Neuropathy Progression Rate in Patients with Familial Amyloidotic Polyneuropathy

Prof. David Adams
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Familial Amyloidotic Polyneuropathy (FAP)

Background

- Autosomal dominant hereditary amyloidosis caused by deposition of mutant and wild-type transthyretin (TTR) in nerves, gastrointestinal tract, heart, eyes and CNS
  - Median survival 10-15 years
- Polyneuropathy is symmetrical with motor, sensory and autonomic components
  - Clinical manifestations (e.g. disease penetrance and rate of progression) influenced by TTR genotype and geographical region
- Continued high unmet medical need for novel therapeutics
  - Liver transplant for early stage disease
  - Tetramer stabilizers
    - EU approval of Pfizer’s Vyndaqel® (tafamidis) for Stage 1 FAP in 2011
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study
  - TTR-lowering drugs in Phase 3 clinical trials
    - Small interfering RNA (siRNA): Patisiran (Alnylam)
    - Antisense oligonucleotide (ASO): ISIS-TTR<sub>RX</sub> (Isis)

1 Coelho T et al., Neurology. 79:785-92 (2012)
*Maximum potential scores shown. In FAP patients, QST and motor strength/weakness scores are approximately the same.
Neuropathy Progression Rate in FAP
Results from Completed Trials of Tetramer Stabilizers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>TTR Genotype</th>
<th>Stage of Disease</th>
<th>Baseline NIS-LL / NIS in placebo arm</th>
<th>Rate of Neuropathy Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tafamidis¹</td>
<td>Phase 3 (n=128)</td>
<td>V30M</td>
<td>FAP Stage 1</td>
<td>11.4 ± 13.5 (NIS-LL)</td>
<td>NIS-LL: 4.1 points/yr in Placebo arm</td>
</tr>
<tr>
<td>Tafamidis²</td>
<td>Phase 2 (n=21)</td>
<td>Non-V30M</td>
<td>FAP Stage 1</td>
<td>48.7 ± 44.3 (NIS; open-label)</td>
<td>NIS: 13.9 points/yr pre-treatment</td>
</tr>
<tr>
<td>Diflunisal³</td>
<td>Phase 3 (n=130)</td>
<td>V30M and Non-V30M</td>
<td>FAP Stages 1-3</td>
<td>45.4 ± 46.3 (NIS)</td>
<td>NIS*: 11.6 points/yr in Placebo arm NIS+7: 13.2 points/yr</td>
</tr>
</tbody>
</table>

*Progression average over two years

¹Coelho T et al., Neurology. 79:785-92 (2012)
²Tafamidis EMA assessment report (2012)
³Berk JL et al., JAMA. 310:2658-67 (2013)
Study of Neuropathy Progression in FAP
Retrospective Cross-Sectional Analysis

Aim

- Characterization of neuropathy severity and rate of progression in multinational population of FAP patients

Methods

- Single NIS measurements and time from symptom onset to NIS collected retrospectively on 283 FAP patients in 4 countries; 5 study investigators:
  - David Adams, CHU Hospital Bicetre, Le Kremlin-Bicetre, France
  - Teresa Coelho, Hospital Geral de Santo Antonio, Porto, Portugal
  - Peter Dyck, Mayo Clinic, Rochester, MN, USA
  - Giampaolo Merlini, University of Pavia, Italy
  - Laura Obici, University of Pavia, Italy
- Where available, PND score, FAP Stage and Grip Strength also collected
- All statistical analyses conducted with R version 3.0.1
  - Linear and polynomial curve fitting
  - Descriptive statistics
  - Continuous variables log-transformed when appropriate, analyzed via ANOVA
## Demographics

<table>
<thead>
<tr>
<th>Country</th>
<th>N</th>
<th>Age (mean, IQR)</th>
<th>Sex</th>
<th>Genotype</th>
<th>PND Score&lt;sup&gt;1,3&lt;/sup&gt;</th>
<th>FAP Stage&lt;sup&gt;2,3&lt;/sup&gt;</th>
<th>On TTR stabilizers at 1st visit N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>M (%)</td>
<td>F (%)</td>
<td>Non-V30M</td>
<td>late onset V30M</td>
<td>early onset V30M&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>France</td>
<td>135</td>
<td>59.3 (48.0, 69.9)</td>
<td>93 (68.9%)</td>
<td>42 (31.1%)</td>
<td>57 (42.2%)</td>
<td>45 (33.3%)</td>
<td>33 (24.4%)</td>
</tr>
<tr>
<td>Italy</td>
<td>31</td>
<td>65.4 (58.9, 73.06)</td>
<td>25 (80.6%)</td>
<td>6 (19.4%)</td>
<td>19 (61.3%)</td>
<td>11 (35.5%)</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Portugal</td>
<td>50</td>
<td>38.5 (33.3, 41.0)</td>
<td>29 (58%)</td>
<td>21 (42%)</td>
<td>0 (0%)</td>
<td>4 (8%)</td>
<td>46 (92%)</td>
</tr>
<tr>
<td>USA</td>
<td>67</td>
<td>59.6 (50.5, 69.0)</td>
<td>52 (77.6%)</td>
<td>15 (22.4%)</td>
<td>38 (64.4%)</td>
<td>18 (26.9%)</td>
<td>3 (4.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>283</td>
<td>56.4 (41.0, 69.6)</td>
<td>199 (70.3%)</td>
<td>84 (29.7%)</td>
<td>114 (40.3%)</td>
<td>78 (27.6%)</td>
<td>83 (29.3%)</td>
</tr>
</tbody>
</table>

