Connecting the Musculoskeletal Dots to Identify the Early Manifestations of Transthyretin-Mediated (ATTR) Amyloidosis

Catherine Summers[1], Emre Aldinc[1], Shaun Bender[1]

[1]Alnylam Pharmaceuticals, Cambridge, MA, US

Conclusions

- **These data represent the first comprehensive analysis exploring the prevalence of MSK manifestations in a broad range of studies, including randomized clinical trials and real-world studies, of patients with ATTR amyloidosis**
- **CTS was the most frequently reported MSK manifestation, followed by OA, according to the past medical and surgical histories of patients with ATTR amyloidosis**
- **Understanding the epidemiology and characteristics of MSK manifestations associated with ATTR amyloidosis may support the awareness and recognition of these symptoms among surgeons and other healthcare professionals, allowing for early diagnosis and improved disease management**
- **Surgeons may consider taking biopsies to detect amyloid deposition in at-risk patients during routine surgical procedures**

Background and Rationale

Transthyretin-Mediated (ATTR) Amyloidosis

- Underdiagnosed, rapidly progressive, debilitating, and fatal disease[1,2]
- Caused by transthyretin (TTR) amyloid deposition and subsequent tissue damage in multiple organ systems, including nerves, heart, gastrointestinal tract, and musculoskeletal (MSK) tissues[1,3–5]
- There are two types of ATTR amyloidosis: hereditary (ATTRv, also known as hATTR amyloidosis) where variants in the *TTR* gene result in misfolded TTR, and wild-type (ATTRwt) amyloidosis where wild-type ATTR misfolds without a variant in the gene[1]

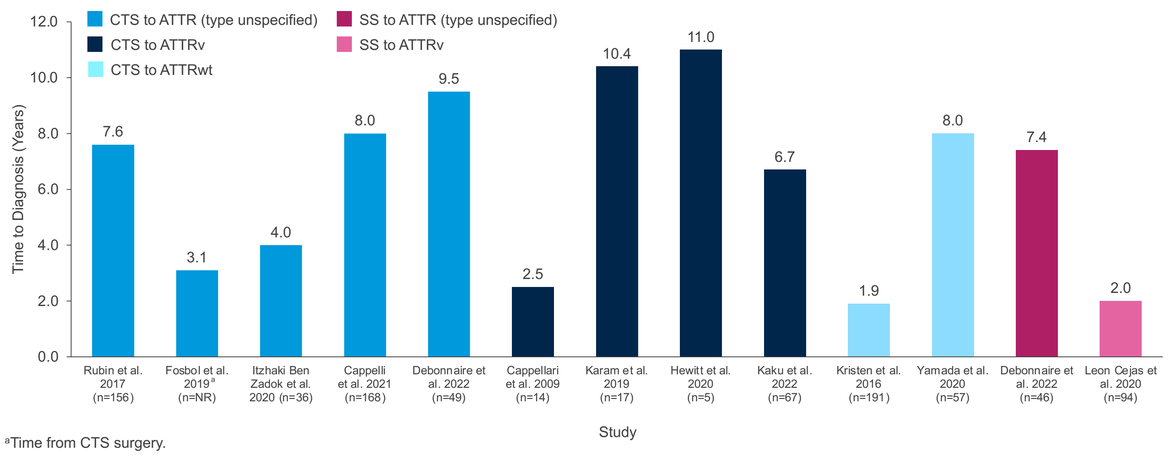
Musculoskeletal Manifestations Associated with ATTR Amyloidosis

- Include carpal tunnel syndrome (CTS), spinal stenosis (SS), biceps tendon rupture (BTR), osteoarthritis (OA), and trigger finger (TF) / finger tenosynovitis[4,6]

The Unmet Need for Early Diagnosis

- Diagnosis can be difficult or delayed due to the heterogeneous, non-specific nature of ATTR amyloidosis and symptom overlap with other diseases[1,3–5]
- The majority of patients develop a mixed phenotype of polyneuropathy and cardiomyopathy that may be diagnosed years after symptoms appear. However, some MSK manifestations may precede appearance of these more severe systemic manifestations (**Figure 1**)[4,7–18]
- Recognizing MSK manifestations could play an important role in supporting early diagnosis and referral to allow for timely treatment

Figure 1. Time between MSK Manifestation and ATTR Amyloidosis Diagnosis



[a]Time from CTS surgery.

