hATTR Amyloidosis and Patisiran

R&D Day 2016
Overview of Transthyretin amyloid (ATTR) amyloidosis

Ole B Suhr, Professor, M.D.
Department of Public Health and Clinical Medicine
Umeå University and University Hospital
Umeå, Sweden.
HereditaryATTR Amyloidosis
(Familial amyloidosis with polyneuropathy, or FAP)


Araki S et al. 1968 Arch Neurol. Chic) 18: 593 (picture courtesy of Ando Y)
## In search of the protein (1980)

<table>
<thead>
<tr>
<th>Amyloid fibril</th>
<th>Preliminary term</th>
<th>Chemical designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light chain protein</td>
<td>AL</td>
<td>A(\lambda)</td>
</tr>
<tr>
<td>A protein</td>
<td>AA</td>
<td>AA (prototype)</td>
</tr>
<tr>
<td>Familial</td>
<td></td>
<td>A protein name</td>
</tr>
<tr>
<td>Portuguese</td>
<td></td>
<td>A protein name</td>
</tr>
<tr>
<td>Japanese, etc.</td>
<td></td>
<td>A protein name</td>
</tr>
<tr>
<td>Endocrine tissue related thyroid, etc.</td>
<td></td>
<td>A protein name</td>
</tr>
<tr>
<td>‘Senile’ amyloid</td>
<td></td>
<td>A protein name</td>
</tr>
<tr>
<td>cardiac brain</td>
<td></td>
<td>A protein name</td>
</tr>
<tr>
<td>Cutaneous (dermal) amyloid</td>
<td></td>
<td>A protein name</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>A protein name</td>
</tr>
</tbody>
</table>
Transthyretin (prealbumin)\textsuperscript{1,2}

Produced by the liver (brain, eye).

- **Hereditary forms of transthyretin amyloidosis** (more than 130 mutations described)\textsuperscript{3}
- **Senile systemic amyloidosis**\textsuperscript{4} wild type TTR

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» Nervous
   - Autonomic-somatic neuropathy
   - Central nervous symptoms

» Cardiac
   - Arrhythmia
   - Cardiomyopathy

» Gastrointestinal

» Kidney

» Eyes

» Misc: Charcot joint, carpal tunnel syndrome

Pictures courtesy of: Andersson R, Westermark P, and Ando Y.
Case report

» Woman of African descent

» At the age of 33 breast cancer, operated, recurrence at the age of 36, re-operated. Heart enlargement noted

» At the age of 39, onset of diarrhea, nausea, and vomiting, nutritional problems receive an endoscopic gastro-enterostomy. Develops faecal incontinence

» At the age of 41, disabling pain and progressive neuropathy

» At the age of 42, cardiac arrest, resuscitated by husband, receives a pacemaker.

» Biopsy: TTR-amyloidosis

» Gene testing: Ala45Gly
Evaluation at our centre:

» Positive bone scintigraphy for amyloidosis.
» Wheelchair bound, **advanced autonomic neuropathy**
» **Adrenal insufficiency**
» Too advanced disease for Tafamidis treatment

Treatment:
Does not tolerate Diflunisal
Heart/liver transplantation discussed, but dies after a new cardiac arrest at the age of 42
Survival estimated to between 3 and 15 years from onset of symptoms

Epidemiology of hATTR Amyloidosis with Polyneuropathy

Estimated 10-15,000 afflicted patients worldwide¹

<table>
<thead>
<tr>
<th>Country</th>
<th>~ Number of Cases of hATTR with Polyneuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>3200²</td>
</tr>
<tr>
<td>Portugal</td>
<td>2000³</td>
</tr>
<tr>
<td>Sweden</td>
<td>250³</td>
</tr>
<tr>
<td>Rest of EU-27</td>
<td>4500⁴</td>
</tr>
<tr>
<td>Brazil</td>
<td>&gt;600⁵</td>
</tr>
<tr>
<td>Japan</td>
<td>400⁶</td>
</tr>
</tbody>
</table>

◆ Steady increase of new mutations in the Swedish population (10 mutations during the last 10 years); likely related to increased disease awareness

