High Dose Vitamin C Treatment of CMT-1A

Richard Lewis
Wayne State University School of Medicine
Detroit, Michigan

Funded by MDA and CMTA
The Rationale for Vitamin C Treatment Trial

- Bunge & Bunge
- SC- Neuronal co-cultures require ascorbic acid to myelinate
- Extracellular matrix

- High dose vitamin c given to a mouse model of PMP-22 over expression produced improved locomotion, lifespan, conduction velocities and remyeliantion of sciatic nerve.


- **Dosing:**
  - 1.12 mg aa/mouse dosage
  - Mice weigh about 25 grams
  - Therefore 45 mg ascorbic acid/kg
  - Human equivalent (70 kg) =3.18 gms
Vitamin C has minimal side effects and toxicity

- GI Upset
- No effects on fertility - single study
- G6PD deficiency - hemolysis
- History of oxalose kidney stones
- Renal disease
The U.S. Trial: FUTILITY DESIGN

- **120 PATIENTS**
  - 96 WITH TREATMENT

- **PRIMARY OUTCOME: FUTILE TO GO FARTHER IF <50% REDUCTION IN CMTNS PROGRESSION COMPARED TO NATURAL HISTORY**
  - If placebo increases CMTNS by 1.3 points, treated patients would need to progress by less than 0.65 points over 2 years
PARTICIPATING CENTERS

- Johns Hopkins  Ahmet Hoke
- U. Rochester  Dave Herrmann
- U. Rochester  Mike McDermott
- Wayne State  Rich Lewis
- Wayne State  Mike Shy
- Safety Monitor  Rick Barohn
- MSG Infrastructure
The People Who Make Things Work

- MSG Coordinating Center
  - Patty Smith
  - Colleen Donlin-Smith
- Wayne State
  - Carly Siskind       Shawna Feely
  - Lindsey Miller     Lisa Rowe
- Johns Hopkins
  - Lori Clawson
1A: Charcot-Marie-Tooth Neuropathy Score (CMTNS)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory symptoms</td>
<td>None</td>
<td>Limited to toes</td>
<td>Extend up to and may include ankle</td>
<td>Extend up to and may include knee</td>
<td>Extends above knees</td>
<td></td>
</tr>
<tr>
<td>Motor symptoms legs</td>
<td>None</td>
<td>Trips, catches toes, slaps feet</td>
<td>AFO on at least 1 leg or ankle support</td>
<td>Cane, walker, ankle surgery</td>
<td>Wheelchair most of the time</td>
<td></td>
</tr>
<tr>
<td>Motor symptoms arms</td>
<td>None</td>
<td>Difficulty with buttons/zippers</td>
<td>Unable to do buttons or zippers, but can write</td>
<td>Can't write or use keyboard</td>
<td>Proximal arms</td>
<td></td>
</tr>
<tr>
<td>Pin sensibility</td>
<td>Normal</td>
<td>Reduced in fingers/toes</td>
<td>Reduced up to and may include wrist/ankle</td>
<td>Reduced up to and may include elbow/knee</td>
<td>Reduced above elbow/knee</td>
<td></td>
</tr>
<tr>
<td>Vibration</td>
<td>Normal</td>
<td>Reduced at fingers/toes</td>
<td>Reduced at wrist/ankle</td>
<td>Reduced at elbow/knee</td>
<td>Reduced above elbow/knee</td>
<td></td>
</tr>
<tr>
<td>Strength legs</td>
<td>Normal</td>
<td>4+,4 or 4- on foot dorsiflexion</td>
<td>≤3 foot dorsiflexion</td>
<td>≤3 dorsi and plantar flexion</td>
<td>Proximal weakness</td>
<td></td>
</tr>
<tr>
<td>Strength arms</td>
<td>Normal</td>
<td>4+,4 or 4- on intrinsics or finger ext</td>
<td>≤3 intrinsics or finger ext</td>
<td>≤5 wrist extensors</td>
<td>Weak above elbow</td>
<td></td>
</tr>
<tr>
<td>Ulnar CMAP (Median)</td>
<td>&gt;6 mV (≥4 mV)</td>
<td>4.5-9.9 mV (2.8 Š 3.9)</td>
<td>2-3.9 mV (1.2 Š 2.7)</td>
<td>0.1-1.9 mV (0.1 Š 1.1)</td>
<td>Absent (Absent)</td>
<td></td>
</tr>
<tr>
<td>Ulnar SNAP (Median)</td>
<td>&gt;9 μV (≥22 μV)</td>
<td>6.8-9.9 μV (14 Š 21.9)</td>
<td>3-5.9 μV (7 Š 13.9)</td>
<td>0.1-2.9 μV (0.1 Š 6.9)</td>
<td>Absent (Absent)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36 MAX</td>
</tr>
</tbody>
</table>
NATURAL HISTORY DATA
OVER 2 YEARS

