TranstHyretin Amyloidosis Outcome Survey

Agenda:

• What is ATTR?

• What is THAOS?

• How can we use THAOS to expand our knowledge of ATTR-related amyloidosis and to improve diagnosis and management?
Apo A immunoglobulin

Lysozime

TTR

pKa His 6.5

pKa Asp, Glu 4.4

pH 7.5

Native State Tetrameric TTR

pH 5.5

Rearranged Tetrameric TTR

pH 5.1–3.9

Monomeric Amyloidogenic Intermediate

(slightly altered tertiary structure)

Amyloid Fibrils

pH 2.0

A–state

Tafamidis-bound tetramer

Free tetramer

Folded monomer

Misfolded monomer

Aggregates

Functional TTR structures

Ligand dissociation

Rate-limiting tetramer dissociation

Monomer misfolding

Aggregation

Fibrillar

Amorphous

TTR structures associated with pathology
“Senile Systemic Amyloidosis” (wt ATTR-related Amyloidosis)

100% 50%
Familial ATTR across the world
TransTHyretin Amyloidosis Outcome Survey

• Worldwide, longitudinal, observational survey

• Symptomatic individuals with wild type or variant ATTR and asymptomatic carriers

• To study differences in disease presentation, diagnosis, and natural history in geographically dispersed populations

• Sponsored by Pfizer Inc. and overseen by an independent Scientific Board

• Since 2007: 1366 individuals from 47 sites in 19 countries enrolled (current analysis referred to 1224 subjects for demographics and to subsets of different size for other variables according to available validated data)
1366 subjects from 47 sites in 19 Countries

June 2012
THAOS: validated and analyzed data

All patients
N=1224*
657M/567F

TTR mutation
N=1111
550M / 561F

Symptomatic
N=781  419M/362F

Asymptomatic
N=330  131M/199F

Wild type TTR
N=108  104M/4F

Symptomatic
N=97   94M/3F

Asymptomatic
N=11   10M/1F

*5 Patients (3M/2F) with Polymorphism are not included above
Worldwide Genotypic Spectrum
1111 subjects

75%

- V30M (n = 834)
- E89Q (n= 24)
- T60A (n = 16)
- I68L (n = 17)
- I107V (n = 10)
- Other (n = 111)

10%

- V122I (n = 49)
- S77Y (n = 16)
- L111M (n = 17)
- F64L (n = 17)

Other 44 mutations each affecting < 10 subjects
Genotypic Spectrum

**Portugal n = 636**
- V30M (n = 627)
- S50R (n = 1)
- V28M (n = 7)
- S52P (n = 1)

98%

**Sweden n = 63**
- V30M (n = 57)
- A97S (n = 1)
- H88R (n = 4)
- A45G (n = 1)

90%

**Japan n = 59**
- V30M (n = 54)
- E42G (n = 1)
- I107V (n = 2)
- S50I (n = 1)

92%
Genotypic Spectrum, USA n = 100

14 other mutations each affecting 1 subject

- V122I (n = 52)
- T60A (n = 15)
- G6S (n = 4)
- V30M (n = 6)
- T59K (n = 2)
- V32A (n = 2)
- L58H (n = 2)
- F64L (n = 3)
- Other (n = 14)
Genotypic Spectrum, Western Europe Excluding Portugal and Scandinavia (and UK) n= 172

32 %

8 other mutations each affecting 1 subject

- V30M (n = 55)
- E89Q (n = 21)
- E89L (n = 2)
- T49A (n = 8)
- I107V (n = 6)
- S77F (n = 4)
- Y116S (n = 3)
- V120I (n = 8)
- I68L (n = 19)
- F64L (n = 15)
- G47A (n = 2)
- T59L (n = 2)
- S50R (n = 3)
- S77Y (n = 13)
- V122I (n = 3)
- Other (n = 8)
Clinical Phenotypes at Presentation Among 776 symptomatic TTRm pts

