Building a Collaboration Network in Transthyretin Cardiac Amyloidosis: Challenges and Opportunities

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Updates in Cardiac Amyloidosis: CME Conference
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Transthyretin Cardiac Amyloidosis (ATTR-CA)

- higher prevalence than previously recognized in patients with HFpEF (ATTRwt / ATTRv)
  - under-diagnosed, under-treated
- often long delay between symptoms onset and definitive diagnosis
  - high utilization of health services in interval before diagnosis
- poor prognosis if untreated
  - median survival (2.5-3yr ATTRv : 3-5 yrs ATTRwt)
- expansion of Rx options
  - TTL silencers and stabilizers (ATTR-CM and ATTR-PN)
- Rx most effective before progression to NYHA class III-IV
  - reinforces priority for early detection
ATTR-CA: The publication tsunami
PubMed Search Term (italics) results by year, quotations represent exact phrase

"cardiac amyloidosis" 1993-2022

"cardiac amyloidosis" 1948-2022

"cardiac amyloidosis therapy"
Transthyretin Cardiac Amyloidosis (ATTR-CA):

- limited Arizona-specific data
  - prevalence/incidence across age, gender, ethnicity, geography, SDoH
  - treatment patterns and outcomes
- majority of national/international data from hospitalized patients and specialized amyloid clinics in academic medical centers
- limited data on Hispanic populations and none on Native American populations
Transthyretin Cardiac Amyloidosis (ATTR-CA)

- transition from invasive endomyocardial biopsy to non-invasive scintigraphic imaging
- development of multi-parameter phenotypic risk scores to select patients for scintigraphic diagnosis versus economically unrealistic imaging of all HFpEF / NP cases
  - clinical, ECG, echocardiographic, ICDs, claims data, non-cardiac predictors (neuropathies, carpal tunnel, synovitis/tenosynovitis, spinal stenosis)
  - new ML/AI algorithms
  - need for validation of risk score metrics across cohorts with variable ATTR-CA prevalence rates
Issues in Transthyretin Cardiac Amyloidosis: Diagnosis and Clinical Management

- improve broader clinical recognition and awareness beyond specialized amyloid centers
- paucity of validated low-cost biomarkers from easily acquired biospecimens (blood, urine)
  - expand cost-effective screening for earlier detection and Rx initiation
  - prognosis and prediction of PN to CM progression risk
  - evaluation of Rx efficacy
  - disease progression monitoring and correlation with functional metrics and QOL
  - screening of asymptomatic ATTRv cohorts for late onset disease due to incomplete mutation penetrance
Issues in Clinical Management of ATTR-CM: Treatment

- comparative efficacy of TTR stabilizers and silencers?
- value of combination Rx
  - additive/synergistic; no benefit; new AE risks?
  - when to transition from monotherapy?
  - agent dose titration, dosing frequency and order of administration?
  - economic feasibility given high cost of individual agents?
- are there thresholds for irreversible progression and lack of Rx efficacy?
- is ATTR-CM reversible (microfibril clearance agents)?
Disease-Modifying Agents in Transthyretin Amyloidosis: Treatment Cost

- currently approved Rx require life-long therapy
- high annual cost of approved Rx ($225-500K)
- age-related prevalence and significant OOP spend for older patients under Medicare-Part D
  - influence on adoption rates and Rx adherence
- substantial reduction in list price for existing Rx to achieve cost-effective QALY thresholds of $50-150K
### The ATTR Therapeutics Pipeline

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| **Cardiomyopathy** |       |        |         |          |            |
| Vyndamox/Vyndaqel |         |        |         |          | Small molecule |
| Pfizer           |         |        |         |          |            |
| Onpattro pasitran |         |        |         |          | siRNA      |
| Akrisya          |         |        |         |          |            |
| Amvuttra valrisiran |       |        |         |          | siRNA      |
| Akrisya          |         |        |         |          |            |
| Eplontersen      |         |        |         |          | Antisense  |
| Ionis, AstraZeneca|       |        |         |          |            |
| Acoramid          |         |        |         |          | Small molecule |
| BridgeBio, Alion |         |        |         |          |            |
| PXX0004           |         |        |         |          | Antisense  |
| Prothena, Novo Nordisk |     |        |         |          |            |
| NIH016            |         |        |         |          | Antibody   |
| Neurimmune, Alexion |     |        |         |          |            |
| NTLA-2003         |         |        |         |          | CRISPR therapy |
| Intellia          |         |        |         |          |            |

|                |         |        |         |          |            |
| **ATTR**        |         |        |         |          |            |
| NPT1189         |         |        |         |          | Fusion protein |
| Preciata        |         |        |         |          |            |
| AT-03            |         |        |         |          | Fusion protein |
| Altrasys         |         |        |         |          |            |
| AT-02            |         |        |         |          | Fusion protein |
| Altrasys         |         |        |         |          |            |
| ATC-202          |         |        |         |          | Chimeric ligand |
| Astrotact        |         |        |         |          |            |

Source: Company websites and BioCentury • *Not approved for ATTR-PN in the U.S.
Transthyretin Cardiac Amyloidosis: A Pending Therapeutic Paradigm Shift?

