THAOS®

Transthyretin Amyloidosis Outcomes Survey

Newsletter

December 2015

THAOS: The Year in Review

On behalf of the THAOS Scientific Board, I want to thank all investigators for their continued hard work in helping to expand and develop the THAOS registry throughout 2015. The work we do ensures that the registry remains an excellent resource that can help to improve clinical practice and the lives of patients with TTR-amyloidosis.

For all those involved, 2015 has been a busy and productive year. Our second Investigators Meeting was held in Madrid, Spain, during May. This offered an opportunity for investigators from around the world to discuss the registry, and also set the foundation for further research and collaboration.

This research and collaboration throughout 2015 has seen a number of data presentations and the development of a number of forthcoming publications. These include:

- Analysis of the clinical course of patients with Val30Met TTR familial amyloid polyneuropathy (FAP) included in THAOS treated with tafamidis and liver transplantation compared to the natural evolution of the disease
- Myocardial contraction fraction: a volumetric index for predicting mortality in transthyretin cardiac amyloidosis
- Clinical and cardiac disease profiles of hereditary and wild type transthyretin amyloidosis in Europe
- Single center analysis of Brazilian patients in THAOS

Further publications allow us to improve our understanding of the complexities of the disease and learn more from each other as investigators. As was emphasized in Madrid this year, publishing findings from THAOS needs to be a key objective, and remain so for 2016 and beyond.

While we have seen success in the past 12 months, we need to continue to push forward, making full use of the available data and continuing to share our learnings and publications with the wider scientific community. We also need to better capture information on patients. Changes to the database aim to make this easier, for example, the patient status form is now much more functional, and allows multiple records to be entered.

There is a need to ensure good quality, accurate follow-up to allow robust scientific conclusions to be drawn.

Finally, at the end of the year, we can also report a further increase in the numbers enrolled in the database. We now have 3005 subjects enrolled in THAOS across 25 countries – and we give a warm welcome to the eight new sites that have joined the registry this year.

THAOS continues to grow, and we must strive to maintain and nurture this growth throughout 2016.

Claudio Rapezzi
Chair of the THAOS Scientific Board
University Hospital S. Orsola-Malpighi, Italy

THAOS Scientific Board

Features of transthyretin cardiomyopathy patients with six specific cardiac genotypes in the THAOS registry

Jennifer Schumacher, Leslie Amass, Denis Keohane, Rajiv Mundayat, Moh-Lim Ong, Pfizer Inc., US

This retrospective, cross-sectional study was designed to describe the disease characteristics of 452 symptomatic patients enrolled into the THAOS registry with the following *TTR* genotypes, associated with cardiomyopathy: Wild-type (WT, n=269); Val122Ile (n=89); Thr60Ala (n=36); Glu89Gln (n=25); Ile68Leu (n=22); Leu111Met (n=11).

Assessments included:

- Basic demographics, age of first cardiac symptom, duration of disease
- Electrocardiogram (ECG) and echocardiographic (EEG) parameters at enrollment

Demographics

- Significant differences existed between patients with WT and mutant forms of *TTR*; WT TTR patients had a higher relative male population, age at first cardiac symptom and age at THAOS enrollment

ECG parameters at enrollment

- The prevalence of ECG parameters reflective of cardiac abnormalities was tested; low voltage was higher in mutant forms of TTR compared to WT, whereas the opposite was observed for atrial fibrillation (Table 1)
- The prevalence of elongated PR intervals (>200 ms) was similar between patients with WT or mutant TTR

EEG parameters

- Mean left ventricular (LV) septum thickness was similar between WT and mutant forms of TTR amyloidosis, with the exception of a comparably thicker LV septum in patients with Thr60Ala, and thinner LV septum in patients with Leu111Met
- Ejection fraction was comparable between WT and mutant forms of TTR amyloidosis

Table 1: ECG parameters

Genotype*	Prevalence of low voltage	Prevalence of PR intervals >200 ms	Prevalence of atrial fibrillation
WT	27.3% (total n=172)	48.7% (total n=113)	65.5% (total n=119)
All mutations	44.3% (total n=97)	37.5% (total n=88)	39.1% (total n=46)
Val122Ile	44% (total n=50)	39.2% (total n=51)	23.1% (total n=26)
Thr60Ala	38.9% (total n=18)	33.3% (total n=15)	50% (total n=8)
Glu89Gln	60% (total n=10)	0% (total n=7)	60% (total n=5)
Ile68Leu	42.1% (total n=19)	53.3% (total n=15)	71.4% (total n=7)

*Data was unavailable for patients with Leu111Met mutation

Conclusions

Several key features of cardiac presentation of disease are similar between patients with WT and mutant form TTR, although significant differences were detected in gender ratio, age at enrollment, and age at onset of cardiac symptoms between these groups. Larger studies of TTR amyloidosis patients may resolve further differences between these two forms of disease.

An overview of the demography, clinical characteristics and genetics of Latin American patients enrolled in THAOS

Márcia Waddington-Cruz, Fabio Barroso, Alejandra González-Duarte, Rajiv Mundayat, Moh-Lim Ong on behalf of the THAOS investigators

Demographics

A total of 248 subjects from three countries across Latin America have been entered into the THAOS registry:

- **Argentina**: n=51; Val30Met comprises 96.1%
- **Brazil**: n=140; Val30Met comprises 92.1%
- **Mexico**: n=57; Ser50Arg comprises 80.7%

Clinical phenotypes

For symptomatic patients entered into THAOS, clinical phenotypes can be classified as cardiac, neurologic or mixed; the distribution of clinical phenotypes varies across countries in Latin America (Table 1).

