THAOS®

Fall 2010

News Update

Issue 5

Inside this issue:

Are You Scheduling Follow Up Visits for Your Patients?

FoldRx is now a wholly owned subsidiary of Pfizer.

Please visit www.Foldrx.com for press release.

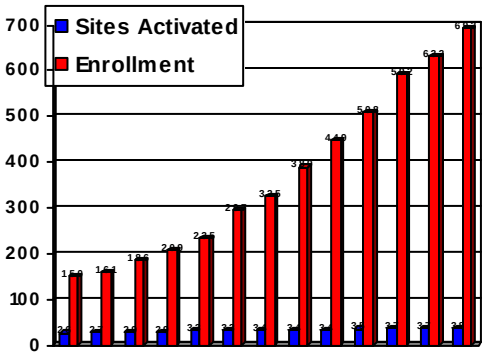
Pfizer FoldRx

Welcome to the Fall edition of the THAOS newsletter! There has been phenomenal growth in the number of subjects enrolled since our last newsletter with 38 active sites in 17 countries (Argentina, Austria, Brazil, Belgium, Cyprus, Denmark, France, Germany, Israel, Italy, Japan, Netherlands, Portugal, Spain, Sweden, Switzerland, The United States) and an enrollment of 693 subjects (31 October 2010). With a terrific effort by all of our THAOS sites, we were able to extract analyzable data for 560 subjects for the upcoming publication. As you will see when reviewing these pages, the baseline data is very informative. These data highlight the importance of providing the minimal dataset and follow up data, which are necessary to get a complete picture of the progression of the disease. The Quality of Life data show that ATTR patients perceive themselves to be generally sicker than patients with other chronic diseases. Remember, the database is here for you. Any THAOS site can propose an analysis of the data for publication. ***Teresa Coelho, Chair, THAOS Scientific Board***

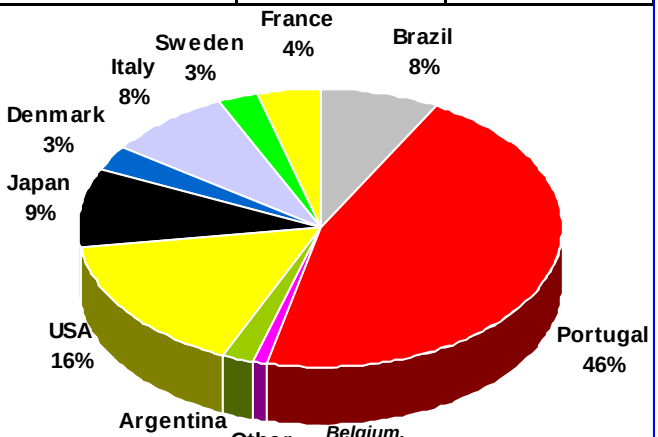
Current Enrollment Status

† indicates data unavailable

	May-10	Oct-10
# sites	34	38
# countries	14	17
# patients	367	693
# patients with mutations	320	603
# patients with wt	42	67
# mutations	21	38
# mutations with 1 patient	13	19
# mutations with 10 patients or more	3	8
# patients with follow-up data	†	58



October 2009-October 2010

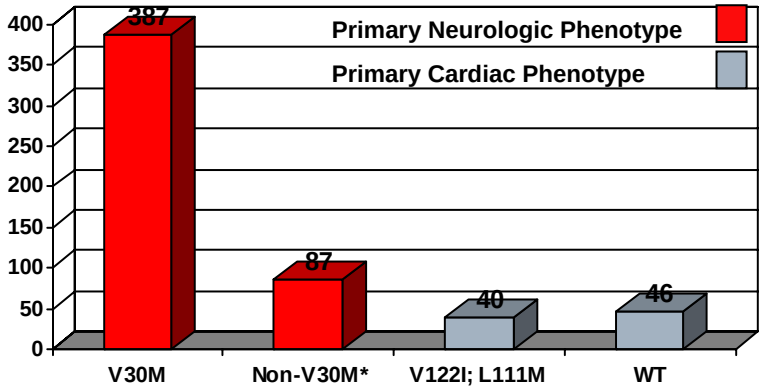


Within the last 6 months, enrollment has more than doubled, number of active sites increased by 4, and countries by 3. The majority (46%) of THAOS subjects come from Portugal, followed by the USA and Japan. The number of sites enrolling subjects with neurology phenotypes (21) is slightly more than sites enrolling subjects with cardiology phenotypes (17).

