [28.3%]) compared with participants with ATTRwt amyloidosis (12 [22.6%] and 8 [15.7%], respectively) **(Table 2)**
- A greater proportion of participants with available data and ATTRwt amyloidosis had a NYHA class ≥II (200 [75.8%]) compared with participants with ATTRv amyloidosis (119 [34.3%]) **(Table 2)**

Table 2. Baseline assessments of polyneuropathy and cardiomyopathy

Parameter	ATTRv amyloidosis (n=386)	ATTRwt amyloidosis (n=315)	Asymptomatic carrier (n=127)
Polyneuropathy Disability Score, n (%)			
Participants with available data[a,b]	242 (62.7)	53 (16.8)	76 (59.8)
0[c]	12 (5.0)	11 (20.8)	75 (98.7)
I	122 (50.4)	30 (56.6)	1 (1.3)
II	46 (19.0)	6 (11.3)	0
IIIA	33 (13.6)	4 (7.5)	0
IIIB	26 (10.7)	2 (3.8)	0
IV	3 (1.2)	0	0
Familial Amyloid Polyneuropathy Stage, n (%)			
Participants with available data[a,d]	233 (60.4)	51 (16.2)	75 (59.1)
0[c]	13 (5.6)	10 (19.6)	75 (100.0)
I	154 (66.1)	33 (64.7)	0
II	62 (26.6)	8 (15.7)	0
III	4 (1.7)	0	0
NYHA Classification, n (%)			
Participants with available data[a,e]	347 (89.9)	264 (83.8)	109 (85.8)
Class I[c]	34 (9.8)	33 (12.5)	3 (2.8)
Class II	85 (24.5)	122 (46.2)	1 (0.9)
Class III	33 (9.5)	76 (28.8)	0
Class IV	1 (0.3)	2 (0.8)	0

[a]Participants with data recorded at a visit during the 180-day window (enrollment date + 6 months). [b]Total participants with PND score not reported: n=457. [c]Percentages calculated as a proportion of the total number of participants with available data. [d]Total participants with FAP stage not reported: n=469. [e]Total participants with NYHA class not reported: n=108.

ATTR treatment prior to or at enrollment

- Approximately two-thirds of all participants (558 [67.4%]) were either currently taking, or had previously taken, ATTR amyloidosis treatment at enrollment
  - The most common treatment for participants with ATTRv or ATTRwt amyloidosis was tafamidis (47.2% and 81.9%, respectively), followed by patisiran (38.3% and 1.0%) **(Table 3)**
- Six asymptomatic carriers were reported to have received ATTR amyloidosis treatment prior to or at enrollment (not considered common practice) **(Table 3)**

Table 3. ATTR treatment prior to or at enrollment

ATTR treatment prior to or at enrollment, n (%)[a]	ATTRv amyloidosis (n=386)	ATTRwt amyloidosis (n=315)	Asymptomatic carrier (n=127)
Any	291 (75.4)	261 (82.9)	6 (4.7)
Tafamidis	182 (47.2)	258 (81.9)	2 (1.6)
Patisiran	148 (38.3)	3 (1.0)	1 (0.8)
Diflunisal	20 (5.2)	2 (0.6)	4 (3.1)
Inotersen	20 (5.2)	0	0
Doxycycline	3 (0.8)	1 (0.3)	0
Tauroursodeoxycholic acid (TUDCA)	1 (0.3)	0	0
Other	29 (7.5)	3 (1.0)	1 (0.8)
Concomitant treatment at enrollment	57 (14.8)	5 (1.6)	1 (0.8)

[a]Percentages may sum to over 100% as patients can have multiple treatments prior to or at enrollment.

Thank you to the participants, their families, investigators, study staff, and collaborators for their participation in the **ConTTRibute registry**.

Acknowledgments: Medical writing assistance was provided by Jack Law, PhD, of Adelphi Communications Ltd, UK, and funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice Guidelines. **Funding:** This study was funded by Alnylam Pharmaceuticals.