² Estimated based on prevalence of ~1/100,000 (Benson. Amyloidosis. In Metabolic and Molecular Basis of Inherited Disease. New York: McGraw-Hill;2000;5345–78);  
⁴ Estimated based on prevalence of ~1/100,000 (Adams et al. Curr Neurol Neurosci Rep 2014;14:435)  
⁵ Center for Studies of Paramyloidosis Antonio Rodrigues de Mello (CEPARM) (http://ceparm.com/en/ceparm/recent-findings/);  
Suggested pathway for amyloid formation\(^1\), and possible treatments

1. Halt production of circulating mutant TTR: Liver transplantation\(^2\)
2. Decrease production of circulating TTR: Gene silencing\(^3,4\)
3. Stabilise the TTR tetramer: Diflunisal, Tafamidis \(^5,6\)
4. Removal of Amyloid deposits: antibodies, Doxycycline \(^7,8\)

None of the available treatments address CNS or eye complications

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Factors related to amyloid fibril formation

» Concentration of amyloidogenic protein. The amyloid fibril formation process is concentration dependent\(^1\)

» Mutant protein decreases stability\(^2\)

» Age:
  – Decreased efficacy of the immune system: antibody formation against misfolded protein\(^3\)
  – Decreased efficacy of housekeeping system for misfolded proteins\(^4\)

Importance of the concentration of the amyloidogenic protein: Regression of amyloid AA-amyloidosis

Henning Waldenström, Acta Chir Scandinavia Vol LXIII (1928)
From the department of surgical tuberculosis at St. Görans' Hospital, Stockholm, Sweden

Case III

Liver size
Outline by ink

16/3 -25
+++ hist.

1/4 -25
3%
Proteinuria
1. Liver transplantation for ATTR amyloidosis

» Why perform liver transplantation and exchange a healthy liver?

– To decrease - eliminate the production of the amyloidogenic mutated transthyretin.

First liver transplanted ATTR amyloidosis patient.

Patient survival (%)

Years after transplantation

- All TTR mutations (n=2044)
- Val30Met - Early onset
- Val30Met - Late onset
- Non-Val30Met - Early onset
- Non-Val30Met - Late onset

3. TTR Stabiliser: Tafamidis/Diflunisal

Tafamidis trial: Efficacy in per protocol analysis, but deterioration on group level with time. Efficacy only shown for ATTR Val30Met amyloidosis patients in stage I (walking without support)\(^1,2,3\). Tafamidis is not approved in the US.

Diflunisal trial: efficacy over 24 months demonstrated in a Phase 3 study, but deterioration noted in treated patients. Long-term outcome unknown. Not indicated for hATTR amyloidosis.

Lack of efficacy of current treatments? additional pathways for ATTR formation?

The majority of ATTR amyloidosis patients currently without effective treatment, a considerable unmet medical demand

Conclusions

» Currently, only a minor proportion of patients have a mutation/disease stage/phenotype that is suitable for available treatments.

» Decrease production of the amyloidogenic protein (TTR), a promising therapeutic method that appears not to depend on amyloid formation pathways.

» However, no treatments are able to depress the amyloid formation caused by local TTR production in the eye or brain.
Thank You!
Patisiran

Akshay K. Vaishnaw
Executive Vice President, R&D and Chief Medical Officer
Hereditary ATTR Amyloidosis (hATTR)

**DESCRIPTION**

Orphan disease caused by mutant transthyretin (TTR) amyloid deposits in nerves, heart, gastrointestinal tract, and other tissues

**PATIENT POPULATION**

~50,000 worldwide

Significant morbidity and fatal within 2-15 years from symptom onset

hATTR Amyloidosis with polyneuropathy: 10,000
hATTR Amyloidosis with cardiomyopathy: 40,000

*Ando et al., Orphanet J Rare Dis, 2013; Ruberg et al., Circulation, 2012*
Hereditary ATTR Amyloidosis with Polyneuropathy
Inexorably Progressive Fatal Disease

Photos courtesy of Yukio Ando (Japan)
Patisiran: Simple Approach to Treating a Complex Disease
Shutting Off Production of Disease-Causing Protein

Production of mutant and wild type TTR

Unstable circulating TTR tetramers reduced

Organ deposition of monomers, amyloid (β-pleated) fibril prevented, clearance promoted