The top 3 enrolling sites are :
Teresa Coelho, Porto, Portugal *261*
Márcia W. Cruz, Rio de Janeiro, Brazil *56*
Isabel Conceiçao, Lisbon, Portugal *53*

ANALYSIS of BASELINE DATA for 560 SUBJECTS

Of the 560 subjects with analyzable data, 514 subjects (91%) had mutations and a median age of 42.3 years. Of the 46 W-T TTR subjects, almost all (97.8%) were male with a median age of 76.6 years. The majority of subjects were Caucasian. Of the 514 subjects with mutations, 70% were symptomatic, while 92% of W-T TTR subjects were symptomatic. 27 genotypes were identified with 92% expressing a primary neurologic phenotype.



*Val28Met, Val32Ala, Phe33Leu, Arg34Thr, Try41Leu, Glu42Gly, Ala45Ser, Thr49Ala, Ser50Arg, Ser50Ile, Ser52Pro, Thr59Lys, Thr60Ala, Phe64Leu, ILe68Leu, Val71Ala, Ser77Phe, Ser77Tyr, His88Arg, Glu89Gln, Glu89Lys, Glu92lys, ILe107Val, Val122Ala

Subjects with TTR Mutations

	Total M/F	%	Median Age (yrs)	Age at Onset (yrs)	Disease Duration (yrs)
Val30Met	387 174/213	75.3	38.2	34.0	4.6
Val122Ile	23 18/5	4.5	72.4	68.6	2.1
Leu111Met	17 10/7	3.3	47.6	42.9	4.3
Glu89Gln	14 5/9	2.7	49.9	50.6	1.9
Phe64Leu	12 6/6	2.3	66.6	62.7	6.0

Symptomatic Subjects with Val30Met

	Portugal N = 154	Brazil N = 40	Japan N = 47	Sweden N = 15
Males (%)	52	53	45	67
Age at onset, yrs	32.6	30.6	39.8	51.6
Disease duration, yrs	3.1	7.5	6.0	5.2
Ethnicity (%)				
Caucasian	100	73		100
Latino American		6		
Asian			100	
Other		21		

The five most common mutations cover 88% of subjects with TTR mutations. Val30Met is the most common of the TTR mutations. Of the 387 subjects with Val30Met, 256 (66.1%) are symptomatic and are clustered in 4 countries. Age of onset varies within the same mutation depending on geographic location and also differs across mutations.

Family History in 514 Subjects with Mutations

	Positive	%
Subjects with Family History	**440**	**85.6**
Father	223	50.7
Mother	190	43.2
Father+mother	4	0.9
Other	5	1.1
Unknown	18	4.1
Pts with no known Family History	**54**	**10.5**
Unknown Family History	**17**	**3.3**
Missing	**3**	**0.6**

Family history was reported for 85.6% of subjects with inheritance almost evenly distributed between mother and father.

