#60

Positive Real-World Effectiveness of Tafamidis for Delaying Disease Progression in Transthyretin Familial Amyloid Polyneuropathy

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BACKGROUND

- Transthyretin (TTR) familial amyloid polyneuropathy (TTR-FAP) is an inherited, progressive sensorimotor and autonomic polyneuropathy caused by systemic deposition of amyloid fibrils in a variety of tissues and organs, including the peripheral nerves and heart.[1]
- The increased propensity for TTR to misfold and form amyloid fibrils in TTR-FAP is due to the presence of ≥1 mutations in the TTR gene.
- More than 100 different TTR mutations have been identified, with the majority leading to amyloidosis, the most common being the Val30Met mutation.
- Liver transplantation in well-selected patients is a recognized treatment for TTR-FAP, although it is associated with substantial risk and is not suitable for all patients.
- The TTR stabilizer, tafamidis (Vyndaqel®), was approved by the European Medicines Agency in 2011 and is emerging as the standard of care for TTR-FAP in clinical settings.[2]
- Efficacy and safety of tafamidis have been demonstrated in clinical trials, yet little is known about its real-world effectiveness.[3,4]
- An ongoing global disease registry, the Transthyretin Amyloidosis Outcomes Survey (THAOS), collects data on both treated and untreated patients from real-world settings.[5]

OBJECTIVE

- To compare outcomes in patients with TTR mutations in the THAOS database receiving tafamidis versus matched untreated controls.

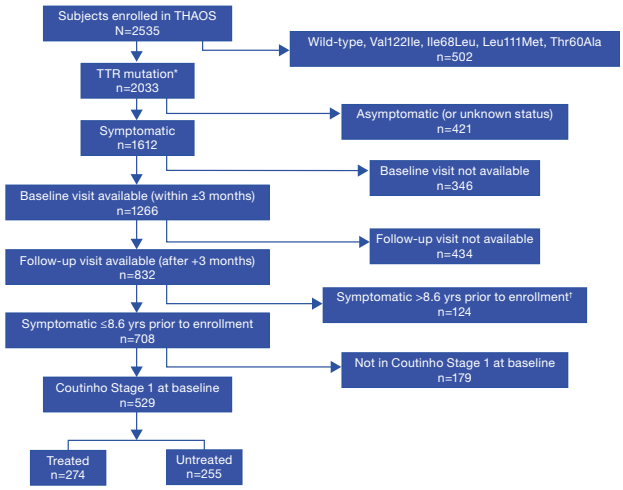
METHODS

- THAOS registry data were used to match tafamidis-treated patients to untreated controls in a non-randomized retrospective cohort study.
- The following genotypes or mutations primarily associated with cardiac presentation were excluded: wild-type, Val122Ile, Ile68Leu, Leu111Met, and Thr60Ala.
- Matching was achieved through a combination of exact matching based on genetic mutation (Val30Met or non-Val30Met), then region of birth, followed by nearest-neighbor matching, using propensity scores within 0.25 standard deviations (SDs; logit scale, treated vs untreated) to capture clinical status at baseline.
  - Propensity scores used for matching reflected the mean of up to 101 individual regression models.
  - Each treated patient was matched with up to 4 untreated controls. Matching with replacement was allowed. Untreated control subjects could be used in multiple matched sets and could have multiple baselines.
- Baseline was defined as follows:
  - Tafamidis-treated patients:
    - Enrollment date if tafamidis treatment started before enrollment.
    - Treatment start date if tafamidis treatment started on or after enrollment.
  - Untreated matched controls:
    - Any visit occurring after symptom onset and not >3 months prior to enrollment.
- Descriptive statistics were calculated. Treatment effects were tested by repeated measures analyses with appropriate covariates (age, gender, disease duration, propensity score, time and treatment by time interaction, and baseline values).
- Analysis endpoints included neurologic assessments, Norfolk Quality of Life-Diabetic Neuropathy total score (TQOL), Karnofsky Performance Status Index, and modified body mass index (mBMI).
- Based on the THAOS neurologic examination, the Neurologic Composite Score (NCS), and subscale scores (NCS-Reflex, NCS-Motor, NCS-Sensory) were calculated for upper and lower limbs; the Neuropathy Impairment Score-Lower Limbs (NIS-LL) was calculated from a subset of the THAOS neurologic items assessing lower limbs.
- Treatment-associated hazard ratios (HRs) for mortality were calculated.

RESULTS

- At the data cut-off date (January 6, 2015) there were 2535 subjects enrolled in THAOS.
- After filtering based on the pre-specified criteria for this analysis, 274 tafamidis-treated patients and 255 untreated controls remained for matching (**Figure 1**).

Figure 1. Selection of study subjects



*Excluding mutations primarily associated with cardiac presentation: Val122Ile, Ile68Leu, Leu111Met, Thr60Ala.
†This removes patients in the uppermost quartile of disease duration.

- In total, 252 treated patients in Coutinho stage 1 were matched with 167 untreated controls.
  - 208 (82.5%) treated patients were matched with 4 untreated controls.
  - The remaining 44 treated patients were matched with 1 to 3 controls.
- Overall, 83.7% of matches were exact for country of birth.
- Mean (SD) difference in propensity scores between treated patients and matched controls was 0.012 (0.013) (**Figure 2**).

