Alternative Therapies for ATTR

What your mother never told you

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Curcumin

• Natural polyphenol (diferuloylmethane)
• Inhibits Aβ aggregation/breaks up Aβ fibrils
• Blocks toxicity of Aβ fragments on brain cells
• Competes T4 binding to TTR
• Inhibits steps of ATTR fibril formation

Comment:
• Mouse model of very early amyloid aggregation
• Blood curcumin levels unachievable in humans

Ferreira N et al. 2013; 1832(1):39
Resveratrol

• Stabilizes TTR tetramer conformation
• Promotes aggregation of potentially toxic TTR monomers

Comment:
• Insufficient data in humans
• Effective dose undefined

EGCG

- 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

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>
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<tbody>
<tr>
<td>6</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>Subst. stability</td>
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<tr>
<td>Discontinue</td>
<td>2</td>
<td></td>
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<tr>
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Diflunisal IND 68092

- 2’,4’-difluorophenyl salicylate derivative
- Non-Steroid Anti-Inflammatory Drug (NSAID)
- High serum concentrations and low toxicity
Study design

• Multi-center, international, RCT

• Primary endpoint:
  • Neurologic Impairment Score + 7 (NIS+7)

• Secondary endpoints:
  • Kumamoto neurologic scale
  • Modified body mass index (mBMI)
  • Quality of Life Questionnaire (SF-36)
249 Participants screened

119 Excluded by ≥ 1 of the following
   - No amyloid
   - No peripheral/autonomic neuropathy
   - Other causes of neuropathy
   - Predicted survival < 2 yrs or OLT < 1 yr
   - Current anticoagulants
   - Age > 75 years

130 Randomized

66 Randomized to placebo
   - 26 Completed the treatment period
     - 40 Discontinued study drug
       - 23 Disease progression
         - 9 OLT
         - 2 Drug related adverse event
         - 1 Death
   - 28 Included in the primary analysis
   - 66 Included in the longitudinal analysis

64 Randomized to diflunisal
   - 37 Completed the treatment period
     - 27 Discontinued study drug
       - 11 Disease progression
         - 7 OLT
         - 4 Drug related adverse event
         - 0 Death
   - 40 Included in the primary analysis
   - 64 Included in the longitudinal analysis
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