Biopsies and Transplants (Symptomatic Subjects)

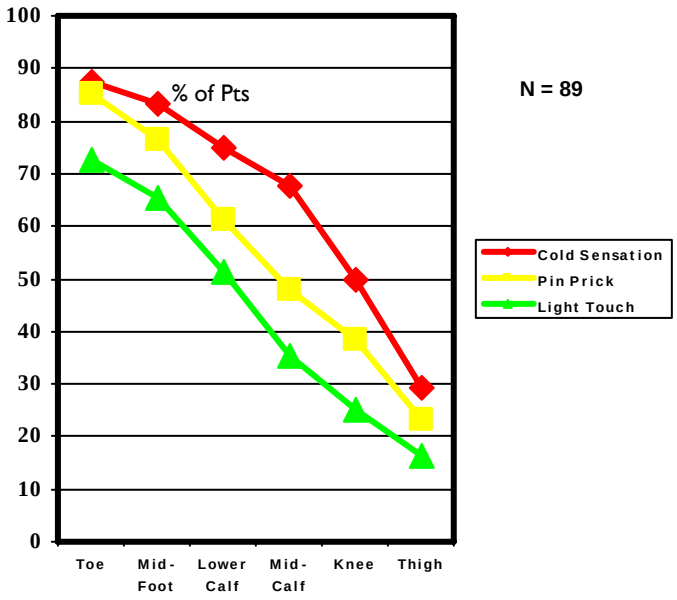
	Mutations N = 364	W-T TTR N = 42
# Pts with Biopsies	236 (64.8%)	42 (100%)
# Biopsies Performed	288	49
# Pts with + amyloid	204	41
Most Common Biopsies		
Salivary Gland	30.0%	0.0%
Abdominal Fat Pad	19.4%	8.2%
Cardiac	13.9%	81.6%
# Pts with Transplants	100 (27.5%)	3 (7.1%)
# Transplants	107	4
Liver only	89	0
Heart only	5	2
Kidney only	0	0
# Pts with 2 Transplants	5	1
# Pts with 3 Transplants	1	0

64.8% of subjects with mutations had biopsies compared with 100% of subjects with W-T TTR. The salivary gland was the most common biopsy tissue for subjects with mutations. 27% of subjects with mutations had transplants.

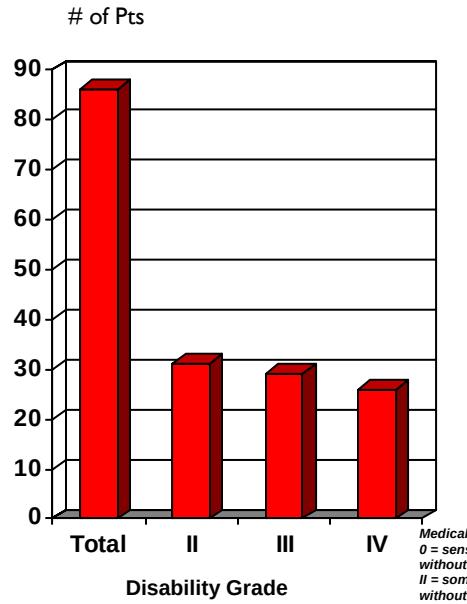
HIGHLIGHTS

Neuropathy Data

DECREASED/ABSENT SENSATIONS IN SYMPTOMATIC SUBJECTS WITH MUTATIONS



WALKING DISABILITY IN SYMPTOMATIC SUBJECTS WITH MUTATIONS



Medical Research Council UK (MRC scale)
0 = sensory disturbance in feet, but walks without difficulty
II = some difficulty walking, but walks without aid
IIIa = walks with one stick or crutch
IIIb = walks with two sticks or crutches
IV = not ambulatory; wheelchair or bedridden

Nearly all patients with mutations (82%) reported sensory neuropathy symptoms. In those with all sensory assessments completed (N = 89), impairment was greater distally than proximally with greater involvement of small fibers (cool and pinprick). 86 patients with mutations had motor impairment as demonstrated by ambulatory difficulties. Actual degree of disability is highlighted in the graph.