Figure 2. Distribution of logit of treatment propensity scores after matching by group

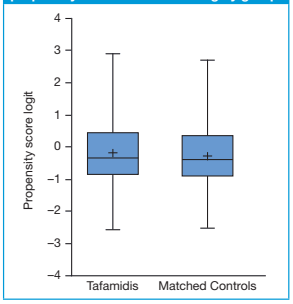


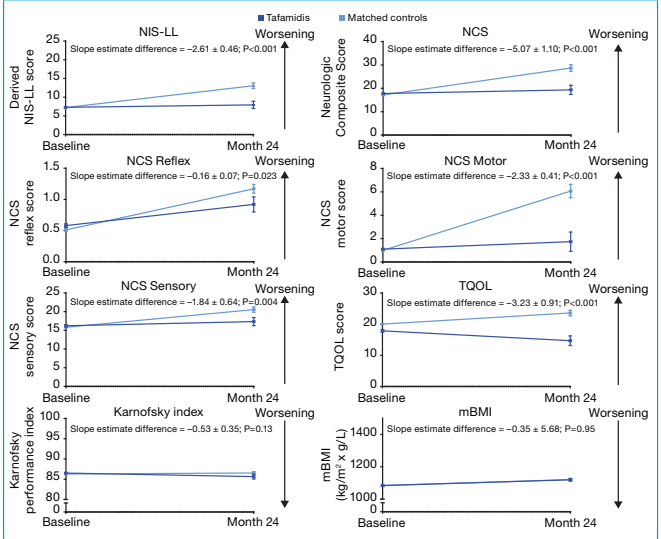
Table 1. Demographics and characteristics of treated patients and untreated matched controls at baseline

Characteristic, mean (SD)	Tafamidis n=252	Matched controls n=252*
Age, y	40.36 (11.9)	40.85 (9.4)
TTR disease duration, y	3.18 (1.9)	3.27 (1.3)
Total time on tafamidis, mo	29.11 (23.0)	–
Derived NIS-LL	8.92 (9.7)	7.57 (7.3)
NCS	21.34 (22.8)	19.18 (19.2)
Reflex score	0.78 (1.5))	0.55 (0.9)
Motor score	1.70 (6.6)	1.10 (2.1)
Sensory score	19.33 (18.5)	17.45 (16.5)
Norfolk TQOL score	23.44 (23.7)	22.26 (15.3)
Karnofsky index	86.39 (6.92)	85.43 (7.8)
mBMI, kg/m² × g/L	1068.09 (248.44)	1049.71 (184.25)

*For matched controls, descriptive statistics were calculated using means within matched sets. The unit of analysis (n) is the matched set rather than the individual.

- Demographics are shown in **Table 1**. The tafamidis group was predominantly Val30Met (92.5%), from Portugal (80.2%), and with roughly equal gender ratio (52% were male).
- Slope estimates from a repeated measures analysis model showed there was less disease progression in the tafamidis treated group over 24 months on neurologic and TQOL endpoints (**Figure 3**).
  - Neurologic endpoints with a statistically significant difference in favor of tafamidis included the derived NIS-LL and NCS, including NCS sensory, reflex, and motor sub-scores.
  - There was also a statistically significant treatment difference in favor of tafamidis for the Norfolk TQOL score.
  - No significant differences were found for the mBMI or the Karnofsky Performance Status Index.

Figure 3. Slope estimates (±SE) from a repeated measures analysis model



The analysis model adjusted for the following covariates: baseline value, follow-up time, baseline treatment propensity score, time and treatment by time interaction, gender, age at baseline, and disease duration at baseline.

- There were no deaths in the tafamidis group and 7 deaths in the matched control group, 2 of which occurred post liver transplant (post censoring).
- Because there were no deaths in the tafamidis group, treatment-associated HRs for survival for the matched cohort were not estimable; however, a secondary analysis of survival from disease onset in unmatched patients, using a delayed entry model and a time-varying treatment indicator, revealed a significant survival benefit of tafamidis treatment.
  - HR (untreated vs treated) 3.95; 95% confidence interval: 1.54–10.14; P=0.004.

CONCLUSIONS

- In this matched cohort analysis of data from THAOS, the largest observational database of TTR-FAP patients, treated patients were generally well matched with untreated controls, enabling a robust analysis of the effects of tafamidis treatment under "real-world" conditions.
- Our findings showed that tafamidis treatment resulted in less neurological disease progression compared with untreated matched controls.
- Tafamidis treatment resulted in directional improvement in TQOL, but no effect was seen on nutritional status or functioning.
- In an analysis of unmatched data, tafamidis treatment was associated with a greater likelihood of survival from disease onset, as revealed by HR estimates.
- These results extend the efficacy observed in clinical trials to real-world clinical settings.

REFERENCES

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CONFLICTS OF INTEREST

SS is an employee of ICON plc. All other authors are employees of Pfizer. The Transthyretin Amyloidosis Outcomes Survey (THAOS) is sponsored by Pfizer.

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