<sup>1</sup>PND Score: I-sensory disturbance but preserving walking capacity; II-impaired walking capacity but ability to walk without stick or crutches; IIIa-walking with help of one stick or crutch; IIIb-walking with help of 2 sticks or crutches; IV-confined to wheelchair or bedridden

<sup>2</sup>FAP Stage: 1-unimpaired ambulation, mostly mild neuropathy in lower limbs; 2-assistance with ambulation required, mostly moderate neuropathy with progression to lower limbs, upper limbs and trunk; 3-wheelchair-bound or bedridden, severe neuropathy of all limbs

<sup>3</sup>Ns for FAP Stage: France, 132

*Onset of symptoms at age <50 yrs*
NIS Distribution
By Region

France
- N = 135
- $\bar{x} = 39.8$
- $\tilde{x} = 37.5$
- $\sigma = 28.8$

Italy
- N = 31
- $\bar{x} = 82.8$
- $\tilde{x} = 87.5$
- $\sigma = 42.4$

Portugal
- N = 50
- $\bar{x} = 15.9$
- $\tilde{x} = 9.0$
- $\sigma = 21.5$

United States
- N = 67
- $\bar{x} = 41.7$
- $\tilde{x} = 32.0$
- $\sigma = 37.5$

Overall
- N = 280
- $\bar{x} = 40.8$
- $\tilde{x} = 32.0$
- $\sigma = 36.1$

$\bar{x}$ = mean
$\tilde{x}$ = median
$\sigma$ = std. dev.
Association of NIS and TTR Genotype

**Pairwise comparison p values:**

* $p < 0.05$

*** $p < 0.001$

(Significance threshold under Bonferroni correction = 0.0167)
Correlation of NIS and PND Score

France + Italy

$p < 0.0001$ (ANOVA)
Correlation of NIS and FAP Stage
France, Portugal, Italy

NIS

FAP Stage

p < 0.0001 (ANOVA)

14 71.1 99

1 2 3

100 150

50 100

0
Correlation of Grip Strength and PND Score

France

\[ p < 0.0001 \text{ (ANOVA)} \]
Symptom Months vs. NIS
Loess Fit

Months Since Symptom Onset

NIS

France
Italy
Portugal
USA
Symptom Months vs. NIS, Gompertz Fit
Estimating Rate of Neuropathy Progression

<table>
<thead>
<tr>
<th></th>
<th>France</th>
<th>Italy</th>
<th>Portugal</th>
<th>USA</th>
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</thead>
<tbody>
<tr>
<td>Median NIS</td>
<td>32.0</td>
<td>14.3</td>
<td>~17.8</td>
<td></td>
</tr>
<tr>
<td>ΔNIS in 12 mos</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ΔmNIS+7 in 12 mos</td>
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</table>

$p < 0.0001$
Summary

Rapid neuropathy progression rate in a multinational FAP population with median NIS of 32

- Cross-sectional analysis shows a ΔNIS rate of 14.3 points/year, consistent with rate of 11.6 points/year observed in the placebo arm of multinational diflunisal Phase 3 trial that included both V30M and non-V30M FAP patients
- NIS is highly correlated with PND Score and FAP Stage
- NIS is associated with TTR genotype
  » Early-onset V30M population from Portugal with significantly lower median NIS compared to late-onset V30M or non-V30M

ΔNIS rate of 14.3 points/year corresponds to ΔmNIS+7 of ~17.8 points/year

- Ongoing Phase 3 trials of patisiran and ISIS-TTRRX in FAP patients with demographics similar to those in this cross-sectional natural history study have potential to show impact of TTR lowering on rapid mNIS+7 progression rate
Acknowledgments

Study Investigators

- David Adams
  » CHU Hospital Bicetre, Le Kremlin-Bicetre, France
- Teresa Coelho
  » Hospital Geral de Santo Antonio, Porto, Portugal
- Peter Dyck
  » Mayo Clinic, Rochester, MN, USA
- Giampaolo Merlini
  » University of Pavia, Italy
- Laura Obici
  » University of Pavia, Italy

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- Brian Bettencourt
- Jared Gollob