Cardiac Amyloidosis: early diagnosis and novel treatments

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Saint Luke’s
MID AMERICA HEART INSTITUTE
Disclosures

- Pfizer – grant support, speaker, and consultant
- Alnylam – consultant
Objectives

- Review epidemiology and workup of cardiac amyloidosis
- Systemic manifestations
- Common misconceptions
- Examine novel treatment strategies in ATTR amyloidosis
Case

- 70 year old white male
- Symptoms of leg swelling and dyspnea with recent HF admission

<table>
<thead>
<tr>
<th>2D ECHO MEASUREMENTS</th>
<th></th>
<th></th>
<th>LVPW Diastolic Thickness</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>LV Diastolic Diameter Base LX</td>
<td>5.1 cm</td>
<td>3.6-5.4</td>
<td>1.4 cm</td>
<td>0.6-1.1</td>
<td></td>
</tr>
<tr>
<td>LV Systolic Diameter Base LX</td>
<td>4.3 cm</td>
<td>2.3-4.0</td>
<td>LVOT Diameter</td>
<td>2.1 cm</td>
<td></td>
</tr>
<tr>
<td>LA Systolic Diameter LX</td>
<td>5.6 cm</td>
<td>2.3-3.8</td>
<td>Aorta at Sinuses Diameter</td>
<td>3.4 cm</td>
<td>2.1-3.5</td>
</tr>
<tr>
<td>IVS Diastolic Thickness</td>
<td>1.5 cm</td>
<td>0.6-1.1</td>
<td>Ascending Aorta Diameter</td>
<td>4.2 cm</td>
<td>2.1-3.4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>DOPPLER</th>
<th></th>
<th></th>
<th>LVOT AV Vel Ratio</th>
<th>0.71</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AV Peak Velocity</td>
<td>104 cm/s</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>AV Peak Gradient</td>
<td>4.3 mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TRICUSPID VALVE DOPPLER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV Systolic Pressure</td>
<td>32.7 mmHg</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
What is amyloidosis?

- Protein misfolding disorder

Diagram:
- Normally-Folded Protein
- Misfolded (Amyloid) Protein
- Protofilaments
- Amyloid Fibril
Over 30 Amyloidogenic Proteins

<table>
<thead>
<tr>
<th>Amyloid protein</th>
<th>Precursor</th>
<th>Distribution</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>Immunoglobulin light chain</td>
<td>Systemic/localised</td>
<td>Primary/myeloma associated</td>
</tr>
<tr>
<td>AH</td>
<td>Immunoglobulin heavy chain</td>
<td>Systemic/localised</td>
<td>Primary/myeloma associated</td>
</tr>
<tr>
<td>AA</td>
<td>Serum amyloid A</td>
<td>Systemic</td>
<td>Secondary</td>
</tr>
<tr>
<td>Aβ Microglobulin</td>
<td>β2 Microglobulin</td>
<td>Systemic</td>
<td>Secondary</td>
</tr>
<tr>
<td>ATTR</td>
<td>Transthyretin</td>
<td>Systemic/localised</td>
<td>Senile systemic/familial</td>
</tr>
<tr>
<td>AANF</td>
<td>Atrial natriuretic factor</td>
<td>Localised</td>
<td>Atrial isolated</td>
</tr>
<tr>
<td>AApoA-I</td>
<td>Apolipoprotein A-I</td>
<td>Localised/systemic</td>
<td>Aortic/familial</td>
</tr>
<tr>
<td>AApoA-II</td>
<td>Apolipoprotein A-II</td>
<td>Systemic</td>
<td>Familial</td>
</tr>
<tr>
<td>Amel</td>
<td>Lactadherin</td>
<td>Localised</td>
<td>Aortic</td>
</tr>
<tr>
<td>Agel</td>
<td>Gelsolin</td>
<td>Systemic</td>
<td>Familial</td>
</tr>
<tr>
<td>Alyes</td>
<td>Lysozyme</td>
<td>Systemic</td>
<td>Familial</td>
</tr>
<tr>
<td>Afib</td>
<td>Fibrinogen α chain</td>
<td>Systemic</td>
<td>Familial</td>
</tr>
<tr>
<td>Acys</td>
<td>Cystatin C</td>
<td>Systemic</td>
<td>Familial</td>
</tr>
<tr>
<td>Aβ</td>
<td>Aβ Protein precursor</td>
<td>Localised</td>
<td>Alzheimer’s disease, aging</td>
</tr>
<tr>
<td>AprP</td>
<td>Prion protein</td>
<td>Localised</td>
<td>Spongiform encephalopathies</td>
</tr>
<tr>
<td>Abri</td>
<td>ABri protein precursor</td>
<td>Localised</td>
<td>Familial dementia</td>
</tr>
<tr>
<td>Acal</td>
<td>(Pro)calcitonin</td>
<td>Localised</td>
<td>Thyroid tumours derived from C cells</td>
</tr>
<tr>
<td>AIAAPP</td>
<td>Islet amyloid polypeptide</td>
<td>Localised</td>
<td>Langerhans islets, insulinomas</td>
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<tr>
<td>Apro</td>
<td>Prolactin</td>
<td>Localised</td>
<td>Prolactinomas, pituitary in elderly</td>
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<tr>
<td>Ains</td>
<td>Insulin</td>
<td>Localised</td>
<td>Iatrogenic</td>
</tr>
<tr>
<td>Aker</td>
<td>Kerato-epithelin</td>
<td>Localised</td>
<td>Familial, cornea</td>
</tr>
<tr>
<td>Alac</td>
<td>Lactoferrin</td>
<td>Localised</td>
<td>Familial, cornea</td>
</tr>
</tbody>
</table>

