Alternative Therapies for ATTR

What your mother never told you

John Berk, MD
Amyloidosis Center
Boston University Medical Center

Biannual Amyloid Support Group Meeting
Chicago, IL
28 October 2017
Neurodegenerative Disease

- Alzheimer’s Disease (AD)
- Parkinson’s Disease (PD)
- Amyotrophic Lateral Sclerosis (ALS)
- Multiple Sclerosis (MS)

Mechanisms of disease

- Inflammation/oxidative stress
- Cell death
Polyphenolic Nutraceuticals

- Flavonoids
  - Vegetables, fruits, grains, bark, stems, teas, wine

- Effects on AD pathology
  - Limit oxidative injury
  - Inhibit Aβ fibril/aggregation, destabilize formed Aβ
  - Inhibit killer cell activation
  - Increase cell survival signaling

- Curcumin (active spice of Tumeric)
- Epigallocatechin gallate (EGCG)
- Resveratrol
Curcumin

- Natural polyphenol (diarylheptanoid)
- Inhibits Aβ aggregation/breaks up Aβ fibrils
- Blocks toxicity of Aβ fragments on brain cells
- Competes T4 binding to TTR
- Promotes clearance of TTR aggregates
- Inhibits steps of ATTR fibril formation
- Crosses blood brain barrier

Ferreira N et al. 2013; 1832(1):39
Curcumin decreases ATTR and injury signals in mouse nerves

COMMENTS
- Prefibrillar aggregates
- 6 weeks curcumin in drinking water
- Poor bioavailability
- Unachievable levels
- Does not recapitulate human disease

Resveratrol

- Damaged grapevines, pines, peanuts
- Stabilizes TTR tetramer conformation (T4 pocket)
- Promotes aggregation of potentially toxic TTR monomers

**Comment:**
- Insufficient data in humans
- Poor bioavailability
- Effective dose undefined

EGCG

- Inhibits neurodegeneration in ALS
- Protects rat brain neurons from Aβ toxicity
- Activates cell survival (PI3K/Akt) pathway
- Stabilizes TTR tetramers
  - Different mechanism than diflunisal
- Inhibits ATTR amyloid fibril formation
- Promotes breakdown of amyloid deposits
  - Early amyloid aggregates
  - Mature/fixed amyloid deposits
**EGCG**

**ATTR**
- 14 ATTR cardiomyopathy patients
- EGCG 500-700 mg/day x 12 months
- Findings
  - Echo: no change in LV wall thickness
  - Cardiac MRI: 12.5% decrease LV mass

**AL**
- 59 patients with AL amyloid cardiomyopathy
- ECGC 600-800 mg/day + **AL amyloid treatments**
- Findings
  - 11 patients -- > 2 mm septal wall decrease
  - 6 months (range, 3-10)

EGCG

AL Amyloid Cardiomyopathy

Diflunisal IND 68092

- 2’,4’-difluorophenyl salicylate derivative
- Non-Steroid Anti-Inflammatory Drug (NSAID)
- High serum concentrations and low toxicity
ANCOVA: NIS+7

Change from Baseline vs. Study Month

- Placebo
- Diflunisal

ANCOVA significance at: * - 0.05 level, ** - 0.01 level, *** - 0.001 level
No Worsening in 30% taking Diflunisal for 2 YRS

** P = 0.007
Conclusions

- Diflunisal inhibits neurologic progression and preserves quality of life in patients with ATTR-FAP
- Effective across gender, mutations, and severity of disease at entry
- Provides a rare example of repurposing old drugs for new indications
Doxycycline/TUDCA

- Doxycycline 100 BID/TUDCA 250 mg TID x 12 m
- 20 Subjects (17 ATTRm, 2 ATTRwt, 1 Domino LT)

<table>
<thead>
<tr>
<th>Months</th>
<th>N</th>
<th>Nerves</th>
<th>Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>Subst. stability</td>
<td>No progress</td>
</tr>
<tr>
<td>Discontinue</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

New TTR Tetramer Stabilizers

**Tolcapone**
- Catechol-\(O\)-Methyltransferase (COMT) Inhibitor used in PD
- Crosses blood-brain-barrier
- Binds T4 docking site on TTR tetramers
- TTR tetramer stabilizing effect \(\sim\)2X similar concentration

**Tafamidis**
- Short half life may require reformulation
Tolcapone inhibits WT & V122I ATTR

Sant’Anna R et al. (2014) Nat Comm 10:10787
New TTR Tetramer Stabilizers

AG10

• Binds T2 docking site
• More selective binding of T4 than Tafamidis or Diflunisal
• No identified toxicities
• Potentially more mg potent than other TTR protein stabilizers