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Genotype and Phenotype of Transthyretin Cardiac Amyloidosis

THAOS (Transthyretin Amyloid Outcome Survey)

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ABSTRACT

BACKGROUND Transthyretin amyloidosis (ATTR) is a heterogeneous disorder with multiorgan involvement and a genetic or nongenetic basis.

OBJECTIVES The goal of this study was to describe ATTR in the United States by using data from the THAOS (Transthyretin Amyloidosis Outcomes Survey) registry.

METHODS Demographic, clinical, and genetic features of patients enrolled in the THAOS registry in the United States (n = 390) were compared with data from patients from other regions of the world (ROW) (n = 2,140). The focus was on the phenotypic expression and survival in the majority of U.S. subjects with valine-to-isoleucine substitution at position 122 (Val122Ile) (n = 91) and wild-type ATTR (n = 189).

RESULTS U.S. subjects are older (70 vs. 46 years), more often male (85.4% vs. 50.6%), and more often of African descent (25.4% vs. 0.5%) than the ROW. A significantly higher percentage of U.S. patients with ATTR amyloid seen at cardiology sites had wild-type disease than the ROW (50.5% vs. 26.2%). In the United States, 34 different mutations (n = 201) have been reported, with the most common being Val122Ile (n = 91; 45.3%) and Thr60Ala (n = 41; 20.4%). Overall, 91 (85%) of 107 patients with Val122Ile were from the United States, where Val122Ile subjects were younger and more often female and black than patients with wild-type disease, and had similar cardiac phenotype but a greater burden of neurologic symptoms (pain, numbness, tingling, and walking disability) and worse quality of life. Advancing age and lower mean arterial pressure, but not the presence of a transthyretin mutation, were independently associated with higher mortality from a multivariate analysis of survival.

CONCLUSIONS In the THAOS registry, ATTR in the United States is overwhelmingly a disorder of older adult male subjects with a cardiac-predominant phenotype. Val122Ile is the most common transthyretin mutation, and neurologic phenotypic expression differs between wild-type disease and Val122Ile, but survival from enrollment in THAOS does not. (Transthyretin-Associated Amyloidoses Outcome Survey [THAOS]; NCT00628745) (J Am Coll Cardiol 2016;68:161–72)

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ABBREVIATIONS AND ACRONYMS

ATTR = transthyretin amyloidosis

BMI = body mass index

EDV = end-diastolic volume

HFpEF = heart failure in the setting of a preserved ejection fraction

LV = left ventricular

LVEDD = left ventricular end-diastolic dimension

mBMI = modified body mass index

MCF = myocardial contraction fraction

mt-ATTR = mutated or hereditary transthyretin amyloidosis

QOL = quality of life

ROW = other regions of the world

SV = stroke volume

TTR = transthyretin

TTR-CM = transthyretin cardiomyopathy

Val122Ile = valine-to-isoleucine substitution at position 122

wt-ATTR = wild-type transthyretin amyloidosis

Transthyretin amyloidosis (ATTR) belongs to a group of severe systemic conditions caused by the extracellular deposition of insoluble protein fibrils within tissues and organs (1). Amyloid formation in ATTR is thought to occur when dissociated transthyretin (TTR) monomers misfold and assemble into amyloid fibrils, with amyloidogenic mutation in the *TTR* gene facilitating the dissociation of the tetramer into monomers (2). Approximately 100 disease-causing *TTR* gene mutations (3) have been reported; some are believed to be associated with particular phenotypes, although considerable variability exists among patients (4).

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There are 2 distinct types of ATTR: hereditary or mutated (mt-ATTR) and wild-type (wt-ATTR; also referred to as senile systemic amyloidosis, age-related amyloidosis, or senile cardiac amyloidosis). Mt-ATTR is a rare autosomal dominant condition caused by mutations in the *TTR* gene with considerable heterogeneity in disease presentation (5); phenotypes can be predominantly neuropathic (known as familial amyloid polyneuropathy) (6), predominantly cardiac (or transthyretin cardiomyopathy [TTR-CM]), or mixed (7). The present article describes ATTR in the United States compared with other regions of the world (ROW). We used data from the global THAOS (Transthyretin Amyloidosis Outcomes Survey) patient registry and specifically focused on differences between the phenotypic expression and outcomes in the majority of U.S. subjects with a valine-to-isoleucine substitution at position 122 (Val122Ile) (n = 91) and wt-ATTR (n = 189).

METHODS

THAOS is an ongoing, global, multicenter, longitudinal, observational survey open to all subjects with ATTR (familial and wild-type) and individuals with *TTR* gene mutations without a diagnosis of ATTR (asymptomatic). The registry collects data on the natural history of ATTR, and its principal aims are to better understand and characterize the natural history of the disease by studying a large, heterogeneous patient population. The data extracted for this study included information on patients from 17 countries. Demographic, clinical, and genetic characteristics of subjects enrolled in the THAOS registry in the United States (n = 390) were compared with those observed in the ROW (n = 2,140). The design and methods of the THAOS registry, including data collection methods and assessments, have been previously described (8). THAOS data are stored in a secure server maintained by Pfizer Inc. Patient information is submitted electronically by participating physicians and remains confidential according to country-specific regulations and guidelines. Data obtained during routine clinical practice are entered into THAOS at each clinic visit by using a secure Internet-based application. There is a suggested minimal dataset that recommends certain testing be performed in all subjects

were derived from the THAOS registry, which is sponsored by Pfizer Inc. Dr. Coelho's institution received support from FoldRx Pharmaceuticals, which was acquired by Pfizer in October 2010; has served on the scientific advisory board of Pfizer and received funding from Pfizer for scientific meeting expenses (travel, accommodation, and registration); currently serves on the scientific advisory board of THAOS. Dr. Damy has received grants and consulting fees from Pfizer. Dr. Dispenzieri has received research dollars from Celgene, Millennium, Pfizer, and Janssen; she has also received funding from Pfizer for meeting expenses (travel). Dr. Witteles has served as a site Principal Investigator for transthyretin trials for Pfizer and Alnylam. Drs. Gottlieb and Hummel have received research funding from Pfizer. Dr. Judge has served as an advisor to Pfizer and GlaxoSmithKline. Dr. Kristen has received research support from and served on advisory boards for Pfizer; and currently serves on the scientific advisory board of THAOS. Dr. Maurer has received support from FoldRx Pharmaceuticals as a clinical investigator and for scientific meeting expenses; his institution has received grant support from Pfizer; has served on the scientific advisory board of and received funding from Pfizer for scientific meeting expenses (travel, accommodation, and registration). Dr. Planté-Bordeneuve received support from FoldRx Pharmaceuticals as a clinical investigator and serves on the THAOS scientific advisory board but did not receive compensation for this involvement. Dr. Rapezzi received research grants and consultant and speaker honoraria from Pfizer. Dr. Shah has received consulting fees from Alnylam. Dr. Silver is a speaker for Amgen and serves on the advisory board for Legacy Heart Care. Dr. Suhr receives support as a clinical investigator financed by Pfizer and Alnylam; his department has received payment for lecturing and participating in educational activities financed by Pfizer. Dr. Waddington Cruz received support from FoldRx Pharmaceuticals as a clinical investigator and has served on the scientific advisory board of Pfizer; currently serves on the THAOS scientific advisory board. Mr. Mundayat is an employee of and holds stock options in Pfizer. Dr. Ventura's institution has received support from Pfizer for a clinical trial. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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