Neuropathy, cardiomyopathy stabilization or improvement

Liver transplantation stops mutant TTR production

Patisiran acts to knock down both mutant and wild type TTR production

Tafamidis stabilizes TTR tetramer
Patisiran Phase 2 OLE Study Design

**hATTR-PN patients previously dosed on Phase 2 trial eligible to roll over onto Phase 2 OLE study**

- Up to 2 years of dosing, 0.30 mg/kg every 3 weeks, with clinical endpoints evaluated every 6 months
- Primary objectives: Safety and tolerability of long-term dosing with patisiran
- Secondary objectives: Effects on neurologic impairment (mNIS+7 and NIS), quality of life, mBMI, disability, mobility, grip strength, autonomic symptoms, nerve fiber density in skin biopsies, cardiac involvement (in cardiac subgroup), serum TTR levels

**Timelines are not to scale**
**Patisiran Phase 2 OLE Preliminary Study Results**

**Serum TTR Knockdown**

- Mean serum pre-dose TTR knockdown of approximately 80%
- Mean serum TTR knockdown at 24 months of 84%
- Mean maximal serum post-dose TTR knockdown of 93%
- Maximal individual patient post-dose knockdown of 97%
- Similar TTR knockdown in patients on patisiran alone or on patisiran + TTR tetramer stabilizers

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**Graph Details**

- N=24-27 at all other time points
- N=23
- N=22
- N=21

**Graph Title:**

Mean \(\pm\) SEM % Serum TTR Knockdown Relative to Baseline

**Graph Labels:**

- **X-axis:** Months
- **Y-axis:** Mean \(\pm\) SEM % Serum TTR Knockdown

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*SEM: Standard Error of the Mean
*Suhr et al., ISA, July 2016; Data as of 12May2016
Patisiran Phase 2 OLE Preliminary Study Results* Change in mNIS+7 Over 24 Months

*Suhr et al., ISA, July 2016; Data as of 12May2016

Partial imputation was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit)
Patisiran Phase 2 OLE Preliminary Study Results*

Change in mNIS+7 Over 24 Months

*Suhr et al., ISA, July 2016; Data as of 12May2016

Partial imputation was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit)
Patisiran Phase 2 OLE Preliminary Study Results*
Change in mNIS+7 at 24 Months

17 out of 24 patients (71%) with no change or an improvement in mNIS+7 at 24 months compared to baseline

Mean ΔmNIS+7 from baseline at 24mos

SEM: Standard Error of the Mean
~ Assessments drawn from studies in patients with similar baseline neurologic impairment and not based on head-to-head studies
1Adams D et al., Neurology. 85;675-682 (2015); 2Predicted progression of median NIS value from Gompertz curve fit
2Berk JL et al., JAMA. 310:2658-67 (2013); 3Linear interpolation from 2-year NIS progression measurement in longitudinal analysis set
† Patisiran results similar in patients with/without concurrent TTR stabilizer therapy; mNIS+7 using full mNIS+7 set; partial imputation was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit)
*Suhr et al., ISA, July 2016; Data as of 12May2016

Individual ΔmNIS+7 at 24mos in Patisiran Ph 2 OLE

Mean (SEM) ΔmNIS+7 from baseline at 24mos~

Mean ΔmNIS+7 Across hATTR Studies at 24 mos~

Patisiran Ph 2 OLE† (N=24)

Placebo (N=66)

Diflunisal (N=64)

Diflunisal Ph 3 Study\(^2\)

Natural History (nonlinear; N=283)\(^1\)

-35 -30 -25 -20 -15 -10 -5 0 5 10 15 20 25 30

-35 -30 -25 -20 -15 -10 -5 0 5 10 15 20 25 30

25.8 (9.4)

29.6 (3.1)

9.2 (2.7)

-6.7 (2.3)
Patisiran Phase 2 OLE Preliminary Study Results*
Correlation of TTR Knockdown with ΔmNIS+7

Note: three patients had missing D17 TTR: one was replaced by D7 and two replaced by D84.
†Percent (%) TTR knockdown from baseline at Day 17 post-first dose of patisiran
*Coelho et al., ISA, July 2016; Data as of 12May2016
Patisiran Phase 2 OLE Preliminary Study Results*
Sweat Gland Nerve Fiber Density (SGNFD): Lower Limb

- Blinded analysis of tandem skin punch biopsies performed at central lab
- Statistically significant increase in distal thigh SGNFD at 12, 18, and 24 months and distal leg SGNFD at 24 months
- In a separate study in hATTR polyneuropathy patients with highly pathogenic A97S mutation, SGNFD correlated to autonomic system involvement and disability burden