Mainly Cardiac 25.5%
Mainly Neurologic 49.7%
Mixed 24.8%

n= 385
Male 50.5%
Age 46 ±14 yrs

n= 198
Male 74%
Age 62 ±12 yrs

n= 193
Male 39%
Age 42 ±13 yrs
Genotypic-Phenotypic Correlation in ATTR

Phenotype

“Neurologic” Phenotype

“Cardiac” Phenotype

V122I
I68L
L111M
T60A
S77Y
E89L
E89Q
G47A
F64L
I107V
T49A
T60A
L111M
I68L
V122I
V30M

early onset
late onset
Genotypic-Phenotypic Correlation in ATTR

Phenotype

“Neurologic” Phenotype

“Cardiac” Phenotype

V122I
I68L
L111M
T60A
S77Y
E89L
E89Q
G47A
F64L
I107V
T49A
V30M

early onset
late onset

V30M

T60A
L111M
I68L
V122I

wt
### Clinical Characteristics of wt ATTR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Wild Type (N = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at THAOS entry (yrs)</td>
<td>75.7</td>
</tr>
<tr>
<td>Males (%)</td>
<td>98.8</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>88.2</td>
</tr>
<tr>
<td>African Descent (%)</td>
<td>3.5</td>
</tr>
<tr>
<td>Age at Onset (yrs)</td>
<td>71.0</td>
</tr>
<tr>
<td>Duration of symptoms (yrs)</td>
<td>3.3</td>
</tr>
<tr>
<td>NYHA class III-IV (%)</td>
<td>35</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>63.3</td>
</tr>
</tbody>
</table>
### Demographics and Baseline Characteristics of mATTR pts with «cardiac mutations»

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Val122Ile (N = 39)</th>
<th>Ile68Leu (N = 15)</th>
<th>Thr60Ala (N = 15)</th>
<th>Leu111Met (N = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at THAOS entry (yrs)</td>
<td>72.5</td>
<td>69.5</td>
<td>60.8</td>
<td>47.6</td>
</tr>
<tr>
<td>Males (%)</td>
<td>76.9</td>
<td>73.3</td>
<td>45.5</td>
<td>58.8</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.0</td>
<td>100.0</td>
<td>93.3</td>
<td>100.0</td>
</tr>
<tr>
<td>African Descent</td>
<td>87.2</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Age at Onset (yrs)</td>
<td>69.4</td>
<td>66.2</td>
<td>61.4</td>
<td>42.8</td>
</tr>
<tr>
<td>Duration of symptoms (yrs)</td>
<td>2.3</td>
<td>3.9</td>
<td>4.8</td>
<td>4.3</td>
</tr>
<tr>
<td>NYHA Class III-IV (%)</td>
<td>53.8</td>
<td>26.7</td>
<td>26.7</td>
<td>23.5</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>25.0</td>
<td>100.0</td>
<td>25.0</td>
<td>-</td>
</tr>
</tbody>
</table>
Onset of Disease in Patients with Cardiac Mutations or Wild Type TTR Amyloidosis

Cumulative Incidence (%)

Age (years) at Onset

Leu111Met N = 10
Ile68Leu N = 11
Thr60Ala N = 11
Val122Ile N = 29
WT N = 74
Baseline Echocardiographic findings of wt ATTR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wild Type (N = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2D Echo structure</strong></td>
<td></td>
</tr>
<tr>
<td>LVIDd (mm)</td>
<td>44.3 (6.3)</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>18.2 (3.5)</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>16.8 (3.5)</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>51.4 (48.4)</td>
</tr>
<tr>
<td><strong>Mitral Doppler</strong></td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>2.1 (1.4)</td>
</tr>
<tr>
<td>RVSP (mmHg)</td>
<td>37.2 (14.3)</td>
</tr>
<tr>
<td><strong>Tissue Doppler</strong></td>
<td></td>
</tr>
<tr>
<td>E’ septal (cm/sec)</td>
<td>4.7 (2.1)</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>45.5 (12.1)</td>
</tr>
</tbody>
</table>
Baseline Echocardiographic findings of mutant ATTR with cardiac phenotype

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Val122Ile</th>
<th>Ile68Leu</th>
<th>Thr60Ala</th>
<th>Leu111Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D Echo structure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVIDd (mm)</td>
<td>40.4 (7.4)</td>
<td>45.3 (3.7)</td>
<td>46.6 (3.3)</td>
<td>44.7 (3.7)</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>18.4 (5.3)</td>
<td>16.3 (5.8)</td>
<td>16.3 (6.1)</td>
<td>13.3 (4.1)</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>16.9 (4.1)</td>
<td>15.5 (4.7)</td>
<td>13.3 (4.7)</td>
<td>14.3 (3.8)</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>42.1 (12.1)</td>
<td>45.5 (10.1)</td>
<td>41.8 (7.8)</td>
<td>40.8 (5.5)</td>
</tr>
<tr>
<td>Mitral Doppler</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>3.1 (0.2)</td>
<td>2.0 (1.2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RVSP (mmHg)</td>
<td>40.2 (4.7)</td>
<td>35</td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td>Tissue Doppler</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E’ septal (cm/sec)</td>
<td>48.5</td>
<td>-</td>
<td>78.0</td>
<td>-</td>
</tr>
<tr>
<td>EF (%)</td>
<td>38.1 (15.6)</td>
<td>56.3 (10.37)</td>
<td>46.7 (11.69)</td>
<td>60.0 (11.73)</td>
</tr>
</tbody>
</table>
General Profile of ATTR patients with Exclusively Cardiac Phenotype

