Amyloidosis: Challenges in Diagnosis and Management

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@Ron_Witteles
# We Only Have 20 Minutes!
## What We Will/Won’t Cover

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<td>- Knockdown agents</td>
<td>Role of heart transplant</td>
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*AL = Amyloid Light Chain, ATTR = Amyloid Tangloulus Ribonucleic Transcript*
Amyloidosis: What is it?

- *Amylum* – Starch (Latin)

- Generic term for *many* diseases:
  - Protein misfolds into β-sheets ➔
  - Forms into 8-10 nm fibrils ➔
  - Extracellular deposition into amyloid deposits
Types of Amyloid – Incomplete List

**Systemic:**
- **Light chains (AL)** – “Primary”
- **Transthyretin (ATTR)** – “Senile” or “Familial”
- **Serum amyloid A (AA)** – “Secondary”

**Localized – Not to be memorized!**
- Beta-2 microglobulin (A-β2) – Dialysis (osteoarticular structures)
- Apolipoprotein A-1 (AApoA-I) – Age-related (aortic intima, cardiac, neuropathic)
- Apolipoprotein A-2 (AApoA-2) – Hereditary (kidney)
- Calcitonin (ACal) – Complication of thyroid medullary CA
- Islet amyloid polypeptide (AIAPP) – Age-related (seen in DM)
- Atrial natriuretic peptide (AANF) – Age-related (atrial amyloidosis)
- Prolactin (APro) – Age-related, pituitary tumors
- Insulin (AIns) – Insulin-pump use (local effects)
- Amyloid precursor protein (ABeta) – Age-related/hereditary (Alzheimers)
- Prion protein (APrPsc) – Hereditary/sporadic (spongiform encephalopathies)
- Cystatin-C (ACys) – Hereditary (cerebral hemorrhage)
- Fibrinogen alpha chain (AFib) – Hereditary (kidney)
- Lysozome (ALys) – Hereditary (Diffuse, especially kidney, spares heart)
- Medin/Lactadherin – Age-related (medial aortic amyloidosis)
- Gelsolin (AGel) – Hereditary (neuropathic, corneal)
- Keratin – Cutaneous
AL: A Brief Dive into Hematology...

- Plasma cells: Make antibodies
  - Reside in bone marrow & elsewhere

- Antibodies: Made up of light chains & heavy chains
  - Heavy chain: Determine class of antibody (IgG, IgM, etc.) and part of antibody’s specificity
  - Light chain: Two types (κ and λ) – determine part of antibody’s specificity

- What happens when someone develops a clonal plasma cell population?
Plasma Cells Gone Wrong

Three things happen:
- Plasma cell clones take over % of bone marrow
- Plasma cells produce a clonal antibody (IgG-λ)
- Plasma cells produce excess light chain (λ)

Possible outcome 1:
- Only small % of marrow taken over, circulating light chains don’t deposit → MGUS

Possible outcome 2:
- Large % of marrow taken over (and possible consequences thereof) → Myeloma

Possible outcome 3:
- Circulating light chains deposit in tissue → AL Amyloidosis

Note: Possibilities 2 & 3 can coexist – but don’t have to
Transthyretin (TTR)

- Transthyretin = “Transports thyroxine and retinol”
  - Primary source: Liver

- Almost completely circulates as a tetramer
  - In steady-state with monomeric form
  - Thyroxine binding $\xrightarrow{}$ stabilizes tetramer

- Monomeric TTR is inherently ‘amyloidogenic’

- Mutations in TTR can make it even more amyloidogenic
  - Some mutations favor cardiac deposition, others nerve deposition
AL vs. ATTR: Diagnostic Clues

**AL:**
- Multiorgan involvement
  - Proteinuria, high alkaline phosphatase, dysphagia, macroglossia
  - Abnormal free light chain ratio

**ATTR:**
- Vital organ involvement: Heart +/- Nerves
- Laboratory: Transthyretin gene testing (hereditary only)

**Both:**
- Carpal tunnel syndrome
- Persistently abnormal troponins
- EKG abnormalities
Biopsy – Gold Standard & Only Way to Diagnose AL

- Our general practice:
  - Biopsy of clinically involved organ

- Testing for amyloid subtype
  - Immunofluorescence or Mass spectrometry

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Technetium Pyrophosphate (PYP) Scanning

- $^{99m}\text{Tc}$-pyrophosphate (PYP)
  - Old nuclear bone scan agent
  - Taken up by hearts infiltrated with ATTR but not AL amyloidosis
  - Similar agent $^{99m}\text{Tc}$-DPD in Europe – but unavailable in USA
Assessments

- **Visual scoring system**
  - 0 = No cardiac uptake
  - 1 = Mild cardiac uptake, less than ribs
  - 2 = Moderate cardiac uptake, equal to ribs
  - 3 = High cardiac uptake, greater than ribs

- **Quantitative**
  - Region of interest drawn around the heart, photon counts measured
  - Identical region of interest drawn around contralateral chest, photon counts measured
  - Ratio of heart:contralateral chest counts (H/CL) measured

How Reliable are PYP Scans – Particularly for ATTR vs. AL?