- currently approved agents require lifelong therapy
- transition from Rx disease modification to curative intervention?
  - CRISPR-cas9 TTR gene editing knockout (Intellia/Regeneron: NTLA-2001)
  - initial efficacy studies in hereditary amyloid polyneuropathies and ongoing expansion to ATTR-CM
  - encouraging duration of reduced TTR expression levels (6-12 months) but clinical benefit to be demonstrated
  - threshold of hepatocyte transduction efficiency required for long term efficacy?
  - monitoring off-target effects (often delayed)?
The Challenges and Opportunities in TTR-Amyloidosis Reflect Many of the Same Elements Shaping Biomedical R&D and Healthcare Delivery At Large
The Contemporary Environment for Biomedical R&D and Healthcare Delivery

- aging populations, economically unsustainable chronic disease burden and major unmet clinical/social needs
- public and political expectations of constant innovation to improve access, availability and quality of care, lower cost, clinical outcomes and QOL
- multiOmics stratification of major diseases into subtypes with distinct molecular pathologies (precision medicine)
- high Rx prices for smaller market of size of subtype-specific Rx (proliferation of ‘orphan status’ designations)
- need for companion Dx in disease subtype Rx selection
The Contemporary Environment for Biomedical R&D and Healthcare Delivery

- escalating scientific and clinical complexity (staying current)
  - pace and diversity of innovation: new concepts; new technologies
  - burgeoning large-scale data sets
- fusion of previously largely separate domains
  - biomedicine, engineering, computing
  - new combination products: Dx-Rx-device-lx algos
- accelerated adoption of ML/AI technologies
  - regulatory validation (SaMD)
- new regulatory and pharmacoeconomic requirements: efficacy, safety and VALUE
Solutions for Major Unmet Medical Needs Require Sophisticated Integration of Multidisciplinary Expertise

The S4 to M4 Paradigm Shift

S4
- single discipline/speciality
- single institution
- subcritical resources
- slow (translation to practical benefit)

M4
- multidisciplinary/specialities
- multiple institutions
- managing scale and integration logistics
- momentum (faster translation and adoption)
Solutions for Major Unmet Medical Needs Require Sophisticated Integration of Multidisciplinary Expertise

- Single discipline/speciality
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- Multidisciplinary/specialities
- Multiple institutions
- Managing scale and integration logistics
- Momentum (faster translation and adoption)

The S4 to M4 Paradigm Shift

SILOS SUBVERT SOLUTIONS
Arizona

- third fastest growing US state (Tx, Fla, Az)
- metro-Phoenix: Maricopa County
  - now fifth largest US urban population (cf. Philadelphia, Houston comps)
  - second fastest population growth in US
- unique demographics
  - Hispanics (24%), Native Americans (5.6%)
- limited number of major healthcare provider systems facilitates development of clinical research collaboration network trials
  - Abrazo, Banner, Dignity (Common Spirit), Honor Health, Mayo, ValleyWise, VA
  - attraction to industry sponsors of turnkey networks to accelerate investigational trials (Dx, Rx, devices, Ix algos)
- rapid growth in university R&D
  - ASU, UA, NAU: $1.5 billion annual grant revenues
Network Arizona: Building State-Wide Consortium Networks

- Aegis Consortium (pandemic preparedness)
- ACCEL: Arizona Coalition for Comprehensive Evaluation of Long COVID
- Arizona Alzheimer’s Consortium
- Arizona Telemedicine Council (platforms, policy)
- Arizona Emergency Medical Reserve System (pandemic and disaster preparedness, emergency supply chain management)
- WearTech Applied Research Center (sensors, remote health monitoring)
Exploration of New Biomarkers for ATTR-Amyloidosis to Facilitate Expanded Diagnostic Screening and Disease Progression Monitoring

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The Arizona Transthyretin Translational Research Network (ATTR-N)

- build state-wide network of research and clinical expertise for advances in the detection and treatment of ATTR-amyloidosis
- generate detailed epidemiological data on ATTR-amyloidosis prevalence in Arizona, clinical interventions and outcomes
  - age, gender, ethnicity, geography
  - new hereditary risk variants in Hispanic/native American populations
- analyze multi-level (patient, provider, payer) barriers and facilitators to implementation of EBP care protocols
- build additional scale via collaboration with other national/international COEs in ATTR-Amyloidosis
Disclosures

- Board of Directors (Oncology Therapeutics)
- Board of Directors (Oncology Molecular Diagnostics)
- Board of Directors (CAR-T Cell Therapy)
- Board of Directors (Next Generation Nanopore Sequencing)
- Scientific Advisory Board (Gene Editing)
- Scientific Advisory Board (Infectious Disease Dx and Rx)
- Co-Founder (ML/AI Computational Modeling of Immune Recognition Epitope)

Slides Available at: https://casi.asu.edu/presentations/
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