The cost of disease progression in ATTRv amyloidosis

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My disclosures

- Advisory work for
  - Pfizer
  - Alnylam
  - Eidos
- Advisory work in the past for
  - GSK
  - Neurochem
Estimating the cost of disease

Different types of direct and indirect costs:¹,²

- Classic approach: Calculating health care resource utilization = HCRU
  - Hospital service usage: outpatient services, inpatient admissions and emergency room visits
  - Physician visits, pharmacy, home health care, assistance devices
- Additional approaches:
  - Productivity loss & early retirement (expressed in terms of disability-adjusted life years; DALYs), loss of paid taxes
  - Societal services; loss of work and income of caregivers

Estimating the cost of disease

Specific factors in ATTRv amyloidosis:

- The long and winding road in non-familial patients diagnosis along multiple specialists\(^1,2\)
- The longer the road the more progressed is disease at diagnosis\(^1,2\)
- Both age at disease onset and rate of progression vary considerably among patients\(^2\)
- Disease spectrum with different clinical pictures at both ends: heart vs. nerves (with a mixed type in between)\(^2,3\)

In order to obtain a clear picture of the costs of progression of the disease itself, the use and effect of disease-modifying drugs (TTR tetramer stabilizers and TTR gene-silencers) have not been looked at in this presentation

ATTRv, hereditary transthyretin amyloidosis; TTR, transthyretin
A complicated path to diagnosis

Often a long journey to diagnosis

- Visits to multiple specialists over many years
- Disease symptoms continue to progress as diagnosis is delayed

Alnylam® data on file (hereditary transthyretin (hATTR) amyloidosis: disease background) 2019.
### Patient journey in the diagnostic delay period

#### Disease course

**Disease onset**
- Symptoms of peripheral and autonomic neuropathy and of heart failure

**Disease progression**
- New and more severe symptoms: disability develops

**Death**
- Median survival of polyneuropathy stage 1 is 12 years following diagnosis, with a reduced survival (4 years) for patients presenting with cardiomyopathy

#### Patient Journey

**Patient presents to GP with multiple symptoms**
- Cardiac, neurological, autonomic

**Patient sent to specialist**
- Neurologic and cardiac exam, diagnostic tests

**Misdiagnosis**
- Multiple specialist visits

**Diagnosis**
- Genetic testing and tissue biopsy

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**Mean interval to diagnosis:** 2-4 years (range: 1-10 years) 

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GP = general physician.
Mean interval until diagnosis is 2-4 years in ATTRv patients without a family history

ATTRv, hereditary transthyretin amyloidosis
Delayed diagnosis in cardiac ATTR is associated with HCRU\(^1\)

Health care resource utilization (HCRU) in 3 years before diagnosis (A) and 3 years after diagnosis (B)

- Diagnostic delay: median 25 months (IQR 4–60) for ATTRv-cardiomyopathy

During the 3 years prior to diagnosis:
- Patients attended hospital a median of 17 times (IQR 9–27)
- Patients experienced a median of 3 inpatient admissions (IQR 1–5)

During the first year after diagnosis:
- 30% of patients were admitted ≥3 times

ER, emergency room; IP, inpatient admissions; OP, outpatient services.
IQR, interquartile range
Increased HCRU increases costs\(^a\)

Newly diagnosed ATTRv patients (N=185) have substantial HCRU and costs in the first year\(^1\)

**Total HCRU $64,066**: inpatient services $34,461, outpatient services $23,853, pharmacy $5752

\(^a\)Retrospective study based on US medical claims data; physician office visits and prescription fills show mean + standard deviation. ATTRv, hereditary transthyretin amyloidosis; HCRU, health care resource utilization.  
Most ATTRv patients use HCRU

Proportion of patients reporting health care resource utilization (HCRU) in preceding 3 months

- Outpatient visits: 80.0%
- Emergency room visits: 21.7%
- Hospitalizations: 15.0%
- Home healthcare services: 6.7%

Data from cross-sectional non-interventional survey in patients from USA (n=44) and Spain (n=16) in the 3 months preceding taking the survey.

ATTRv patients: increased use of HCRU

HCRU use in the year prior to enrolment in the APOLLO trial

On average, patients require ≈15-16 visits per year, split by general practitioners and specialists

About 1 out of 4 patients with ATTRv require hospital emergency care and/or hospitalization

ATTRv = hereditary transthyretin amyloidosis; FAP = familial amyloidotic polyneuropathy, staged I and II; HCRU, health care resource utilization.