Proteins involved in the cardiovascular system are in bold.
Pathology: Diffuse involvement

- Increase in LV mass without dilatation
- Atrial infiltration impairing atrial contraction
- Conduction system / valves
- Microvascular ischemia
Normal heart

Cardiac amyloid
HCM

Amyloid

HTN heart w/ renal failure

Fabry disease
2 Main Types of Systemic Amyloidosis

- **AL**
  - Light chain amyloidosis

- **ATTR**
  - Transthyretin amyloidosis

**AA < 5%**
- Isolated atrial (ANF)
- Apolipoprotein A1
- Other hereditary
Which type of amyloidosis is this?

AL Amyloidosis

ATTR Amyloidosis
Why do you need to tell the amyloid subtype?

Different treatments
Different prognosis
Genetic component
Prognosis and treatment in amyloidosis

(A) Survival of ATTR and AL amyloidosis patients over time to mortality (years).

(B) Survival comparison between treated and untreated ATTR and AL amyloidosis patients.

Source: J Am Heart Assoc. 2016 Subtype-Specific Prognosis in Cardiac Amyloidosis Sperry et al
2 Types of Amyloid that Affect the Heart

AL

Light chain amyloidosis
Immunoglobulins
i.e. antibodies

Free kappa+lambda light chains
Serum immunofixation
Urine immunofixation
SPEP/UPEP

SPEP
MGUS

Waldenstrom Macroglobulinemia

Multiple Myeloma

AL Amyloidosis

20%

IgM MGUS

Light chain MGUS

Non-IgM MGUS
Serum Free-Light Chain Assay
- Useful for Diagnosis, Prognosis, Response

**Principle**

Free kappa+lambda light chains serum
Serum immunofixation
Urine immunofixation 99%
2 Types of Amyloid that Affect the Heart

- **ATTR**
  Transthyretin amyloidosis

- Wild type or Mutant
Transthyretin (TTR) "Prealbumin"

Transport protein for thyroxine and retinol

Homotetramer: 4 identical monomers 127 amino acids each
> 100 mutations described: single amino acid substitutions
**ATTRwt** = amyloid transthyretin wild type

“Wild type transthyretin amyloidosis”
“Senile systemic amyloidosis” (SSA)
“Senile cardiac amyloidosis”
Median age 73
Bilateral carpal tunnel / spinal stenosis common
*Median survival about 4 years*

**ATTRm** = amyloid transthyretin mutant

“Hereditary transthyretin amyloidosis”
“Familial amyloid cardiomyopathy (FAC)
“Familial amyloid polyneuropathy (FAP)
Age of onset different depending upon mutation
*Most common mutation V122I seen in 3.5% AA*
*Median survival for V122I mutation 2.5 years*