- CMTNS: 0.7 points/ year
  - 1.35 POINTS over 2 years
- NIS: 3-4 POINTS

Shy ME, Chen L, Swan E, Taube R, Krajewski KM, Herrmann D, Lewis RA, McDermott MP. Neuropathy progression in Charcot Marie Tooth Disease 1A (CMT1A). Neurology 2008; 29;70:378-83
SECONDARY OUTCOME MEASURES

- Neuropathy Impairment Score (NIS)
- PMP22 mRNA levels from skin biopsy
- Change in ulnar motor NCV
- SF-36
INCLUSION CRITERIA

- The patient has CMT1A, defined by the duplication on chromosome 17p11.2 (performed by either Pulse Field Gel Electrophoresis or Fluorescence In Situ Hybridization (FISH) by a CLIA certified laboratory).
- The patient is between 14 and 70 years of age
- CMTNS $\leq$ 25
EXCLUSION CRITERIA

- A known neuropathy from another source (Diabetes, drug induced, alcohol etc)
- The patient is receiving vincristine during or preceding the trial
- The patient has a known history of G6PD deficit
- The patient has a known allergy to ascorbic acid
- The patient has known uncorrected oxalosis.
STUDY DESIGN: FLOW CHART

<table>
<thead>
<tr>
<th>period</th>
<th>Screen</th>
<th>Baseline</th>
<th>Visit 1 M 6</th>
<th>Visit 2 M 12</th>
<th>Visit 3 M 18</th>
<th>End of study visit M24</th>
<th>Follow up visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>-21/-1</td>
<td>0</td>
<td>1-180</td>
<td>181-365</td>
<td>366-545</td>
<td>546-720</td>
<td>30 days after end of study</td>
</tr>
</tbody>
</table>

- Lab Testing
- Chemistry, CBC, Hgb A1C, U/A, Urine oxalate at screen, month 12 and month 24
- Ascorbic Acid levels every 6 months
Medication and Adherence

- 500 mg tablets/capsules, 8 daily
- Placebo tablets/capsules, 8 daily
- Analysis based on intent to treat
- Vitamin C concentration levels
  - Baseline and at each visit
- Returned bottles
Where We Are

- FUNDING FROM MDA AND CMTA 3 YEARS BEGAN JULY 2006 with extension
- FIRST PATIENT ENROLLED APRIL 15, 2007
- 110 (120 planned) patients enrolled with enrollment ending on April 30, 2009
  - Hopkins = 33
  - U or R = 19
  - WSU = 59
- 19 completed by Sept 2009
- Dropouts = 21!!
- Continuing = 70 patients
Baseline Information

- 63 Females (57%) and 44 Males (43%)
- Mean age = 42.3 ± 14.5 (14-68)
- CMTNS = 16.55 ± 4.5 (6-25)
- Ulnar MNCV (m/s) = 20.2 ± 5.7 (9.1-37.9)
- CMAP amp. (mV) = 3.4 ± 2.0 (0.0-9.1)
- Vit C levels = 0.86 ± 0.48 (0.1-3.1)
Next Steps

- Secure funding to complete study
  - MSG, pharmacy must be funded for an additional 2 years. Per patient costs reduced with drop outs.
- Complete study on April 30, 2011
- Try to limit drop outs
- Complete analysis and report by end of 2011
Other Ascorbic Acid Trials for CMT-1A

- Italian/English study using 1.5 grams/day
  - Completed with results pending
- French study using 1 gm or 3 gms/day
  - Completed and reported.
  - In press - Lancet Neurology
- Australian study in children
  - Burns J, Ouvrier RA et al. Lancet Neurology
    8: 537 2009
Australian Study: Design