Objective

- To identify the prevalence of MSK manifestations reported in the medical and surgical histories of patients with ATTR amyloidosis who had participated in seven Alnylam-sponsored studies

Methods

- Retrospective analysis of the prevalence of MSK manifestations (CTS, SS, BTR, TF, and OA) in patients with ATTR amyloidosis who were enrolled in seven Alnylam-sponsored studies (**Table 1**)
- Patient medical and surgical histories that were captured in the enrollment / baseline assessment from each study were analyzed for the prevalence of MSK manifestations
- The prevalence of MSK manifestations is reported for all patients, and also separately for ATTRv and ATTRwt amyloidosis patient groups
- The prevalence of CTS is reported for CTS diagnosis and/or history of carpal tunnel decompression, as well as co-occurrence with SS for all patients, and in ATTRv and ATTRwt amyloidosis patient groups

Table 1. Overview of Studies Included in the Analysis

Study (NCT Number)	Total Number of Patients N=1010 (%)	Study Description
OLE (NCT01961921)[19]	27 (2.7)	Open-label extension of the Phase 2 study evaluating the safety and tolerability of long-term dosing with patisiran in patients with ATTRv amyloidosis with mild-to-moderate neuropathy who had previously received patisiran
APOLLO (NCT01960348)[20]	225 (22.3)	Phase 3 global study evaluating the safety and efficacy of patisiran in patients with ATTRv amyloidosis with polyneuropathy
EAP (NCT02939820)[21]	154 (15.2)	Study providing expanded access of patisiran to patients with ATTRv amyloidosis with polyneuropathy
Post-OLT (NCT03862807)[22]	23 (2.3)	Phase 3b global study evaluating the efficacy, safety, and pharmacokinetics of patisiran in patients with ATTRv amyloidosis with polyneuropathy progression after liver transplant
APOLLO-B (NCT03997383)[23]	359 (35.5)	Phase 3 global study evaluating the efficacy and safety of patisiran in patients with ATTR amyloidosis with cardiomyopathy
Observational study (NCT04201418)[24]	58 (5.7)	Phase 4 US study evaluating the effectiveness of patisiran in patients with ATTRv amyloidosis with polyneuropathy who have a V122I or T60A mutation
HELIOS-A (NCT03759379)[25]	164 (16.2)	Phase 3 global study evaluating the efficacy and safety of vutrisiran in patients with ATTRv amyloidosis with polyneuropathy

Results

Baseline Demographics and Characteristics

- Medical and surgical histories were analyzed from 1010 patients
- The majority of patients were male (77.2%) with ATTRv amyloidosis (71.6%) and had a mean (range) age of 65.8 (24–85) years (**Table 2**)

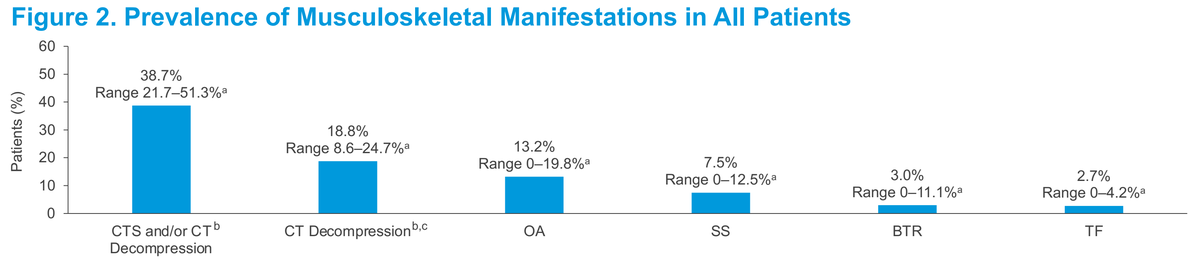
Table 2. Baseline Patient Demographics and Disease Characteristics

Characteristic	Total (N=1010)
Age at screening, mean (range)	65.8 (24–85)
Age, n (%)	
18 to <65	393 (38.9)
≥65	617 (61.1)
Sex, n (%)	
Male	780 (77.2)
Female	230 (22.8)
Ethnicity, n (%)	
Hispanic or Latino	96 (9.5)
Not Hispanic or Latino	891 (88.2)
Not reported	10 (1.0)
Unknown	13 (1.3)
ATTR amyloidosis type, n (%)	
ATTRv amyloidosis	723 (71.6)
ATTRwt amyloidosis	287 (28.4)