*Quarta, NEJM 2015*
Familial Amyloid Cardiomyopathy = FAC

112+ mutations causing disease

“Neurologic” Phenotype “Cardiac”
**AL**
- Age 40s-70s
- Men = women
- Proteinuria
- Macroglossia, periorbital purpura, petechiae
- Carpal tunnel syndrome
- Orthostatic hypotension
- GI involvement (diarrhea)

**ATTR**
- Age 60s-80s
- Men > women
- African Americans (V122I mutation)
- HFpEF
- Low-flow low-gradient AS
- Bilateral carpal tunnel syndrome
- Spinal stenosis
- Peripheral neuropathy (in some variants)
Non cardiac manifestations

• Polyneuropathy
  • Small fiber neuropathy most common
  • Carpal tunnel syndrome

• Autonomic neuropathy
  • Hypotension, orthostatic hypotension
  • GI motility issues

• Tendon/ligament issues
  • Carpal tunnel syndrome
  • Biceps tendon rupture
  • Trigger finger
  • Spinal stenosis
• 98 patients
• 12% of men ≥ 50 and women ≥ 60 years old with bilateral carpal tunnel syndrome undergoing carpal tunnel release had amyloid deposits in the wrist
• 2 had previously unknown cardiac involvement
• 1 had previously unknown hATTR neuropathy (Leu58His)
• 1 had Ala81Thr mutation without cardiac or neuropathic involvement
Tenosynovial and Cardiac Amyloidosis in Patients Undergoing Carpal Tunnel Release

Brett W. Sperry, MD, a,b Bryan A. Reyes, MD, c Asad Ikram, MBBS, a Joseph P. Donnelly, MD, a Dermot Phelan, MD, PhD, b Wael A. Jaber, MD, a David Shapiro, MD, c Peter J. Evans, MD, PhD, c Steven Maschke, MD, c Scott E. Kilpatrick, MD, d Carmela D. Tan, MD, d E. Rene Rodriguez, MD, d Cecilia Monteiro, MD, e W.H. Wilson Tang, MD, a Jeffery W. Kelly, PhD, a William H. Seitz, Jr, MD, c Mazen Hanna, MD a
Non cardiac manifestations

• Renal
  • Proteinuria
  • Nephrotic syndrome

• Gastrointestinal
  • Liver infiltration
  • Autonomic GI neuropathy
  • Direct GI mucosal infiltration
Clinical Susicion of Cardiac Amyloidosis

Serum Free Light Chain (sFLC) Ratio
- Serum Immunofixation
- Urine Immunofixation

$^{99m}$TcPyrophosphate Scan

AL
- Abnormal sFLC ratio
  - High ($>1.65$) = kappa ($\kappa$)
  - Low ($<0.26$) = lambda ($\lambda$)
- M-protein spike on immunofixation
- Grade 0 or 1 Myocardial $^{99m}$TcPYP Uptake (none or less than bone)

ATTR
- Normal sFLC ratio
  - No M-protein spike on immunofixation
  - Grade 2 or 3 Myocardial $^{99m}$TcPYP Uptake (equal to or greater than bone)

Endomyocardial biopsy with LC/MS for typing
- Diagnostic Gold Standard

Bone marrow biopsy to confirm & quantify plasma cell clone

Genetic testing to determine mutation or wild-type

LC/MS = liquid chromatography/mass spectrometry
# Red Flags for Cardiac Amyloidosis

**Echocardiography:**
- Low voltage on ECG and thickening of the septum/posterior wall > 1.2 cm
- Thickening of right ventricle free wall, valves

- Intolerance to beta-blockers or ACE inhibitors
- Low normal blood pressure in patients with a previous history of hypertension
- History of bilateral carpal tunnel syndrome, often requiring surgery

