Promising Therapies On The Horizon For Treatment Of ATTR Amyloidosis

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• Off-label use – Diflunisal, Doxycycline, TUDCA/Ursodiol
Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

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Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis


Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

Objectives

• Discuss the use of TTR ‘Silencers’ for the treatment of ATTR amyloidosis
• Discuss the use of TTR ‘Stabilizers’ for the treatment of ATTR amyloidosis
• Discuss the use of ATTR ‘Degraders’ for the treatment of ATTR amyloidosis
• Will not be discussing issues related to conventional cardiovascular management of ATTR amyloidosis patients
**Therapeutic Targets of the Amyloidogenic TTR Cascade**

**Silencers:** Suppress hepatic TTR production

**Stabilizers:** Stabilize circulating TTR from dissociation

**Degraders:** Breakdown amyloid fibril tissue deposits

Myocardial deposition causing ‘cardiac amyloidosis’ clinical syndrome

*Castano et al. Heart Fail Rev 2015;20:163*
TTR Silencers

- Suppress hepatic production of transthyretin
- Two agents have recently shown benefit in phase III clinical trials, both for mutant ATTR polyneuropathy
  - Inotersen - antisense oligonucleotide
  - Patisiran - small interfering RNA
ATTR Pharmacologic Therapies

Liver

Circulation

End-organs

PATISIRAN
INOTERSEN

Silencers

Vranian et al. Curr Cardiol Rep 2015;17:100
Inotersen

- Weekly subcutaneous dosing
- NEURO-TTR RCT (N=172) enrolled ambulatory patients with mATTR polyneuropathy, Inotersen vs placebo, 17 month FU
- Significantly ↓ neuropathy progression, 36% improved
- Safety
  - 3 pts had plt <25, 1 ICH death
  - 3 pts had glomerulonephritis
  - Plt, renal monitoring improved safety
- Approved by Health Canada Oct 2018
  - Plts >100, eGFR >45, vitamin A suppl

Benson et al. NEJM 2018;379(1):22
Inotersen - Improved Cardiac Endpoints

- Neuro-TTR study sub-analysis of pts with cardiac involvement

- Single-center open-label investigator-sponsored trial of ATTR CA patients receiving Inotersen
  - 6MWD improved by 13.7 m after 3 years (N=13)
Patisiran

- Intravenous dosing every 3 weeks
- APOLLO RCT (N=225) enrolled ambulatory patients with mATTR polyneuropathy, Patisiran vs placebo, 18 months FU
- Significantly ↓ neuropathy progression, 56% improved
- Safety
  - Similar adverse event rates between groups
  - 19% infusion rxn (9% placebo), none serious
  - Vitamin A supplementation
- Under Health Canada review

Adams et al. NEJM 2018;379(1):11
Patisiran – Improved Cardiac Endpoints

• APOLLO study sub-analysis of 126 pts with cardiac involvement

  NTproBNP

• Similar results for LV mass and wall thickness, longitudinal systolic strain, 6MWD

Cardiac hospitalizations and all-cause mortality

Solomon et al. Circ 2019;139:431
TTR Stabilizers

- Bind to the TTR tetramer and prevent its dissociation into monomers
  - Tafamidis
  - Diflunisal
  - AG10
ATTR Pharmacologic Therapies

Vranian et al. Curr Cardiol Rep 2015;17:100
Tafamidis

- Once daily oral dosing
- ATTR-ACT RCT (N=441) enrolled patients with mutant (25%) or wtATTR (75%) cardiac amyloidosis, Tafamidis vs placebo, 30 months FU
  
  - Significant ↓ all-cause mortality
  - Reduced decline in 6WMD, QoL
  - Similar adverse events b/w groups
  - Under Health Canada review
  - FDA approval Monday

Maurer et al. NEJM 2018;379(11):1007
TTR Stabilizers

- **Diflunisal**
  - NSAID, twice daily oral dosing, limited cardiac data, no clear evidence of efficacy
  - Caution in patients with impaired renal function
  - Off-label use

- **AG10**
  - Twice daily oral dosing
  - Mimics stabilizing TTR mutation (T119M) – forms hydrogen bonds between serine residues on neighboring monomer
  - Well tolerated in phase II trial ATTR CA (N=49), 28 day FU
  - Normalized serum TTR levels
  - Phase III RCT starting

Castano et al. Congest Heart Fail 2012;310:2658
ATTR Degraders

- Enhance resorption of amyloid tissue deposits
- Doxycycline Plus TUDCA/Ursodiol
  - May attenuate disease progression
  - 10-15% intolerance, GI and derm
  - Off-label use
- Epigallocatechin 3-gallate (EGCG, green tea extract)
  - May attenuate disease progression
  - Well tolerated, rare GI side-effects

Vranian et al. Curr Cardiol Rep 2015;17:100
Obici et al. Amyloid 2012;19 (supple I):34
Karlstedt et al. J Card Fail 2019;25:147
Kristen et al. Clin Res Cardiol 2012;101:805
Phase III RCTs for ATTR CA

- Inotersen
- Patisiran
- Vutrisiran
  - TTR silencer, siRNA, SC q 3 months
- AG10
- Doxy/TUDCA
- PRX004
  - Amyloid degrader, monoclonal Ab that binds to dissociated monomers, aggregates and amyloid deposits
  - Phase I trial

Higaki et al. Amyloid 2016;23:86
Summary

- Today there is no approved therapy for ATTR cardiac amyloidosis in Canada
- **But not for long, the horizon is here!**
- Emerging therapeutic options act at different points in the TTR amyloidogenic cascade
  - **Silencers** – suppress TTR production
    - Inotersen, Patisiran – slow polyneuropathy progression, RCTs coming for CA
  - **Stabilizers** – stabilize TTR from dissociation
    - Tafamidis – survival benefit in ATTR CA
  - **Degraders** – reduce amyloid tissue deposit
    - Doxy/TUDCA, EGCG – role uncertain
- More therapies in development
- **Combination therapy??**
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• Thank you
• Questions or comments?
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