Clinical progression

The Coutinho Stage[1] was used to determine disease severity and clinical progression. The majority of patients in Latin America are at Coutinho Stage 1*. The transition to Stage 2 takes the longest length of time (median 4.5 years [IQR: 2.2])

Table 1: Clinical phenotypes across countries in Latin America

Clinical phenotype in Latin America
Majority (>55%) have a neurologic phenotype
Mixed phenotype was the second most common • Argentina <15%, Brazil and Mexico >20%
Cardiac phenotype was the least common • Mexico >12%, Brazil and Argentina <5%

Conclusions

Investigations using the THAOS registry can provide valuable, regional information as to common *TTR* mutations, clinical phenotypes and natural history of the disease.

*Coutinho Stages[1]: 0: no symptoms; 1: mainly mild sensory, motor and autonomic neuropathy; 2: assistance with ambulation required, moderate impairments move to trunk, lower and upper limbs; 3: requiring a wheelchair or bedridden, severe sensory, motor and autonomic dysfunction in all limbs.

Reference

1. Coutinho P, et al. Forty years of experience with type 1 amyloid neuropathy: review of 483 cases. In: Glenner GG, e Costa PP, de Freitas AF, eds. Amyloid and Amyloidosis. Amsterdam: Excerpta Medica; 1980:88–98.

Spotlight

Each edition of the THAOS newsletter features a 5-minute interview with an investigator who will explain their rationale for being part of the registry, how it works within their clinic and their aspirations for THAOS in the future.

Isabel Conceição is a Consultant in Neurology and Clinical Neurophysiology at Centro Hospitalar Lisboa Norte-Hospital de Santa Maria, Lisbon, Portugal. Her clinical practice focuses on neuromuscular outpatient care and clinical neurophysiology, namely electromyography and evoked potentials. She has been the Head of the Familial Amyloid Polyneuropathy outpatient unit, Hospital de Santa Maria, Lisbon, since 2004, where she monitors more than 300 TTR-FAP patients and asymptomatic carriers.

What was the most important reason for your center to join THAOS?

The main reason for my site to join the THAOS registry was the existence of a high number of patients with clinical information organized in a non-structured and non-uniform way.

The longitudinal evaluation in a structured way enables regular follow-up with a strong impact on the perception of the natural history of the disease and of the efficacy of the several therapeutic options.

Also, the opportunity to interact with other THAOS sites scattered worldwide, those that had great experience in approaches to follow-up and evaluation of patients.

How is THAOS organized in your clinic?

The patients followed in our FAP outpatient clinic have different frequencies of follow-up depending on their disease stage: asymptomatic carriers have yearly visits and symptomatic patients visit every 4–6 months.

The patients in our clinic are asked for their informed consent to register their clinical data into the THAOS database. Once informed consent is given, the consultation is conducted according to clinical protocols used in THAOS: global clinical evaluation, neurological evaluation, conduction velocities, and analytical evaluation. These data are not only collected in THAOS but also stored in the patient's clinical file. We also capture data on cardiologic, ophthalmologic or renal evaluation.

Whenever the patient is lost to follow-up, we establish contact via telephone with the patient or with a family member. This helps us keep the clinical file updated, and, if necessary, discontinue THAOS data collection.

What do you see as the key value of THAOS for patients and physicians?

THAOS has been an extremely useful tool for research, to learn about genotype/phenotype correlation, and the natural evolution of the disease, as well as the response to treatment.

The interaction between THAOS sites is very important to learn more about other mutations and phenotypes, and has a great impact on our clinical practice.

Participation in this type of study guarantees that clinical data are collected according to standardized clinical questionnaires and ensures the harmonization of clinical information for patients' benefit.

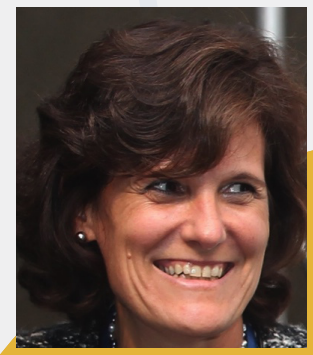
What do you hope THAOS will contribute over the next 5 years?

THAOS will increase our knowledge on the natural history of the disease and on therapeutic intervention. The rigorous maintenance of the registry will allow us to increase our knowledge of the genotype/phenotype correlation that is not clearly understood in some cases.

Additionally, exchange between experts might lead to changes in the clinical approach, particularly for the management of these patients.

If you could give one piece of advice to a new THAOS center, what would it be?

Although rigorous data collection might appear time consuming, this minimal data set is of the upmost importance to ensure that no information is lost in the global evaluation of patients.



Dr Isabel Conceição
Centro Hospitalar Lisboa Norte-Hospital de Santa Maria, Lisbon, Portugal

The importance of patient follow-up

From January through to the end of November 2015, the registry indicates that only 47.9% of active subjects either have had a follow-up visit or status update. Among this group, there were total of 96 Patient Status pages completed, amounting to 7.5% of the total follow-up visits during this period. Despite this figure effectively being double that of the value from 2014, the patient status update scheme was only launched late 2014 and, as such, a direct comparison is not valid.

Given approximately half of all patients did not have any follow-up this year, it is important that we better utilize the Patient Status page to follow-up with those patients who are unable to return to the clinic. This can be achieved through a site visit, telephone assessment or reporting from a family member.

We need to better capture information on patients – only with quality, accurate follow-up will we be able to draw scientific conclusions that will improve the understanding of this disease and improve outcomes for our patients.

The form allows for the entry of the current patient status, categorized as one of the following:

- Patient withdrew consent
- Patient lost to follow-up
- Patient died
- Patient is asymptomatic
- Patient well, not visiting PI
- Patient transferred to another site
- Patient participating in double-blind trial
- Patient status unknown
- Other