<table>
<thead>
<tr>
<th>AL</th>
<th>ATTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HfPef</td>
<td>White male age ≥ 60 with HfPef</td>
</tr>
<tr>
<td></td>
<td>+ history of carpal tunnel syndrome and/or spinal stenosis</td>
</tr>
<tr>
<td></td>
<td>African American age ≥ 60 with HfPef</td>
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<tr>
<td></td>
<td>without a history of hypertension</td>
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<tr>
<td></td>
<td>New diagnosis of hypertrophic cardiomyopathy in an elderly patient</td>
</tr>
<tr>
<td></td>
<td>New diagnosis of low flow, low gradient aortic stenosis in an elderly patient</td>
</tr>
<tr>
<td></td>
<td>Family history of ATTRm amyloidosis</td>
</tr>
<tr>
<td>Macroglia and/or periorbial purpura</td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td>MGUS</td>
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</tr>
</tbody>
</table>
Pseudoinfarct pattern, Low voltage *
Echo – wall thickness

2D ECHO MEASUREMENTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bas 4.3 cm</th>
<th>3.6-5.4</th>
<th>1.9 cm</th>
<th>0.6-1.1</th>
<th>3 cm</th>
<th>2.3-4.0</th>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV Systolic Diameter Base</td>
<td>3 cm</td>
<td>2.1-3.5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aorta at Sinuses Diameter</td>
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<td>LA Systolic Diameter LX</td>
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<td>2.3-3.8</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ascending Aorta Diameter</td>
<td>3.2 cm</td>
<td>2.1-3.4</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>IVS Diastolic Thickness</td>
<td>1.8 cm</td>
<td>0.6-1.1</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Phelan, Sperry et al. AJC 2017
Echo
Apical Sparing Pattern: “Relative strain”

Relative apical strain = 14 / 5 = 2.8
Clinical Suspicion of Cardiac Amyloidosis

Serum Free Light Chain (sFLC) Ratio

Urine Immunofixation

Serum Immunofixation

$^{99m}$TcPyrophosphate (tCtPYP) Scan

AL

Abnormal sFLC ratio
High ($>1.65$) = kappa ($\kappa$)
Low ($<0.26$) = lambda ($\lambda$)

M-protein spike on immunofixation

Grade 0 or 1 Myocardial $^{99m}$TcPYP Uptake (none or less than bone)

ATTR

Normal sFLC ratio

No M-protein spike on immunofixation

Grade 2 or 3 Myocardial $^{99m}$TcPYP Uptake (equal to or greater than bone)

Endomyocardial biopsy with LC/MS for typing
Diagnosis Gold Standard

Bone marrow biopsy to confirm & quantify plasma cell clone

Genetic testing to determine mutation or wild-type

LC/MS = liquid chromatography/mass spectrometry
Bone Scintigraphy enables the diagnosis of ATTR to be made reliably without the need for histology in patients who do not have a monoclonal gammopathy.
Perugini score

0 – absent uptake - NEGATIVE
1 – less than rib – INDETERMINATE
2 – equal to rib – LIKELY POSITIVE
3 – greater than rib – POSITIVE
Clinical Suspicion of Cardiac Amyloidosis

Serum Free Light Chain (sFLC) Ratio
Serum Immunofixation
Urine Immunofixation

AL
Abnormal sFLC ratio
High (>1.65) = kappa (κ)
Low (<0.26) = lambda (λ)
M-protein spike on immunofixation
Grade 0 or 1 Myocardial $^{99mTc}$PYP Uptake
(equal to or less than bone)

Endomyocardial biopsy with LC/MS for typing
Diagnostic Gold Standard

Bone marrow biopsy
+ Fat pad biopsy

ATTR
Normal sFLC ratio
No M-protein spike on immunofixation
Grade 2 or 3 Myocardial $^{99mTc}$PYP Uptake
(to determine mutation or wild-type)

Genetic testing

LC/MS = liquid chromatography/mass spectrometry
Congo red –

Apple green birefringence

H&E

Thioflavin-S

Amyloid Kappa

Fringence

Thiochrome
MUST SUBTYPE THE AMYLOID!!

Congo Red only tells you if it is amyloid
(What type, AL? TTR?, other?)