ATTRv amyloidosis: increased use of aids

Patient-Reported need for assistance devices at baseline (APOLLO trial)

Any mobility assistance device

Mobility assistance devices breakdown

ATTRv = hereditary transthyretin amyloidosis; FAP = familial amyloidotic polyneuropathy, staged I and II.

The cost of ATTRv-polyneuropathy

- In a Portuguese study\(^1\) a prevalence-based approach including direct and indirect costs was focused on health care resource use (HCRU)
- The burden of disease was expressed in terms of disability-adjusted life years (DALYs)
- The total annual cost-of-illness (COI) of ATTRv-PN in Portugal in 2016 was \(\approx \€50,000,000\) (N=1850) and the mean cost per patient was \(\approx \€30,000\) (80% direct; 20% indirect costs)
- Treatments accounted for \(\approx 50\%\) of total costs, while \(\approx 0.2\%\) were devoted to disease prevention. A total of \(\approx 2,000\) DALYs were lost, 25% due to disability and 75% due to death
- Annual costs and burden of ATTRv-PN were considerable but within the range of other rare diseases

ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy.
## Table 1. Costs per ATTRv-PN patient (€, 2016) in Portugal.

<table>
<thead>
<tr>
<th>Item</th>
<th>Users</th>
<th>Total annual cost</th>
<th>Annual mean cost per user</th>
<th>Annual mean cost per patient</th>
<th>% Total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic counselling visits</td>
<td>109</td>
<td>10,137</td>
<td>93</td>
<td>5</td>
<td>0.02</td>
</tr>
<tr>
<td>Medically assisted reproductive interventions</td>
<td>18</td>
<td>83,906</td>
<td>4661</td>
<td>45</td>
<td>0.16</td>
</tr>
<tr>
<td>Drugs</td>
<td>1865</td>
<td>27,120,879</td>
<td>14,542</td>
<td>14,542</td>
<td>51.66</td>
</tr>
<tr>
<td>Medical tests</td>
<td>1537</td>
<td>206,507</td>
<td>134</td>
<td>110</td>
<td>0.39</td>
</tr>
<tr>
<td>Medical and Nurse visits</td>
<td>2551</td>
<td>657,702</td>
<td>257</td>
<td>352</td>
<td>1.25</td>
</tr>
<tr>
<td>Hospitalisations</td>
<td>493</td>
<td>3,287,260</td>
<td>6667</td>
<td>1762</td>
<td>6.26</td>
</tr>
<tr>
<td>Health material</td>
<td>1865</td>
<td>949,781</td>
<td>509</td>
<td>509</td>
<td>1.81</td>
</tr>
<tr>
<td>Healthcare transport</td>
<td>2338</td>
<td>545,251</td>
<td>233</td>
<td>292</td>
<td>1.04</td>
</tr>
<tr>
<td><strong>Direct healthcare costs</strong></td>
<td></td>
<td>32,767,382</td>
<td>–</td>
<td>–</td>
<td>62.59</td>
</tr>
<tr>
<td>Professional formal caregiver and social services</td>
<td>68</td>
<td>99,721</td>
<td>1461</td>
<td>53</td>
<td>0.19</td>
</tr>
<tr>
<td>Informal caregiver</td>
<td>1481</td>
<td>8,711,216</td>
<td>5882</td>
<td>4670</td>
<td>16.59</td>
</tr>
<tr>
<td><strong>Direct non-healthcare costs</strong></td>
<td></td>
<td>8,810,938</td>
<td>–</td>
<td>–</td>
<td>16.78</td>
</tr>
<tr>
<td>Direct costs</td>
<td></td>
<td>41,672,364</td>
<td>–</td>
<td>22,344</td>
<td>79.37</td>
</tr>
<tr>
<td>Sick leave</td>
<td>438</td>
<td>4,442,382</td>
<td>10,142</td>
<td>2382</td>
<td>8.46</td>
</tr>
<tr>
<td>Early retirement</td>
<td>469</td>
<td>6,389,549</td>
<td>13,614</td>
<td>3,426</td>
<td>12.17</td>
</tr>
<tr>
<td><strong>Indirect costs</strong></td>
<td></td>
<td>10,831,931</td>
<td>–</td>
<td>5808</td>
<td>20.63</td>
</tr>
<tr>
<td><strong>Total costs</strong></td>
<td></td>
<td>52,504,295</td>
<td>–</td>
<td>28,152</td>
<td>100.00</td>
</tr>
</tbody>
</table>

ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy.
HCRU and costs by PND stage and NT-proBNP level in the UK\(^1\)