- Male gender
- Average age ~ 65 yrs
- No family history of ATTR
- Heart failure symptoms
- Concentric “LV hypertrophy”
- Absent or mild LV dilatation
- Mild LV systolic dysfunction
- (Normal or near normal QRS voltages)
Frequent but usually restricted to conduction disturbances. Cardiomyopathy rare (age-dependent). No isolated myocardial involvement. Symptomatic CMPs relatively frequent among late onset pts in nonendemic areas.
Main Determinants of Phenotypic Heterogeneity in ATTR

- Geographic Area
- Type of Mutation
- Age
- Type of Aggregation:
  - Endemic
  - Non-endemic
- Gender
- Gender of the Transmitting Parent
Onset of Disease in Patients with Val30Met Mutation: Geographic variation

Brazil: N = 48
Portugal: N = 267
Japan: N = 52
Sweden: N = 23

Cumulative Incidence (%)

Age (years) at Onset
Age of Onset of Symptomatic Patients: TTRm & TTRwt
Cumulative Onset of Symptomatic Disease
Patients with Val30Met and Non-Val30Met Mutations

Val30Met Mutation

Non-Val30Met Mutations
LV Wall Thickness by Age

<table>
<thead>
<tr>
<th>Age at Echo</th>
<th>&lt; 50 yrs</th>
<th>≥ 50 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>«Cardiac» TTR Mutations</td>
<td>Mean 9.3, n = 59</td>
<td>Mean 11.7, n = 6</td>
</tr>
<tr>
<td>Val30Met TTR</td>
<td>Mean 12.0, n = 27</td>
<td>Mean 16.5, n = 29</td>
</tr>
</tbody>
</table>

p < 0.0003

p < 0.0221
Male Prevalence in V30M, «Cardiac Mutations» and wtATTR

- V30M: 44%
- T60A: 45.5%
- L111M: 58.8%
- I68L: 73.3%
- V122I: 76.9%
- wtATTR: 98.8%
**Multivariate Regression Analysis**
*(parameter estimate and p values)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Cardiac mutations</th>
<th>V30M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>0.0082 (p=0.023)</td>
<td>0.0042 (p=0.65)</td>
<td>0.0044 (p=0.187)</td>
</tr>
<tr>
<td>Age at ECHO</td>
<td>0.0087 (p&lt;0.0001)</td>
<td>0.0141 (p=0.0011)</td>
<td>0.0064 (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

*data from 227 pts with complete echocardiographic evaluation*

Male gender and age = positive independent predictors of increasing mean parietal LV thickness in the overall population (age also among cardiac mutations and V30M)
Onset of Disease
dependence of parental inheritance

Maternal transmission
N=203

Paternal transmission
N=211

p<0.0001

Earlier onset of ATTR amyloidosis with maternal transmission
Main Determinants of Phenotypic Heterogeneity in ATTR

- Geographic Area
- Type of Mutation
- Type of Aggregation
  - endemic
  - non endemic
- Age
  - Gender
  - Gender of the transmitting parent
Conclusions:

✓ THAOS registry offers a unique opportunity to assess the worldwide phenotypic and genotypic spectrum and correlations in ATTR.

✓ Both genotype and phenotype are highly heterogeneous.

✓ Phenotypic heterogeneity is not only linked to genotype, but also to geographic distribution, age, gender of the patient and of the transmitting parent.

✓ Myocardial involvement is less pronounced in women, supporting the hypothesis that some biologic characteristic may protect women against myocardial TTR-related amyloid infiltration.
Conclusions:

✓ A clinically relevant subset of mutant Caucasian and African-American patients (around 10%, mainly associated with four different mutations) and all wt-ATTR have a dominant cardiac phenotype at presentation mimicking HCM.

✓ Symmetric LVH and mildly depressed LVEF especially in elderly men should prompt the suspicion of ATTR among patients with apparently unexplained LVH.

✓ THAOS registry will hopefully gain insight into the natural history of the disease and offer the opportunity to evaluate novel therapeutic modalities.