Prevalence of Musculoskeletal Manifestations

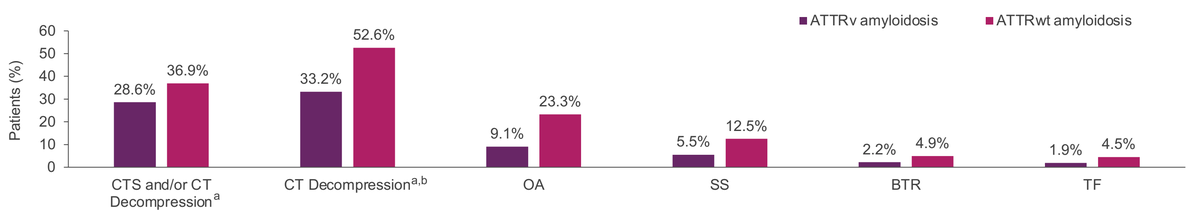
- CTS (38.7%) was the most common MSK manifestation in all patients, followed by OA (13.2%), SS (7.5%), BTR (3.0%), and TF (2.7%) (**Figure 2**)
- All MSK manifestations were reported in a higher proportion of patients with ATTRwt amyloidosis versus patients with ATTRv amyloidosis (**Figure 3**)
- Overall, 19.9% of patients reported CTS but not CT decompression surgery (**Figure 4**), and this occurred in a higher proportion of patients with ATTRwt amyloidosis versus patients with ATTRv amyloidosis (**Figure 5**)

Figure 2. Prevalence of Musculoskeletal Manifestations in All Patients



[a] Data range for the prevalence of musculoskeletal manifestations in the individual studies. [b] CTS and CT decompression surgery are not mutually exclusive. [c] Includes patients who had undergone CT decompression surgery, with or without reporting a diagnosis of CTS.

Figure 3. Prevalence of Musculoskeletal Manifestations in ATTRv Amyloidosis and ATTRwt Amyloidosis Patient Groups



[a] CTS and CT decompression surgery are not mutually exclusive. [b] Includes patients who had undergone CT decompression surgery, with or without reporting a diagnosis of CTS.

Figure 4. Percentages of Patients Who Reported CTS and/or CT Decompression

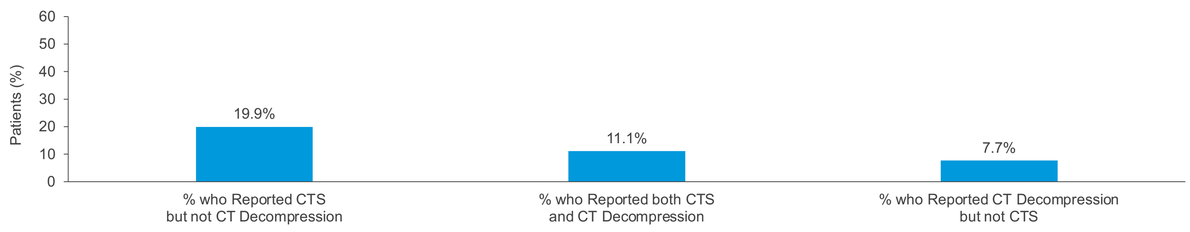
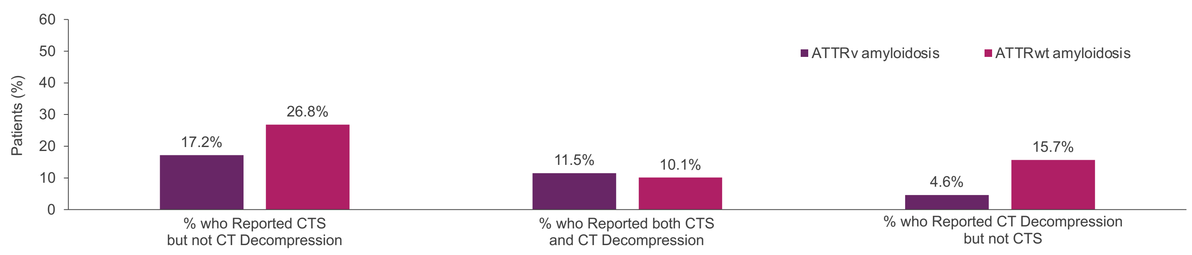


Figure 5. Percentages of Patients Who Reported CTS and/or CT Decompression in ATTRv Amyloidosis and ATTRwt Amyloidosis Patient Groups



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Disclosures: The authors are employees of Alnylam Pharmaceuticals. **Abbreviations:** ATTR, transthyretin-mediated; ATTRv, hereditary ATTR; ATTRwt, wild-type ATTR; BTR, biceps tendon rupture; CT, carpal tunnel; CTS, carpal tunnel syndrome; EAP, extended access program; hATTR, hereditary ATTR; MSK, musculoskeletal; NR, not reported; OA, osteoarthritis; OLE, open-label extension; OLT, orthotopic liver transplantation; SS, spinal stenosis; TF, trigger finger. **References:**

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