### Costs of polyneuropathy-related resources by PND stage

<table>
<thead>
<tr>
<th>PND 0</th>
<th>PND I</th>
<th>PND II</th>
<th>PND IIIa</th>
<th>PND IIIb</th>
<th>PND IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average cost per patient per 6 months</td>
<td>£233</td>
<td>£1,825</td>
<td>£2,499</td>
<td>£4,553</td>
<td>£7,203</td>
</tr>
<tr>
<td>Average one-off costs per patient</td>
<td>£0</td>
<td>£0</td>
<td>£2,997</td>
<td>£8,075</td>
<td>£9,938</td>
</tr>
</tbody>
</table>

### Costs of cardiomyopathy-related resources by NT-proBNP level

<table>
<thead>
<tr>
<th>NT-proBNP &lt;3000 ng/mL</th>
<th>NT-proBNP &gt;3000 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average cost per patient per 6 months</td>
<td>£5,559</td>
</tr>
<tr>
<td>Resources with highest average cost per patient per 6 months:</td>
<td>1. Cardiac resynchronization therapy 2. Sinoatrial node ablation 3. Rivaroxaban</td>
</tr>
</tbody>
</table>

Note: All costs estimates are additive and mutually exclusive. NT-proBNP, N-terminal pro b-type natriuretic peptide; PND, polyneuropathy disability. 1. Alnylam data on file (Patisiran for the treatment of hereditary transthyretin amyloidosis) 2019.
Modelling of the fiscal life course

Using a public economic framework for the Netherlands. The economic impact per person between ages 40-80. Looking at:

- Total money transfers:
  - Health costs (HCRU)
  - Disability payments (government transfers)
  - Pensions
- Lifetime earnings
- Gross tax:
  - Direct tax
  - Indirect tax

1. Connolly MP et al. Orphanet J Rare Dis 2019;14:220
The fiscal life course of ATTRv amyloidosis can be modelled using a public economic framework for the Netherlands

Scenario 1
- Early onset (age 45, PND Stage 1)
- Median progression
- Death at age 55 (PND Stage 4)
- No severe cardiomyopathy

“Early PN, median progression”

Scenario 2
- Early onset (age 45, PND Stage 1)
- Slow progression
- Death at age 65 (PND Stage 4)
- No severe cardiomyopathy

“Early PN, slow progression”

Scenario 3
- Late onset (age 60, PND Stage 1)
- Median progression
- Death at age 70 (PND Stage 4)
- No severe cardiomyopathy

“Late PN, median progression”

Scenario 4
- Late onset & diagnosis (age 60, PND Stage 2)
- Severe cardiomyopathy
- Death within 4 years (PND Stage 3b)

“Late onset, severe CM”

ATTRv, hereditary transthyretin amyloidosis; CM, cardiomyopathy; PN, polyneuropathy; PND, polyneuropathy disability

1. Connolly MP et al. Orphanet J Rare Dis 2019;14:220
Indirect costs depend on duration of illness

Transfer payments: Patients living longest with the disease incur the highest total transfers

1. Connolly MP et al. Orphanet J Rare Dis 2019;14:220

PN, polyneuropathy
Earnings and taxes paid depend on disease onset

Patients with early onset disease have lowest lifetime earnings and pay least total taxes\(^1\)

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**Lifetime earnings**
**Gross tax**
**Direct tax**
**Indirect tax**

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1. Connolly MP et al. Orphanet J Rare Dis 2019;14:220
Productive years are least in patients with early onset disease

Only 40% of life aged ≥40 is productive in patients with early onset and slow progression\(^1\)

1. Connolly MP et al. Orphanet J Rare Dis 2019;14:220
Early onset disease presents the highest fiscal burden

Halting disease progression early would generate economic benefits alongside health benefits.¹

<table>
<thead>
<tr>
<th>Scenario 1: “Early PN, median progression”</th>
<th>Scenario 2: “Early PN, slow progression”</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Have lowest lifetime earnings</td>
<td>– Live longest with disease and require most public funding</td>
</tr>
<tr>
<td>– Pay least in total taxes</td>
<td>– Incur highest health costs/disability payment</td>
</tr>
<tr>
<td>– Have fewest years alive after age 40 with second lowest proportion of productive years (44%)</td>
<td>– Have lowest proportion of productive years after age 40 (40%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scenario 3: “Late PN, median progression”</th>
<th>Scenario 4: “Late onset, severe CM”</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Have highest lifetime earnings</td>
<td>– Incur the lowest government spending</td>
</tr>
<tr>
<td>– Pay most in total taxes</td>
<td>– Have second highest lifetime earnings and total taxes paid</td>
</tr>
<tr>
<td>– Live longest after age 40 with second highest proportion of productive years (62%)</td>
<td>– Have highest proportion of productive years after age 40 (71%)</td>
</tr>
</tbody>
</table>