How Reliable are PYP Scans – Particularly for ATTR vs. AL?

Largest Study of PYP/DPD

- Study across 8 centers in 5 countries (N=1217)
- All patients with suspected or proven ATTR amyloidosis received:
  - Bone scintigraphy (PYP or DPD or HMDP)
  - SPIE/UPIE
  - Serum FLC
- 27% (!) of AL amyloid patients had positive PYP scans, but...
- The key – HIGH specificity for ATTR amyloidosis when you combine r/o monoclonal protein with scintigraphy
  - Sensitivity: 74%
  - Specificity: 100%

Diagnostic Algorithm

Clinically Suspect Amyloidosis

FLC Ratio Normal

PYP Scan

- No Amyloidosis

Genetic Testing

+ hATTR Amyloidosis

- wtATTR Amyloidosis

FLC Ratio Abnormal

Biopsy clinically involved organ with IF or Mass Spec

ATTR

AL

AL Amyloidosis
Treatment: AL Amyloidosis
It’s All About the Free Light Chains!

• One therapy is not in and of itself better than another
  • Considerations:
    • Effect on FLC
    • Tolerability
  • True for:
    • Chemotherapy
    • Immunotherapy
    • Stem cell transplant
AL Amyloid: NEJM Trial MP vs. Colchicine

Adapted from Kyle et al. NEJM. 1997;336:1202-7.
Only Randomized Data: French Intergroup, 2007

- 100 patients randomized to melphalan/dexamethasone vs. stem-cell transplant

- Note: No newer chemo regimens (!)
Overall Survival: Favors “Standard” Chemo!

Landmark Analysis: Lived 6 months & Completed Rx

New Paradigm: Much More Effective Chemotherapy

- Immunomodulatory & anti-angiogenic agents
  - Lenalidomide
  - Pomalidomide
- Proteasome inhibitors:
  - Bortezomib
  - Carfilzomib
  - Ixazomib
- Monoclonal antibodies
  - Daratumumab (antibody to CD38)
  - Elotuzumab (antibody to SLAMF7 – on myeloma/NK cells)
- 2018 light-chain directed therapy:
  - Combination of proteasome inhibitor, immunomodulatory agent, steroid, and alkylator in some form (usually 1-2 + dex)
  - Daratumumab early (?)
Daratumumab

- Daratumumab: CD38-directed monoclonal antibody approved for myeloma
- Stanford study of 25 consecutive AL amyloidosis patients with inadequate responses to prior chemotherapy
  - Median # of prior therapies: 3
- Extremely well-tolerated
  - Only mild infusion reactions

Figure 1. Waterfall plot demonstrating percent reduction of the dFLC in response to daratumumab. Best hematologic response is color coded; 100% of patients had a decrease in the dFLC.

ANDROMEDA Trial

- Phase 3 randomized trial of 370 newly diagnosed AL amyloidosis patients
  - CyBorD
  - CyBorD + Daratumumab

- Primary outcome:
  - % of patients with complete hematologic response (negative SPIE/UPIE, normal FLC ratio)

- Secondary outcomes:
  - Many – including organ response rates, progression free survival, overall survival

- Currently enrolling – new standard of care?

Adapted from clinicaltrials.gov, NCT03201965.
ATTR Amyloidosis
Strategies to Prevent TTR Amyloid Deposition

- Stabilize tetrameric form of TTR
  - Tafamidis
  - NSAIDs (diflunisal)
  - AG10

- Knock down production of TTR in all forms
  - RNA inhibition/interference
Tafamidis Trial in “FAP”

- Phase 3 trial conducted at 8 sites in Europe & South America

- 128 patients with FAP due to V30M mutation randomized to tafamidis or placebo x 18 months
  - Primary endpoint: “Responder” or “Nonresponder”
  - Occurrence of liver transplant → “Nonresponder”
    - 69% on liver transplant list at start of study (!)
    - 13 patients in each group (21%) transplanted during study
Tafamidis FAP Trial

Tafamidis FAP Trial

Secondary Endpoints

Tafamidis Approval for FAP
Tafamidis Approval for FAP
Tafamidis Approval for FAP
Tafamidis Approval for FAP
NSAIDs/Diflunisal

- NSAIDs – Found on screening to stabilize transthyretin
- Diflunisal: FDA approved for arthritis pain
  - Found to be most effective NSAID at binding to TTR
- Double-blind, placebo-controlled clinical trial for FAP reported in December, 2013

Adapted from Berk et al. JAMA. 2013;310:2658-2667.
Diflunisal Study: NIS+7 Score

Change from baseline

1 year 2 years

Placebo Diflunisal

P=.02

P<.001

Adapted from Berk et al. JAMA. 2013;310:2658-2667.
RNA Interference & Antisense

- Knocks down total amount of circulating transthyretin (TTR)

- Two similar approaches attempted:
  - Patisiran (siRNA)
  - Inotersen (anti-sense)

Patisiran: APOLLO Trial

- 225 patients with hATTR polyneuropathy

- Randomized to patisiran (q3 week IV) vs. placebo (2:1 randomization), double-blind
  - Premeds: Dexamethasone, acetaminophen, diphenhydramine, H2 blocker

- Primary endpoint
  - Change in mNIS+7 score at 18 months

- Well-tolerated – only mild infusion reactions

- Results… Spectacular!