- 12 month double blind placebo controlled
- 81 children (2-16 years)
  - 45 aged 2-8
  - 36 aged 9-16
- 58% boys
- 30 mg/kg vitamin C or placebo
- Primary endpoint = Median motor NCV
- Secondary endpoints
  - CMAP amp
  - Foot and hand strength
  - Walking
  - QoL
Australian Study: Results

- No statistical difference (1.7 m/s) in MNCV
- 5 Vit c patients increased by 6-17 m/sec and one placebo dropped 12.5 m/sec
  - The 5 had mildest phenotype and best baseline physiology?
  - Is it real or non-physiologic?
- 10 children with conduction block (undefined)
- Strength actually did better in the placebo group (not significant)
- Vitamin C levels increased from 49 µM-111 vs 52-70 in placebo
Australian Study: Lessons

- Need to develop good outcome measures for children
  - CMTNS not validated for kids
  - MNCV does not clearly correlate with clinical weakness
- Studies of less than 2 years unlikely to show effect
- Studies need to be powered to see small effects.
French Study: Design

- 12 month double blind placebo controlled
  - 56 pts – 1 gm/day  
  - 61 – 3 gm/day  
  - 62 – placebo

- Ages 18-70

- Women – 63%

- CMTNS – primary outcome
  - Mean Baseline- 15.8 ± 4.7

- QMT, walk, disability, QoL - secondary
French Study: Results

- No significant difference in change in CMTNS

- Placebo 1g/d AA 3g/d AA

<table>
<thead>
<tr>
<th>Placebo</th>
<th>1g/d AA</th>
<th>3g/d AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=56)</td>
<td>(n=62)</td>
<td>(n=61)</td>
</tr>
<tr>
<td>0.5</td>
<td>0.7</td>
<td>-0.4</td>
</tr>
<tr>
<td>(-0.3 to 1.4)</td>
<td>(-0.0 to 1.4)</td>
<td>(-1.2 to 0.4)</td>
</tr>
</tbody>
</table>

High dose Vit C group had mild improvement in CMTNS but placebo and 1 gm/kg had increase in CMTNS consistent with previous report
#### French Study: Looking for Significance

- **CMTES = CMTNS without CMAP and SNAP**
  - Should one look at subscores of composite scale?

<table>
<thead>
<tr>
<th>Placebo</th>
<th>1 gm</th>
<th>3gms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base</strong></td>
<td>10.9 (4.8)</td>
<td>10.9 (3.7)</td>
</tr>
<tr>
<td><strong>12 m</strong></td>
<td>12 (4.4)</td>
<td>11.6 (3.4)</td>
</tr>
<tr>
<td><strong>Change</strong></td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

\[ (0.1-1.7) \quad (0.1-1.3) \quad (-0.8-0.6) \]

The high dose effect includes clinical variables - symptoms and signs.
## French Study: Vit C levels

- **AA concentration (μmol/L)**

  - **Placebo**
    - Base: 49.2 (28.3)
    - 12 mo: 51.6 (22.8)
    - Change: 4.8 (-5 to 14.6)

  - **1gm**
    - Base: 44.6 (20.1)
    - 12 mo: 86.0 (43.3)
    - Change: 38.0 (24.2 to 51.7)

  - **3gm**
    - Base: 48.7 (19.8)
    - 12 mo: 106.3 (58.0)
    - Change: 56.0 (37.9 to 74.1)

Vitamin C levels increase with higher doses suggesting that there is continued absorption of vitamin as doses go beyond 1 gram/day.
Lessons from French Study

- Higher doses of Ascorbic Acid correlate with higher blood levels
- Study too short to show significance
- CMTNS longitudinal data consistent with published results and points to sensitivity to change
- Encouraging data that higher doses may actually have an effect.
- The US High Dose Trial results will be very interesting
My Personal Lessons

- A 2 year clinical trial takes at least 4 years from time of funding to complete
  - Must recognize this and budget accordingly
- Recruitment always is harder than you think and takes twice as long as planned
- Patient concepts of study may not be the same as yours despite discussions
- Unanticipated things happen
  - Deal with them as best you can
Conclusions

- Recently completed studies, while underpowered and not long enough provide evidence that clinical trials in CMT can be accomplished.

- CMTNS is sensitive to longitudinal change and is a reasonable outcome measure.

- High Dose Vitamin C may have an effect on the disease.

- The combined results of the Anglo-Italian trial and US trial should provide interesting results.
THANKS