*Suhr et al., ISA, July 2016; Data as of 12May2016

1Chao C et al., Ann Neurol. 78:272-83 (2015)
22-sided p values from paired t-test comparing post-baseline vs baseline

Distal thigh sweat gland innervation† in Patient 010-0004

†Green: PGP 9.5 (nerve fibers)
Red: CD31 (blood vessels)
Blue: DAPI (nuclei)
Patisiran Phase 2 OLE Preliminary Study Results*
Summary of Safety and Tolerability

Common Adverse Events (AEs) in ≥10% of patients

<table>
<thead>
<tr>
<th>AE by Preferred Term</th>
<th>Patisiran (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>Wound</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>3 (11.1%)</td>
</tr>
</tbody>
</table>

- 6 patients (22.2%) with 9 reports of serious adverse events (SAEs); not related to study drug
  - One discontinuation for gastroesophageal cancer at ~20 months; patient subsequently died
  - One death due to myocardial infarction after patient completed 24 months of treatment
  - One patient with 3 reports (distal femur fracture/proximal tibia fracture/osteonecrosis/ligament rupture, dehydration/acute prerenal failure/urinary tract infection and thermal burn); one patient with 2 reports (ankle fracture/foot fracture/osteonecrosis and ankle arthrodesis); one patient with venous thrombosis of the lower limb; one patient with foot abscess and osteomyelitis
- Majority of AEs were mild or moderate
  - 4 patients (14.8%) had severe AEs not related to study drug
  - Most common related AEs reported in > 3 patients were flushing (6 patients [22.2%]) and infusion related reaction (5 patients [18.5%]), all of which were mild
- No clinically significant changes in liver function tests, renal function, or hematologic parameters, including platelets

*Suhr et al., ISA, July 2016; Data as of 12May2016
Phase 3 Study Design

Enrollment Complete

N=225

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

2:1 RANDOMIZATION

Patisiran IV q3W 0.3 mg/kg
OR
Placebo IV q3W

Primary Endpoint at 18 months
- mNIS+7

Key Secondary Endpoints
- Norfolk QOL-DN
- NIS-weakness
- mBMI
- 10-meter walk

All completers eligible for patisiran treatment on Phase 3 OLE study (APOLLO-OLE)

Enrollment completed; mid-2017 data readout, supporting 2017 NDA/MAA if positive

APOLLO DMC met October 7, 2016 at Company’s request and recommended continuing Phase 3 study of patisiran in patients with hATTR amyloidosis without modification
APOLLO Patisiran Phase 3 Study
Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>N=225</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>62 years (24-82)</td>
</tr>
<tr>
<td>Gender, n (%) males</td>
<td>167 (74)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>51 (23)</td>
</tr>
<tr>
<td>Black/African or African American</td>
<td>6 (3)</td>
</tr>
<tr>
<td>White / Caucasian</td>
<td>162 (72)</td>
</tr>
<tr>
<td>Other/Missing</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Previous tetramer stabilizer use, n (%)</td>
<td>119 (53)</td>
</tr>
<tr>
<td>mBMI, kg/m² x albumin [g/dL]</td>
<td>978.7 (522.1-1530.0)</td>
</tr>
<tr>
<td>Patients with cardiac involvement, n (%)</td>
<td>122 (54)</td>
</tr>
<tr>
<td>Mean NT-proBNP, ng/L (range)</td>
<td>1461 (40-7895)</td>
</tr>
<tr>
<td>Mean troponin, ng/mL (range)</td>
<td>0.1 (0.1-1.0)</td>
</tr>
<tr>
<td>LV wall thickness, cm (range)</td>
<td>1.67 (1.3, 2.6)</td>
</tr>
<tr>
<td>Ejection fraction (range)</td>
<td>60.6 (31.8, 82.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR genotype, n (%)</td>
<td></td>
</tr>
<tr>
<td>V30M</td>
<td>95 (42)</td>
</tr>
<tr>
<td>nonV30M*</td>
<td>130 (58)</td>
</tr>
<tr>
<td>FAP Stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>104 (46)</td>
</tr>
<tr>
<td>2</td>
<td>119 (53)</td>
</tr>
<tr>
<td>3</td>
<td>2 (1)</td>
</tr>
<tr>
<td>PND Score, n (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>57 (25)</td>
</tr>
<tr>
<td>II</td>
<td>65 (29)</td>
</tr>
<tr>
<td>IIIA</td>
<td>63 (28)</td>
</tr>
<tr>
<td>IIIB</td>
<td>38 (17)</td>
</tr>
<tr>
<td>IV</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Neuropathy Impairment Scores, mean (range)</td>
<td></td>
</tr>
<tr>
<td>mNIS+7</td>
<td>78.8 (8.0-165.0)</td>
</tr>
<tr>
<td>NIS</td>
<td>59.3 (6.0-141.6)</td>
</tr>
</tbody>
</table>