APOLLO Results: mNIS+7

mNIS+7: Change from Baseline

Placebo

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

APOLLO Results: mNIS+7

Just How Low Is that P-Value???

- Major heart failure trials
  - Carvedilol (COPERNICUS)
    - $P=0.00002$, $N=2289$
  - Enalapril (SOLVD)
    - $P=0.0036$, $N=2569$
  - Metoprolol (MERIT-HF)
    - $P=0.0062$, $N=3991$

- Put another way…
  - Result is about a thousand million trillion times more likely to be real/true than the major HF trials… and with an $N$ of 225!!!
Another Way of Looking at It

- There are approximately $7.5 \times 10^{18}$ grains of sand on earth

- Imagine we have the sand from 1 million Earths
  - 2 people randomly chose a single grain of sand
  - The chances that the result isn’t true would be the chances of 2 people randomly picking the same single grain
“So You’re Telling Me There’s a Chance!”
APOLLO Cardiac Subgroup Data

Inotersen: Neuro-TTR Trial

- 172 patients with mATTR polyneuropathy (Stage 1/2)
- Randomized to inotersen (weekly SQ) vs. placebo (2:1 randomization), double-blind
- Safety concerns (all in inotersen arm):
  - Thrombocytopenia (low platelet count): 3 Serious Adverse Events (SAE) – including 1 death due to intracranial hemorrhage
  - Kidney events: 6 SAE
  - Deaths: 5 (inotersen), 0 (placebo)

- Cardiac subgroup analysis (inotersen vs. placebo), N=108:
  - LV septal wall thickness (mm): -0.42, +0.15 (P=0.27)
  - No significant changes in GLS, EF, LV mass

mNIS+7: Patisiran vs. Inotersen


Mean TTR Reduction:

Patisiran: 81%
Inotersen: 71%
# Patisiran vs. Inotersen: Tale of the Tape

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ATTR-ACT Study – Tafamidis for ATTR Cardiomyopathy

- Phase 3, Randomized, Placebo-Controlled clinical trial of tafamidis for ATTR cardiomyopathy
  - Wild-type or familial
  - 441 patients worldwide x 2.5 years
  - Primary endpoint:
    - Mortality & CV Hospitalization
    - Hierarchical endpoint (Finkelstein-Schoenfeld method)
- Key secondary endpoints:
  - Change in Quality of life (KCCQ)
  - Change in 6MWT

Adapted from Maurer et al. N Engl J Med. Published online before print August 27, 2018.
## Primary Endpoint

### A Primary Analysis, with Finkelstein–Schoenfeld Method

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NNT to prevent 1 death at 30 months: 7.5 (!)
Survival

Adapted from Maurer et al. N Engl J Med. Published online before print August 27, 2018.
### Frequency of Cardiovascular-Related Hospitalizations

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<td>total no. (%)</td>
<td>no. per yr</td>
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CV Hospitalizations

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NNT to prevent 1 hospitalization/yr: 4.5 (!)
Time to First CV Hospitalization

Adapted from Maurer et al. N Engl J Med. Published online before print August 27, 2018.
6-Minute Walk Test

Adapted from Maurer et al. N Engl J Med. Published online before print August 27, 2018.
Quality of Life

B Change from Baseline in KCCQ-OS

Pooled tafamidis

P<0.001

Placebo

LS Mean Change from Baseline

Month

No. of Patients
Tafamidis 264 241 221 201 181 170
Placebo 177 159 145 123 96 84

Adapted from Maurer et al. N Engl J Med. Published online before print August 27, 2018.
Safety

• Remarkably safe/well-tolerated
• No adverse events at higher rate than placebo
• More discontinuation of placebo from ‘adverse events’
  • 26% vs. 20%
• No dosing issues in renal dysfunction

Adapted from Maurer et al. N Engl J Med. Published online before print August 27, 2018.
NT-BNP: Placebo - Tafamidis

Difference in NT-BNP (pg/mL)

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The Bottom Line: We Have Effective ATTR Treatments Now!

- Wild-type ATTR Cardiomyopathy:
  - Tafamidis

- Familial ATTR Cardiomyopathy (FAC):
  - Tafamidis

- Familial ATTR Polyneuropathy (FAP):
  - Patisiran

- Mixed familial phenotype:
  - Patisiran or tafamidis

- The future?
  - Knockdown agents for ATTR cardiomyopathy
  - Easier knockdown administration
  - Better stabilizers (AG10)
  - Combined stabilizer/knockdown approach
Take Home Points

• Think about amyloidosis!
  • It’s a not-so-rare “rare” disease

• Importance of determining subtype
  • Biopsy = gold standard
  • PYP/DPD scans: Useful, but only once you have ruled out AL

• AL amyloidosis treatments:
  • We have effective chemotherapy now
  • Limited role for stem cell transplant

• ATTR: New effective therapies are here!

• Importance of multidisciplinary approach, centers of excellence, clinical trials
Stanford Amyloid Center Team

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Thank you!