Disclosures: M.P. reports consultancy for Akcea Therapeutics, Alnylam Pharmaceuticals, Biogen Idec, Pfizer, and Vertex Pharmaceuticals, and participation in clinical trials for Akcea, Alnylam Pharmaceuticals, and Pfizer; **L.L.** reports grants or contracts from Alnylam Pharmaceuticals and Minisetero della Salute della Repubblica Italiana, payment or honoraria for lectures, presentations, speakers bureaus or educational events from Akcea Therapeutics, Alnylam Pharmaceuticals, and SOBI, and support for attending meetings from Alnylam Pharmaceuticals and SOBI; **A.E-L.** reports grants or contracts and data safety monitoring and/or advisory board membership from Alnylam Pharmaceuticals, consulting fees from Alnylam Pharmaceuticals, Intellia Therapeutics, and Pfizer, and payment or honoraria for lectures, presentations, speakers bureaus or educational events and support for attending meetings from Alnylam Pharmaceuticals and Pfizer; **J.D.G.** reports research funding from Alnylam Pharmaceuticals, consulting and speaker fees from Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio, Intellia Therapeutics, and Ionis Pharmaceuticals, and data safety monitoring and/or advisory board membership from Alnylam Pharmaceuticals, BridgeBio, and Intellia Therapeutics;
F.K. reports consulting fees and payment or honoraria for lectures, presentations, speakers bureaus or educational events from Alnylam Pharmaceuticals, AstraZeneca, and Pfizer; **D.P.** reports grants from AFM-Telethon, Telethon-Italy Foundation, and the NIH, participation in clinical or scientific advisory boards for Alnylam Pharmaceuticals, Akcea, Augustine Therapeutics, Digital Therapeutics, and InFlectis Bioscience, and editorial positions at *Neurological Sciences* and *Neurology Genetics*; **B.D.** reports consultancy for Alnylam Pharmaceuticals; **H.N.** reports consulting fees and payment or honoraria for lectures, presentations, speakers bureaus or educational events from Alnylam Pharmaceuticals, Novartis, and Pfizer, and membership of the advisory board of the Dutch amyloidosis patients advocacy group; **G.S.** reports research funding from Alnylam Pharmaceuticals and Pfizer, and payment or honoraria for presentations from Alnylam Pharmaceuticals; **J.S.** reports no conflicts of interest; **S.B.**, **C.M.**, **C.S.**, and **K.C.** are employees of Alnylam Pharmaceuticals; **M.S.M.** reports grants or contracts from Alnylam Pharmaceuticals, Attralus, Eidos Therapeutics, Ionis Pharmaceuticals, and Pfizer, consulting fees and support for attending meetings from Novo Nordisk, and data safety monitoring and/or advisory board membership for Intellia Therapeutics and Prothena.

Abbreviations: ATTR, transthyretin-mediated; ATTRv, hereditary (v for variant); ATTRwt, wild-type; FAP, familial amyloid polyneuropathy; HCP, healthcare provider; KCCQ, Kansas City Cardiomyopathy Questionnaire; NIS, Neuropathy Impairment Score; NYHA, New York Heart Association; PND, polyneuropathy disability; QOL-DN, Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin.

References: 1. Hawkins et al. *Ann Med* 2015;47:625–38; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 3. Adams et al. *Nat Rev Neurol* 2019;15:387–404; 4. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 5. Koike & Katsuno. *Biomedicines* 2019;7:11; 6. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 7. Conceicao et al. *Amyloid* 2019;26:3–9; 8. Pfizer. US prescribing information: Vyndaqel/Vyndamax capsules. 2019; 9. European Medicines Agency. Summary of product characteristics: Vyndaqel 20 mg soft capsules. 2016; 10. Alnylam Pharmaceuticals. US prescribing information: ONPATTRO® (patisiran) lipid complex injection, for intravenous use. 2020; 11. European Medicines Agency. Summary of product characteristics: ONPATTRO®. 2020; 12. Alnylam Pharmaceuticals. US prescribing information: AMVUTTRA™ (vutrisiran) injection, for subcutaneous use. 2022; 13. European Medicines Agency. Summary of product characteristics: AMVUTTRA™. 2022; 14. Akcea Therapeutics. US prescribing information: TEGSEDI. 2018; 15. Akcea Therapeutics. Summary of product characteristics: TEGSEDI. 2023.

Presented at the International ATTR Amyloidosis Meeting, November 2–3, 2023, Madrid, Spain.