†Represents 57 different mutations, including GLU-89-GLN (n=13); THR-60-ALA (n=13); ALA-97-SER (n=15); SER-50-ARG (n=8); as well as numerous other mutations with ≤5 patients per group
*Adams et al., ISA, July 2016; Data as of 01 March 2016
## Patient Advocacy & Scientific Leadership

### Patient Advocacy

- Implementation of Alnylam Assist to help improve diagnosis rates
  - Free third-party genetic screening and counseling programs
  - >900 individuals tested over past 2 years
- Invited to attend >25 patient meetings over past 2 years

### Education

- 15 primary abstracts and publications since 2013
- Attendance at >30 congresses and >2000 peer engagements
- Symposia and facilitation of dialogue among specialists to increase awareness of disease burden

### Collaboration

- Initiation of Expanded Access Program (EAP)
- Numerous pre-clinical and clinical investigator-initiated studies to date (IIS)
hATTR Amyloidosis Market Landscape

Limited available therapies; no approved drugs that halt disease progression and improve patient quality of life

- **US**: No approved drugs; limited use of diflunisal
- **EU**: tafamidis approved for Stage 1 polyneuropathy patients only; limited access (e.g., not reimbursed in UK)
  - Some patients receiving tafamidis may experience worsening of symptoms, often within first year of treatment
  - Multiple studies that document disease progression during tafamidis treatment
- Orthotopic liver transplantation (OLT) use declining worldwide
  - Generally limited to younger patients with V30M mutation
  - Involves significant risks and may still result in disease progression
- Few investigational therapies in clinical development

### Cortese et al. Study Results

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline NIS-LL</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Month 18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>61</td>
<td>+4.5 (62% of patients)</td>
<td>+5.9 (65% of patients)</td>
<td>+8.0 (65% of patients)</td>
</tr>
</tbody>
</table>

Cortese A. J Neurol. 2016 Mar 16;
Randomized controlled trial in 61 patients with hATTR Amyloidosis
NIS-LL = neuropathy impairment score-lower limb

NIS-LL = neuropathy impairment score-lower limb
hATTR Amyloidosis Market Opportunity

~50,000 patients WW

- Some mutations endemic to certain regions
- Often misdiagnosed due to heterogeneity of disease
  - Variable disease penetrance, age of onset, symptoms at presentation, and comorbidities

Patisiran has potential to address unmet medical needs

- Evidence for potential halting or improvement of neuropathy in Phase 2 OLE study
- APOLLO Phase 3 study will evaluate mNIS+7 and multiple QOL secondary endpoints
- Ongoing support for programs to improve diagnosis rates and enable earlier intervention

Patisiran Program Summary & Next Steps

Current therapies for hATTR Amyloidosis insufficient to meet patient needs; unmet medical need remains
- Progressive sensorimotor and autonomic neuropathy, cardiomyopathy; often fatal within 10 years
- Primary treatment option is liver transplantation
- No approved therapies in US
- Published evidence of disease progression on TTR stabilizers

Phase 2 OLE continues to provide preliminary evidence of acceptable safety profile and clinical activity at 24 months

APOLLO Phase 3 Ongoing
- Phase 2 Open-Label Extension (OLE) study has completed; majority of patients rolled onto APOLLO-OLE study
- APOLLO top-line expected in mid-2017; results in late 2017
- Assuming positive outcome, NDA/MAA filings expected year-end 2017

Preparing for commercialization following approval in US, Canada, Western Europe
- Preparing for ROW commercialization with Sanofi Genzyme following ROW approvals