CM, cardiomyopathy; PN, polyneuropathy

¹ Connolly MP et al. Orphanet J Rare Dis 2019;14:220
Societal burden:
Direct costs to the patients, families and care givers
69% of those in the APOLLO trial reported being unable to work

Patients’ functional status and ability to work by FAP stage

Ability to work and requirement for assistance to live independently were associated with FAP stage, increasing from 47% unable to work to 87% between FAP stages I (no aids) and II (one or more canes)

FAP, familial amyloidotic polyneuropathy, staged I and II.
Patients in the APOLO trial reported an average of 39 work-days lost, and 24% received government compensation due to illness.

**Patient work-days lost**

- Employed Patients:
  - Overall: 39 days
  - FAP I: 24 days
  - FAP II: 63 days

**Government compensation received due to illness**

- Overall:
  - Yes: 24%
  - No: 76%

- FAP I:
  - Yes: 18%
  - No: 82%

- FAP II:
  - Yes: 30%
  - No: 70%

Lost work days numerically increased from 24 to 63 days in FAP stage I vs FAP stage II (P=0.061).

Need for government compensation increased from 18% to 30% in FAP stage I vs stage II (P=0.03).

FAP, familial amyloidotic polyneuropathy, staged I and II.

Productivity is impaired in patients with ATTRv amyloidosis\(^a\)

Patients who have both neuropathy and cardiac symptoms are most affected\(^1\)

Work and productivity impairment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATTRv-PN only</th>
<th>ATTRv-PN + ATTRv-CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work time missed</td>
<td><strong>10.6%</strong></td>
<td><strong>50.1%</strong></td>
</tr>
<tr>
<td>Overall work impairment</td>
<td><strong>34.7%</strong></td>
<td><strong>76.3%</strong></td>
</tr>
<tr>
<td>Activity impairment</td>
<td><strong>47.5%</strong></td>
<td><strong>73.6%</strong></td>
</tr>
</tbody>
</table>

\(^a\)Data from cross-sectional non-interventional survey in patients from USA (n=44) and Spain (n=16). ATTRv-PN, transthyretin amyloidosis with peripheral neuropathy; ATTRv-CM, transthyretin amyloidosis with cardiomyopathy; SD, standard deviation.\(^1\) Stewart M et al. Neurol Ther 2018;7:349-64.
ATTRv amyloidosis impacts on caregivers’ ability to work\(^1\)

Inability to hold a paying job rose from 6% to 22% for those caring for a patient with FAP stage I vs Stage II in the year prior to enrolment in APOLLO.

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**Caregivers’ ability to work**

<table>
<thead>
<tr>
<th></th>
<th>FAP I</th>
<th>FAP II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can only work part-time</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Cannot hold a job</td>
<td>6%</td>
<td>22%</td>
</tr>
</tbody>
</table>

**Caregiver work loss**

<table>
<thead>
<tr>
<th></th>
<th>FAP I</th>
<th>FAP II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed Caregivers</td>
<td>16 days</td>
<td>14 days</td>
</tr>
<tr>
<td>Mean Work Days Lost in Year Prior to Enrollment</td>
<td>Question only answered if the patient’s caregiver was able to work</td>
<td></td>
</tr>
</tbody>
</table>

ATTRv = hereditary transthyretin amyloidosis; FAP, familial amyloidotic polyneuropathy, staged I and II.

Learning Points
For patients, healthcare systems and society

- The cost of disease progression is not only related to HCRU, but also to societal support, loss of productivity, early retirement, loss of taxes, and work loss of caregivers.
- The long and winding road to diagnosis in non-familial cases is expensive before diagnosis and increases risks of progressed disease and costs at diagnosis.
- Age at onset, rate of progression and organ dominance (heart vs. nerves) are important determinants of the costs of disease.
- HCRU costs rise with progression of polyneuropathy and of cardiomyopathy.

HCRU, health care resource use.
Learning Points
For patients, healthcare systems and society

• Productivity is most impaired in patients with both polyneuropathy and cardiomyopathy

• Patients living longest with the disease incur the highest total transfers

• Patients with early onset disease have lowest lifetime earnings and pay least total taxes

• Complete stabilization of early disease by early detection and highly effective treatment will - alongside obvious health benefits - reduce the current economic and societal burden of the disease
Relevant references used in the presentation (1)

Literature:


Relevant references used in the presentation (2)

Poster presentations at The International Symposium on Amyloidosis (ISA); March 2018; Kumamoto, Japan:
