Treatment of ATTR amyloidosis

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Treatment strategies in amyloidosis

- Enhance removal of existing amyloid
  - Immunotherapy
  - SAP depletion

- Reduce supply of amyloid precursor protein

- Stabilise amyloid-forming proteins
  - β sheet breakers

- Reversion to normally folded protein

<table>
<thead>
<tr>
<th>Precursor protein</th>
<th>Fibril formation</th>
<th>Amyloid</th>
</tr>
</thead>
</table>

- Precursor protein
- Reversion to normally folded protein
- Stabilise amyloid-forming proteins
  - β sheet breakers
- Enhance removal of existing amyloid
  - Immunotherapy
  - SAP depletion
Reducing the supply of the amyloid fibril precursor protein

Table 3. Unadjusted Relative Risk of Death Associated with the Most Recent Median Annual SAA Concentration during Follow-up. *

<table>
<thead>
<tr>
<th>SAA Concentration (mg/liter)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥4 to &lt;9</td>
<td>3.9 (2.5–10.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥9 to &lt;16.7</td>
<td>5.1 (2.7–9.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>≥16.7 to &lt;28</td>
<td>7.0 (3.7–13.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥28 to &lt;45.6</td>
<td>9.2 (4.8–17.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>≥45.6 to &lt;87</td>
<td>12.1 (6.9–21.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥87 to &lt;155</td>
<td>17.0 (8.8–33.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥155</td>
<td>17.7 (8.7–36.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* The SAA value is the median concentration within each 12-month period and was incorporated into the Cox regression model as a time-dependent covariate.
Liver transplantation in hATTR amyloidosis

First liver transplant performed in a Swedish patient with V30M-hATTR amyloidosis in 1990

>98% of variant TTR removed from the plasma


>2000 liver transplants performed for hATTR amyloidosis (FAP WTR)

Accelerated cardiac amyloidosis post-OLT in non-V30M hATTR amyloidosis

Novel Therapies

Novel drug technologies for ATTR amyloidosis

– ‘Stabilizer’ treatments to inhibit amyloid formation
  • Diflunisal
  • Tafamidis
  • AG10

– Gene ‘silencing’ therapies to inhibit production of TTR
  • Patisiran
  • Inotersen
Background
Diflunisal – ‘old’ NSAID which stabilizes TTR tetramer in vitro
Hypothesis is that diflunisal will slow or halt progression of neuropathy in FAP

Methods
RCT (multicentre international centre study) of diflunisal vs placebo in hATTR amyloidosis
Inclusion: hATTR amyloidosis with PN (any variant, severity not specified)
Primary endpoint - Change in Neurologic Impairment score (NIS+7)
FU for 2 years (evaluations at 0, 6, 12 and 24 months)

Results
130 subjects enrolled (64 diflunisal, 66 placebo)
At entry - 31% participants required support while walking
67 patients discontinued study Rx prematurely most commonly due to ‘disease progression’
Evaluable for response – 28 (placebo) vs 40 (diflunisal)

Berk JL et al, JAMA 2013:310;2658-2667
## Diflunisal Study

Intention to treat analysis of Primary (NIS+7) and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Placebo Change From Baseline</th>
<th>Mean (95% CI)</th>
<th>Difference, Placebo-Diflunisal</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Change From Baseline</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NIS+7 score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 year</td>
<td>12.5 (8.6 to 16.4)</td>
<td>6.2 (2.8 to 9.6)</td>
<td>6.4 (1.2 to 11.6)</td>
<td>.02</td>
</tr>
<tr>
<td>At 2 years</td>
<td>26.3 (20.2 to 32.4)</td>
<td>8.2 (2.9 to 13.6)</td>
<td>18.0 (9.9 to 26.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NIS score</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>At 1 year</td>
<td>10.1 (6.9 to 13.3)</td>
<td>4.1 (1.2 to 6.9)</td>
<td>6.0 (1.7 to 10.3)</td>
<td>.007</td>
</tr>
<tr>
<td>At 2 years</td>
<td>23.2 (17.8 to 28.5)</td>
<td>6.4 (1.6 to 11.2)</td>
<td>16.8 (9.6 to 24.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NIS-LL score</td>
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</tr>
<tr>
<td>At 1 year</td>
<td>6.0 (3.9 to 8.2)</td>
<td>3.2 (1.3 to 5.2)</td>
<td>2.8 (-0.1 to 5.7)</td>
<td>.06</td>
</tr>
<tr>
<td>At 2 years</td>
<td>12.1 (8.9 to 15.3)</td>
<td>3.8 (0.9 to 6.6)</td>
<td>8.3 (4.1 to 12.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Kumamoto score</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>At 1 year</td>
<td>4.1 (2.1 to 6.2)</td>
<td>1.9 (0.1 to 3.7)</td>
<td>2.3 (-0.5 to 5)</td>
<td>.10</td>
</tr>
<tr>
<td>At 2 years</td>
<td>8.0 (5.8 to 10.3)</td>
<td>3.1 (1.1 to 5.1)</td>
<td>5.0 (1.9 to 8.0)</td>
<td>.002</td>
</tr>
<tr>
<td>Modified BMI(p)</td>
<td></td>
<td></td>
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<tr>
<td>At 1 year</td>
<td>-38.5 (-74.9 to -2.1)</td>
<td>-18.7 (-51.6 to 14.1)</td>
<td>-19.8 (-68.8 to 29.2)</td>
<td>.43</td>
</tr>
<tr>
<td>At 2 years</td>
<td>-67.9 (-108.1 to -27.7)</td>
<td>-33.7 (-69.3 to 1.8)</td>
<td>-34.1 (-87.8 to 19.5)</td>
<td>.21</td>
</tr>
<tr>
<td>SF-36 physical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>component score</td>
<td>At 1 year</td>
<td>-1.9 (-3.9 to 0.2)</td>
<td>0.7 (-1.1 to 2.5)</td>
<td>-2.6 (-5.3 to 0.1)</td>
</tr>
<tr>
<td>At 2 years</td>
<td>-4.9 (-7.6 to -2.1)</td>
<td>1.2 (-1.2 to 3.7)</td>
<td>-6.1 (-9.8 to -2.5)</td>
<td>.001</td>
</tr>
<tr>
<td>SF-36 mental</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>score</td>
<td>At 1 year</td>
<td>0.8 (-2 to 3.6)</td>
<td>2.5 (0.0 to 5.1)</td>
<td>-1.7 (-5.5 to 2.1)</td>
</tr>
<tr>
<td>At 2 years</td>
<td>-0.9 (-4.4 to 2.5)</td>
<td>3.5 (0.4 to 6.7)</td>
<td>-4.5 (-9.2 to 0.2)</td>
<td>.06</td>
</tr>
</tbody>
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Berk JL et al, JAMA 2013:310;2658-2667
Tafamidis ‘Neurological’ Study

• Background
  – Tafamidis is a small molecule that stabilizes the TTR tetramer
  – Hypothesis was that it would slow or halt progression of neuropathy in hATTR amyloidosis

• Methods
  – RCT of tafamidis vs placebo in V30M-associated hATTR amyloidosis
  – Inclusion: hATTR amyloidosis with early stage disease
  – Diabetic polyneuropathy scoring system for disease progression used (NIS-LL – 88 point score)
  – Modified BMI as measure of autonomic progression used (BMI x serum albumin)
  – Norfolk Quality of Life score
  – FU for 18 months

• Results
  – 128 patients randomised (65 tafamidis, 63 placebo)
  – Stage 1 (mild) neuropathy
  – No evidence of tafamidis toxicity
  – 60% in tafamidis group were ‘NIS-LL responders’ vs 38% in placebo group (P=0.04)

Coelho T et al, Neurology 2012;79:785-792
Tafamidis Study
Change from Baseline in NIS-LL and mBMI

Criticisms of Study

Unvalidated endpoints of unknown clinical relevance (responder = change of <2 in NIS-LL)

BUT first drug to be licensed for treatment of amyloidosis (Pfizer)
Not funded by NICE in the UK

Coelho T et al, Neurology 2012;79:785-792
Tafamidis 12 month open label extension ‘neuropathy’ study

- Stable rate of progression (NIS-LL score) among patients who received Tafamidis in parent study
- Decline in rate of progression (NIS-LL score) among those who received placebo in parent study
- Treatment benefits greater when Tafamidis given early in disease course
- Well tolerated
- No drug-related AEs

Coelho T et al, J Neurol 2013:260;2802-2814
Patient population
- History of HF (≥1 prior hospitalization for HF or clinical evidence of HF)
- TTR amyloid cardiomyopathy
  - Mutant or WT TTR
- IVS wall >12 mm
- 6-min WT >100 m
- NYHA class <IV

2:1:2 Randomization

Primary endpoint measures
- All-cause mortality and frequency of CV-related hospitalizations to Month 30

Other endpoints
- 6-min WT, KCCQ
Figure 2. Primary Analysis and Components.
Panel A shows the results of the primary analysis as determined with the use of the Finkelstein–Schoenfeld method. Panel B shows an analysis of all-cause mortality for pooled tafamidis and for placebo, a secondary end point. Panel C shows the frequency of cardiovascular-related hospitalizations, also a secondary end point.
TTR-lowering RNAi therapy
Alnylam

Design
Phase 1 - Healthy volunteer study
Dose escalation study

Results
Plasma TTR concentration reduced by ~85%
Mild injection site reactions only toxicity

Patient Population
- hATTR amyloidosis: any TTR mutation, FAP Stage 1 or 2
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

2:1 Randomization
Patisiran 0.3 mg/kg IV q3w*

or

Placebo IV q3W*

Primary Endpoint
• Change in mNIS+7 from baseline at 18 months

Secondary Endpoints
• Norfolk QOL-DN
• NIS-weakness
• R-ODS
• 10-meter walk
• mBMI
• COMPASS-31

Select Exploratory Endpoints
• EQ-5D QOL
• NIS+7
• Serum TTR levels
• Cardiac assessments
• Grip strength
• Skin biopsies for nerve fiber density and amyloid

†Stratification factors for randomization include: neuropathy impairment score (NIS: < 50 vs. ≥ 50), early onset V30M (< 50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs. no previous tetramer stabilizer use.

*To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine).
Enrollment and Disposition

**Randomized (1:2) (N=225)**

- **Placebo (N=77)***
  - D/C Treatment (N=29; 37.7%)
    - AE 9.1%
    - Death: 5.2%
    - Progressive disease: 5.2%
    - Physician decision: 2.6%
    - Protocol deviation: 0%
    - Withdrawn by patient: 15.6%
  - Study Withdrawal (N=22; 28.6%)
  - Completed Study (N=55, 71.4%)

- **Patisiran (N=148)***
  - D/C Treatment (N=11; 7.4%)
    - AE 2.0%
    - Death: 3.4%
    - Progressive disease: 0.7%
    - Physician decision: 0%
    - Protocol deviation: 0.7%
    - Withdrawn by patient: 0.7%
  - Study Withdrawal (N=10; 6.8%)
  - Completed Study (N=138, 93.2%)

*Study populations: modified intent-to-treat (mITT) population: All patients who were randomized and received at least 1 dose of patisiran or placebo (placebo, N=77; patisiran, N=148)
Discontinued (d/c) treatment: patients who permanently stopped treatment prior to the last scheduled dose (Week 78 visit);
Discontinued (d/c) study: patients who stopped the study before any Month 18 (Week 79-80) assessments were performed
Progressive disease: patients who stopped treatment due to rapid disease progression
Rapid disease progression: patients who have ≥24-point increase in mNIS+7 from baseline [based on an average of 2 measurements] and FAP Stage progression relative to baseline at 9 months and had no major protocol deviations
Safety and Tolerability

<table>
<thead>
<tr>
<th>Type of Adverse Event, number of patients (%)</th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event (AE)</td>
<td>75 (97.4)</td>
<td>143 (96.6)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>28 (36.4)</td>
<td>42 (28.4)</td>
</tr>
<tr>
<td>Serious adverse event (SAE)</td>
<td>31 (40.3)</td>
<td>54 (36.5)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>11 (14.3)</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>AE leading to study withdrawal</td>
<td>9 (11.7)</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (7.8)</td>
<td>7 (4.7)</td>
</tr>
</tbody>
</table>
Patisiran Phase 3 APOLLO Study Results

- **Serum TTR Reduction**

  87.8% mean max serum TTR reduction from baseline for patisiran over 18 months

<table>
<thead>
<tr>
<th>TTR Change</th>
<th>Change from baseline at 9 months</th>
<th>Change from baseline at 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=77)</td>
<td>Patisiran (N=148)</td>
</tr>
<tr>
<td>Mean (SEM) Serum TTR Knockdown</td>
<td>1.5% (4.47)</td>
<td>82.6% (1.36)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=77)</td>
<td>Patisiran (N=148)</td>
</tr>
<tr>
<td>Mean (SEM) Serum TTR Knockdown</td>
<td>4.8% (3.38)</td>
<td>84.3% (1.48)</td>
</tr>
</tbody>
</table>
Patisiran Phase 3 APOLLO Study Results

Primary Endpoint: mNIS+7 change from Baseline

Better

Worse

Difference at 18 mos (Pati – PBO): -33.99
p-value: 9.26 \times 10^{-24}

LS mean (SEM) change in mNIS+7 from baseline

Baseline

9 Months

18 Months

M RM, mixed-effects model repeated measures; mITT, modified intent to treat; Pati, patisiran; PBO, placebo; CFB, change from baseline, mNIS+7 reference range: 0-304 points
Secondary Endpoint: Norfolk QOL-DN change from Baseline

Difference at 18mos (Pati – PBO): -21.1
p-value: 1.10 × 10^{-10}

MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; Pati, patisiran; PBO, placebo; CFB, change from baseline
Norfolk QOL-DN reference range: -4 to 136
mNIS+7: Change from Baseline to Month 18

Overall
Age
<65
≥65
Sex
M
F
Race
White
Non-White
Region
North America
Western Europe
Rest of World
NIS
<50
≥50
Genotype
V30M
Other
Genotype Class
Early onset V30M
All other mutations
Previous Tetramer Stabilizer Use
Yes
No
FAP Stage
1
2 & 3
Cardiac Subpopulation
Yes
No

Treatment (Patisiran – Placebo)
LS Mean Difference
95% CI
-33.99
(-39.86,-28.13)
-30.63
(-37.98,-23.28)
-38.55
(-48.27,-28.83)
-35.10
(-41.82,-28.39)
-31.72
(-44.64,-18.8)
-33.89
(-40.72,-27.05)
-33.73
(-46.49,-20.98)
-46.95
(-62.78,-31.11)
-36.80
(-45.37,-28.24)
-27.70
(-37.91,-17.49)
-28.00
(-35.51,-20.49)
-39.09
(-47.77,-30.42)
-37.10
(-44.83,-29.37)
-31.70
(-40.64,-22.77)
-22.25
(-35.9,-9.5)
-36.10
(-42.58,-29.61)
-38.30
(-46.11,-30.49)
-29.94
(-39.12,-20.77)
-29.65
(-37.4,-21.91)
-38.24
(-47,-29.49)
-37.81
(-46.73,-28.89)
TTR-lowering ‘ASOT’ (Inotersen) therapy
IONIS/AKCEA

Design

- Phase 1 - Healthy volunteer study
- Dose escalation study (SC administration)
- 4 week treatment (D1,3,8,15,22)
- 10 week FU

Results

- Full dose 300 mg
- 80% reduction in plasma TTR concentration
- Transient CRP rise, abnormal LFTs, retinol reduction
Inotersen Phase 3 NEURO-TTR: Study Design

- Randomised, placebo-controlled Phase 3 study in 172 hATTR patients with Stage I or II PN
- Once weekly SC administration of Inotersen, 300 mg
- Stratification:
  - Stage 1 versus Stage 2
  - Val30Met TTR mutation versus non-Val30Met TTR mutation
  - Previous treatment with either tafamidis or diflunisal versus no known previous treatment

- Two primary endpoints: Norfolk QoL-DN and mNIS+7
Safety Overview

- Acceptable safety and tolerability profile
- 77.7% of inotersen treated subjects completed dosing, 86.7% placebo
- 96% of Phase 3 completers enrolled in OLE
- No signal for negative effect on biochemistry, liver, red or white cells, ECG, vital signs
- No evidence of cumulative or additional toxicities with long term dosing
  - Safety profile similar in the OLE study

- Principle safety concerns related to thrombocytopenia and renal decline (potentially monitorable)
  - Thrombocytopenia (1 fatal intracranial hemorrhage from serious thrombocytopenia)
    - No serious thrombocytopenia observed following implementation of frequent monitoring
  - Renal events
  - Other SAEs: inotersen 24.1%; placebo 21.7%
mNIS+7 Primary Endpoint

Statistically significant difference was observed at both 8 months and 15 months.

Placebo Inotersen
Baseline (absolute value) 74.12 79.35
Change from baseline to month 15 25.53 5.80
Statistically significant difference was observed at both 8 months and 15 months.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Inotersen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (absolute value)</td>
<td>48.60</td>
<td>48.57</td>
</tr>
<tr>
<td>Change from baseline to month 15</td>
<td>12.67</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Hope for the heart
### Timelines & UK ‘State of Play’ with new drugs for hATTR amyloidosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>MA by FDA</th>
<th>MA by EMA</th>
<th>NICE HST Evaluation</th>
<th>EAP (Home Infusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patisiran (TTR-lowering)</strong></td>
<td>Aug 2018</td>
<td>Aug 2018</td>
<td>Nov 2018 (outcome expected 2019)</td>
<td>(n=32 in UK)</td>
</tr>
<tr>
<td><strong>Inotersen (TTR-lowering)</strong></td>
<td>July 2018</td>
<td>Oct 2018</td>
<td>Nov 2018 (outcome expected 2019)</td>
<td></td>
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<tr>
<td><strong>Tafamidis (Stabiliser)</strong></td>
<td></td>
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<tr>
<td><strong>Diflunisal (Stabiliser)</strong></td>
<td></td>
<td></td>
<td></td>
<td>(but supplies unreliable)</td>
</tr>
<tr>
<td><strong>AG10 (new Stabiliser)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Phase 3 clinical trial in cardiac ATTR amyloidosis to start shortly</td>
</tr>
</tbody>
</table>
Summary

• Exciting times in ATTR amyloidosis

• Several drugs in late phase development
  – TTR-lowering therapy for hATTR amyloidosis with PN
  – Stabilizers for cardiac ATTR amyloidosis (soon in EAP)

• TTR-lowering (?2\textsuperscript{nd} generation) to be tested in cardiac ATTR amyloidosis

• Combination therapy with TTR-lowering + TTR Stabiliser is (theoretically) attractive
Acknowledgements

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Hadija Trojer
Ania Zaremba

Statistics
Aviva Petrie

Colleagues referring and treating patients