Clinical trial and registry Update II

THAOS: TranstHyretin Amyloidosis Outcomes Survey: an international Registry

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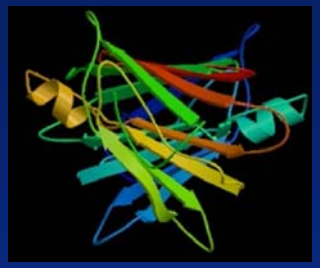
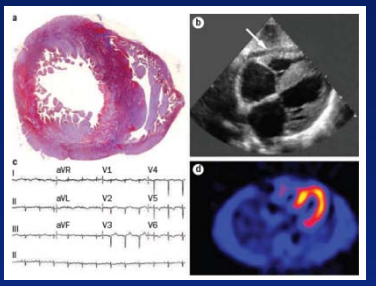
Disclosure slide for potential conflicts of interest

Relationships with Industry

- Research funding (grant):
  - To me: no / To my institution: yes (Genzyme, Actelion)
- Consulting/advising fees: no
- Stockholder of a healthcare company: no
- Royalties for intelectual properties: no
- Patents: no with Industry (but patent with Iserm-transfert institution)
- Speaker fees: no
- Advisory board fees: no



Context



(hereditary form of) transthyretin-related amyloidosis (ATTR)

- Rare disease (but quite prevalent in Portugal, Sweden, Japan)
- Underdiagnosed or delayed diagnosis
- Fatal condition (at least for neurodegenerative disorders)
- Natural history, and determinants, are poorly understood
- No specific / effective treatment currently available regarding heart impairement (orthotopic liver transplantation for neurologic forms)

Rapezzi et al., Nat Rev Cardiol 2010; Dungu et al, Heart 2012

Main findings of THAOS registry

- The largest collection of patients reported so far: 1219 subjects with validated data (108 with WT ATTR & 1111 with hereditary ATTR)
- Description of TTR mutations spectrum: 51 mutations, 9 predominant, Val30Met as the most frequent one (75%), 4 mutations with exclusive/main cardiac phenotype (Val122Ile, Leu111Met, Thr60Ala, Ile68Leu)
- Features suggestive of hereditary ATTR: symmetric left ventricular hypertrophy (LVH), normal diastolic LV volume, mildly depressed LVEF, male gender and age > 60
- Determinant of age at onset: gender of the patient, gender of the transmitting parent, type of mutation and (for V30M) by geographic area.

Potential weaknesses and limitations (1)

- Design and potential bias: Role of funding (Pfizer)? Selection bias? Measurement bias? Information bias? Missing information? → More information on the design of the registry and data analysis (ex: Echographic data for 227 patients only?)

- Features suggestive of hereditary ATTR: based on a limited population (<100 patients?) and lack of comparison → clarify the population and suggest comparison with AL amyloidosis, wt ATTR and sarcomeric HCM

Potential weaknesses and limitations (2)

- Determinant of age at onset: only univariate analyses are reported → suggest multivariate analyses

- Statistical analyses: potential impact on phenotype of specific mutations and respective « weight » of families (large/small) → suggest to take into account such co-variates

- No data on severity/complications at baseline and no follow-up: → additional analyses pending?

Conclusion

- THAOS registry offers a unique opportunity to assess the phenotypic and genotypic spectrum and correlations in ATTR and can represent a model for the study of rare diseases with worldwide impact.

- Preliminary results are very promising. Additional analyses are suggested

- This registry will facilitate comprehension of the natural history of the disease and offer the potential to evaluate novel therapeutic modalities (tafamidis? diflunisal? siRNA?) in diverse patient subpopulations.