Health-Related Quality of Life

PERCEIVED HEALTH IN SUBJECTS vs CONTROLS

Age group	Symptomatic	Asymptomatic	Controls*
18-34	0.81 (N=70)	0.93 (N=50)	0.92
35-49	0.68 (N=70)	0.89 (N=27)	0.88
50-64	0.56 (N=45)	0.81 (N=9)	0.84
65+	0.64 (N=40)	0.91 (N=4)	0.79

*** 6,000-12,000 subjects per age group PW Sullivan et al, *Med Care*:2005;43:736-749**

EQ-5D IN VARIOUS DISEASE STATES

Disease	Age, yrs	N	EQ-5D index
THAOS patients with symptoms	**50-64**	**45**	**0.56**
Diabetes*	60	2,854	0.758
Stroke*	67	995	0.694
Emphysema*	66	597	0.680
Congestive Heart Failure*	71	284	0.636
Rheumatoid Arthritis*	59	235	0.661
General US population	**50-64**	**8,275**	**0.838**

EQ-5D index scores were calculated for all patients with mutations. Different age groups of symptomatic and asymptomatic subjects were compared to Controls (US) and to patients with other chronic diseases. These data demonstrate that symptomatic subjects with ATTR report worse quality of life when compared to controls, asymptomatic subjects and patients with other chronic diseases.

UPDATE on Minimal Dataset for Evaluation

At the THAOS Scientific Board Meeting in September, 2010, the Board recommended that two more tests be added to the Minimal Dataset for Evaluation. As the BNP or NT-Pro BNP test may not be available at all sites, the Board recommended that an echocardiogram be added to the dataset. Serum prealbumin (transthyretin) levels are also to be added. The following is the recommended minimal dataset for each patient enrolled in THAOS, regardless of genotype, including asymptomatic carriers:

- **Registration**
- **TTR data**
- **Family History**
- **Medical History**
- **Physical Exam**
- **Serum Albumin Levels**
- ***Serum Prealbumin (transthyretin) levels ****
- **Serum NT-ProBNP or BNP levels (if abnormal, then echocardiogram would be recommended)**
- ***Echocardiogram (if NT-Pro BNP or BNP levels are not measured)****
- **Electrocardiogram**
- **Pinprick, touch and vibration of great toe (both sides); ankle and patellar reflexes; muscle strength of toes and ankles (if abnormal, then either perform full neurologic examination or refer to neurology for evaluation.)**

Yearly follow-up is recommended with re-evaluation of the minimal assessments at the least. It is requested that complete clinic visit evaluation data along with Quality of Life are entered into THAOS.

* ***New***

THAOS Presentations

Scientific Meetings:*

XXIV Brazilian Congress of Neurology, August 24-27, Rio de Janeiro, BRA – Oral Presentation

Heart Failure Society of America (HFSA), September 12 – 15, San Diego, CA, Poster - Clinical Trial Row

European Federation of Neurological Societies (EFNS), September 25-28, Geneva, Switzerland - Oral Presentation, Booth

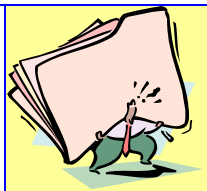
Advancing Neuromuscular, Musculoskeletal, & Electrodiagnostic Medicine (AANEM), Oct 6 – 9, Quebec, CAN - Booth

American Society of Human Genetics (ASHG), November 2 – 6, Washington, DC – Booth

Neuropathy Associations' Neuropathy Summit, December 3 – 5, Washington, DC - Booth

**Abstracts from prior meetings can be viewed via the Investigator's portal on the THAOS Website (www.thaos.net)*

THAOS is a registry. The goals are to enhance the understanding of the disease natural history, to better understand genotype-phenotype relationship, and to compare the progression of the disease and overall survival in patients with ATTR with and without liver transplant. To achieve these goals, it is critical to have genotypic diversity and enough patients in each genotype to assess genotype-phenotype relationship. There also must be sufficient data for each patient and enough follow-up data to assess disease progression. Because these data are so critical, follow-up appointments and data collection are crucial to the success of THAOS.



Remember

to

Schedule Follow Up Visits for Your Patients!!!!