- Prognosis
- Treatment

Immunofluorescence

Mass Spectrometry
Common misconceptions

• Rare
  • 13% of patients admitted with HFpEF and septal thickness >12mm
  • 16% of patients undergoing TAVR (22% of men undergoing TAVR)
  • 30% of patients with LFLG AS with EF <50%
  • 12% of men ≥ 50 and women ≥ 60 years old with bilateral carpal tunnel syndrome undergoing carpal tunnel release

EHJ (2015) 36, 2585-2594
Castano et al EHJ 2017
Treibel et al Circ Imaging 2016
Sperry et al JACC 2018
Common misconceptions

• Rare
  • Under-appreciated and under-recognized cause of HFpEF

• Low voltage on ECG is a good screening test
Cyrille, Maurer et al. AJC 2014
Common misconceptions

• Rare
  • Under-appreciated and under-recognized cause of HFpEF

• Low voltage on ECG is a good screening test
  • Many patients with amyloidosis do not meet low voltage criteria

• Fat pad biopsy has high sensitivity
## Diagnostic sensitivity of fat pad fine needle aspiration in different cardiac amyloidoses

<table>
<thead>
<tr>
<th>Amyloid type</th>
<th>n</th>
<th>Number positive by Congo red staining</th>
<th>Diagnostic sensitivity (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic AL amyloidosis</td>
<td>216</td>
<td>181</td>
<td>84% (78–88%)</td>
</tr>
<tr>
<td>ATTRm</td>
<td>113</td>
<td>51</td>
<td>45% (36–54%)</td>
</tr>
<tr>
<td>Val122Ile</td>
<td>69</td>
<td>23</td>
<td>33%</td>
</tr>
<tr>
<td>Thr60Ala</td>
<td>21</td>
<td>14</td>
<td>67%</td>
</tr>
<tr>
<td>ATTRwt</td>
<td>271</td>
<td>42</td>
<td>15% (11–20%)</td>
</tr>
</tbody>
</table>
Common misconceptions

• Rare
  • Under-appreciated and under-recognized cause of HFpEF

• Low voltage on ECG is a good screening test
  • Many patients with amyloidosis do not meet low voltage criteria

• Fat pad biopsy has high sensitivity
  • 85% for AL, but only 15% for wild type ATTR

• SPEP is sufficient to exclude AL amyloidosis
  • Usually NORMAL

• Cardiac amyloidosis is the great masquerader

• Need an invasive and risky endomyocardial biopsy for diagnosis
  • Not for ATTR. For AL, will need some tissue diagnosis → non cardiac options = bone marrow, fat pad, skin lesion, kidney
Common misconceptions

• Everyone dies so it is not worth diagnosing
Treatments

• AL amyloidosis
A TRIAL OF THREE REGIMENS FOR PRIMARY AMYLOIDOSIS: COLCHICINE ALONE, MELPHALAN AND PREDNISONE, AND MELPHALAN, PREDNISONE, AND COLCHICINE

ROBERT A. KYLE, M.D., MORIE A. GERTZ, M.D., PHILIP R. GREIPP, M.D., THOMAS E. WITZIG, M.D., JOHN A. LUST, M.D., PH.D., MARTHA Q. LACY, M.D., AND TERRY M. THERNEAU, PH.D.
## AL Amyloidosis Therapeutic Options

<table>
<thead>
<tr>
<th>Decreased light chain production</th>
<th>Fibril destabilizers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steroids</strong></td>
<td><strong>Proteasome Inhibitors</strong></td>
</tr>
<tr>
<td>Prednisone</td>
<td>Bortezomib (Velcade)</td>
</tr>
<tr>
<td>Dex</td>
<td>Carfilzomib (Kyprolis)</td>
</tr>
<tr>
<td></td>
<td>Ixazomib (Ninlaro)</td>
</tr>
<tr>
<td></td>
<td>Marizomib</td>
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<tr>
<td></td>
<td>Oprozomib</td>
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</table>
Kaplan-Meier curve representing the association between treatment regimen and all-cause mortality. There was a significant association between treatment regimen and survival ($p < 0.001$), with the lowest mortality seen in the bortezomib, dexamethasone, and alkylating agent (BDex+AA) cohort.

