High Dose Vitamin C Treatment of CMT-1A

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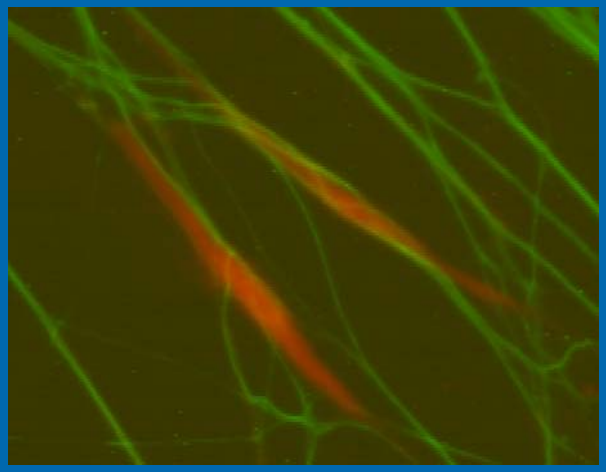
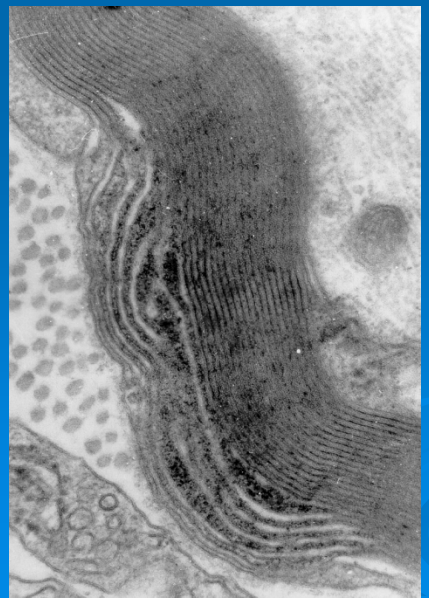
Funded by MDA and CMTA

The Rationale for Vitamin C Treatment Trial





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

Passage E, Norreel JC, Noack-Fraissignes P, et al. Ascorbic acid treatment corrects the phenotype of a mouse model of Charcot-Marie-Tooth disease. *Nat Med 2004; 10: 396–401.*

- 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.
- Subsequent paper by Kaya F, Belin S et al Ascorbic acid inhibits PMP22 expression by reducing cAMP levels. *Neuromuscul Disord 2007; **17: 248–53.***
- 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
  - Lindsey Miller
  - Shawna Feely
  - Lisa Rowe
- Johns Hopkins
  - Lori Clawson

1A: Charcot-Marie-Tooth Neuropathy Score (CMTNS)

Parameter	0	1	2	3	4	Score
Sensory symptoms	None	Limited to toes	Extend up to and may include ankle	Extend up to and may include knee	Extends above knees	
Motor symptoms legs	None	Trips, catches toes, slaps feet	AFO on at least 1 leg or ankle support	Cane, walker, ankle surgery	Wheelchair most of the time	
Motor symptoms arms	None	Difficulty with buttons/zippers	Unable to do buttons or zippers, but can write	Can't write or use keyboard	Proximal arms	
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to and may include wrist/ankle	Reduced up to and may include elbow/knee	Reduced above elbow/knee	
Vibration	Normal	Reduced at fingers/toes	Reduced at wrist/ankle	Reduced at elbow/knee	Reduced above elbow/knee	
Strength legs	Normal	4+,4 or 4- on foot dorsiflexion	≤3 foot dorsiflexion	≤3 dorsi and plantar flexion	Proximal weakness	
Strength arms	Normal	4+,4 or 4- on intrinsics or finger ext	≤3 intrinsics or finger ext	<5 wrist extensors	Weak above elbow	
Ulnar CMAP (Median)	>6 mV (>4 mV)	4-5.9 mV (2.8 Š 3.9)	2-3.9 mV (1.2 Š2.7)	0.1-1.9 mV (0.1 Š 1.1)	Absent (Absent)	
UlnarSNAP (Median)	>9 µV (>22µV)	6-8.9 µV (14 Š 21.9)	3-5.9 µV (7 Š 13.9)	0.1-2.9 µV (0.1 1 6.9)	Absent (Absent)	
Total						36 MAX

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

ɔeriod	Screen	Baseline	Visit 1 M 6	Visit 2 M 12	Visit 3 M 18	End of study visit M24	Follow up visit
Days	-21/-1	0	1-180	181-365	366-545	546- 720	30 days after end of study

- 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 ± .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 years0
  - 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 $\pm$ 4.7
- QMT, walk, disability, QoL - secondary

French Study: Results

- No significant difference in change in CMTNS
- **Placebo** **1g/d AA** **3g/d AA**

(n=56)	**(n=62)**	**(n=61)**
0.5	0.7	-0.4
(-0.3 to 1.4)	(-0.0 to 1.4)	(-1.2 to 0.4)

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?

	Placebo	1 gm	3gms
Base	10.9 (4..8)	10.9 (3.7)	10.6 (3.5)
12 m	12 (4.4)	11.6 (3.4)	10.4 (4.0)
Change	0.9	0.7	-0.1
	(0.1-1.7)	(0.1- 1.3)	(-0.8- 0.6)

The high dose effect includes clinical variables- symptoms and signs

French Study: Vit C levels

- AA concentration (µmol/L)

	Placebo	1gm	3gm
Base	49.2 (28.3)	44.6 (20.1)	48.7 (19.8)
12 mo	51.6 (22.8)	86.0 (43.3)	106.3 (58.0)
Change	**4.8**	**38.0**	**56.0**
	(-5 to 14.6)	(24.2 to 51.7)	(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 under powered 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