Treatments

• AL cardiac amyloidosis
  • Bortezomib + cyclophosphamide + dexamethasone (CyBorD)
  • Daratumumab
  • CyBorD + daratumumab
  • High dose melphalan + ASCT → considered in patients with less cardiac involvement

• ATTR cardiac amyloidosis
Figure 2: Transthyretin protein production and drug mechanisms of action

The TTR gene is transcribed into mRNA and translated into a protein. The protein folds into monomers which are aggregated into a tetramer. Translation of TTR mRNA can be blocked by using either small interfering RNA (siRNA) or an antisense oligonucleotide. siRNA is a synthetic double-stranded RNA which uses the RNA-induced silencing complex (RISC) to cleave TTR mRNA. Antisense oligonucleotides are short complementary DNA sequences which bind to the mRNA, which is recognized and cleaved by a RNase. Tafamidis, Diflunisal or EGCG work on the folded TTR protein by stabilizing the tetramer and preventing dissociation into monomers which can form fibrils. TUDCA/Doxycycline and anti-SAP antibodies act by allowing re-uptake of deposited fibrils and also preventing some fibril deposition.
Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorff, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Raperzzi, M.D., for the ATTR-ACT Study Investigators*

• Placebo controlled RCT
• 441 patients
• 30 month follow up
• 30% RRR for mortality
• Lower rate of decline in 6MW and KCCQ scores

A Change from Baseline in 6-Minute Walk Test

B Change from Baseline in KCCQ-OS

Hazard ratio, 0.70 (95% CI, 0.51–0.96)
Patisiran, an RNAi Therapeutic, for Hereditary Inherited transthyretin Amyloidosis

David Adams, M.D., Ph.D., Alejandra Gonzalez-Duarte, M.D., William D. O’Riordan, M.D., Coleen Turner, M.D., Hartmut H. Schmidt, M.D., Teresa Coelho, M.D., John L. Hedia, M.D.

• IV infusion q3 weeks
• 225 patients → 18 month follow up
• Results: difference in mNIS+7 (34 points) and Norfolk QOL-DN (21 points)
• Side effects: infusion reactions in 20% of patients (10% in placebo)
Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

Merrill D. Benson, M.D., Márcia Waddington-Cruz, M.D., Ph.D., John L. Berk, M.D., Michael Polydefkis, M.D., M.H.S., Peter J. Dyck, M.D., Annabel K. Wang, M.D., Violaine Planté-Bordeneuve, M.D., Fabio A. Barroso, M.D., Giampaolo Merlini, M.D., Laura Obici, M.D., Morton Scheinberg, M.D., Thomas H. Brannagan, III, M.D., et al.

• Placebo controlled RCT
• 172 patients
• 15 month follow up
• hATTR with polyneuropathy
• Weekly SQ inotersen
• Results: improved mNIS+7 (19.7 points) and Norfolk QOL-DN (11.7) neuropathy scores
• Side effects: 5 deaths in inotersen group, none in placebo.
  • Glomerulonephritis (3%) and thrombocytopenia (3%)
Treatments

• **AL cardiac amyloidosis**
  • Bortezomib + cyclophosphamide + dexamethasone (CyBorD)
  • Daratumumab
  • CyBorD + Daratumumab
  • High dose melphalan + ASCT ➔ considered in patients with less cardiac involvement
  • Doxycycline, turmeric/curcumin
  • Advanced therapies

• **ATTR cardiac amyloidosis**
  • Green tea extract (EGCG 600-800mg/day), doxycycline/TUDCA, turmeric (curcumin)
  • Patisiran (IV infusion) or Inotersen (SQ injection) for hATTR neuropathy
  • Tafamidis (oral) for wtATTR and hATTR cardiomyopathy
  • Clinical trials
  • Advanced therapies
Research and Development

• AG10 (TTR stabilizer)
• Patisiran in cardiomyopathy
• Vutrisiran in cardiomyopathy
• Akcea-TTR-LRx (newer version of inotersen)
Summary

• High clinical suspicion for amyloidosis in the right situation
• Look for red flags
• Initial workup:
  • Serum studies for AL → free light chains kappa/lambda, serum IFE, urine IFE
  • CV myocardial PYP imaging (ie technetium pyrophosphate) for ATTR
• Don’t miss AL amyloidosis! Cardiac / hematologic emergency
• Novel treatment options
Saint Luke’s MAHI Amyloidosis Program

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THANK YOU