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Real-world versus trial patients with transthyretin amyloid cardiomyopathy

Transthyretin (TTR) amyloid cardiomyopathy (ATTR-AC) is caused either by single-point mutations in the TTR gene (ATTRv-AC) or by deposition of the wild-type protein (ATTRwt-AC).[1] Long been considered a rare disease, ATTR-AC has been increasingly recognized in recent years, particularly among the elderly,[1] mostly due to the possibility of a non-invasive diagnosis through bone scintigraphy.[2]

Recent trials have demonstrated that treatment with medications that silence TTR production or stabilize the TTR tetramer may favourably alter the progression of ATTR-AC.[3,4] In particular, tafamidis, a compound that inhibits TTR dissociation, has demonstrated to improve the prognosis of both ATTRv-AC and ATTRwt-AC patients enrolled in the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT).[3] However, whether the sample enrolled in the ATTR-ACT could be representative of a real-world (RW) ATTR-AC population remains unknown. To get some insight into this question, we compared the main characteristics of subjects treated with tafamidis ($n = 264$) in ATTR-ACT,[3] with those of a large Italian cohort of ATTR-AC patients.

We included in the present analysis all consecutive ATTR-AC patients diagnosed according to international recommendations[2] at five Italian referral centres between January 2010 and August 2018, regardless of their clinical status at diagnosis and vital status at follow-up. We excluded patients with other form of amyloid cardiomyopathy, as well as those ATTR-AC subjects enrolled in the ATTR-ACT trial (29 patients enrolled in Bologna, Florence and Pavia). ATTRv-AC patients with a prevalent neurological phenotype were also excluded according to the ATTR-ACT protocol.[5] Participating centres were requested to include main patients' characteristics at first clinical evaluation in a centralized anonymized database. All patients had signed an informed consent for processing of personal data for scientific research purpose. Characteristics of the two samples were compared using one-sample *t*-test or Wilcoxon test, or test for proportion as appropriate.

Our RW sample included 507 Caucasian patients (*Table 1*). The distribution of ATTRv-AC and ATTRwt-AC was comparable in ATTR-ACT vs. RW patients, although 19 RW ones refused to undergo genetic testing. Age was similar in the two groups, but RW patients were less frequently males, and had higher prevalence of hypertension and diabetes. In addition, their clinical conditions were significantly better, including higher blood pressure and heart rate and a lower New York Heart Association (NYHA) functional class. Results of blood tests were available for more than 50% of the RW sample, and showed lower natriuretic peptide and troponin levels, and higher creatinine clearance. At echocardiography, RW patients displayed similar wall thickness, but larger left atrial dimension and a greater left ventricular ejection fraction than ATTR-ACT subjects. They were also more likely to receive cardiovascular medications, including diuretics, beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

In this RW sample enrolled over the past 8 years, ATTR-AC patients *at diagnosis* had an apparently milder disease in terms of NYHA functional class, haemodynamics and biomarkers when compared to trial subjects. Such a healthier RW clinical profile may be the result of the greater awareness that ATTR-AC has gained in the recent years[6] and of the widespread use of cardiac imaging techniques allowing an earlier and non-invasive

Table 1 Characteristics of transthyretin amyloid cardiomyopathy trial patients at enrolment versus real-world patients at diagnosis

	ATTR-ACT trial	Real-world	*P*-value
Total population	264 (tafamidis pooled)	507 (Italian cohort)	
Age (years)	74.5 ± 7.2	74.5 ± 8.7	0.988
Male sex	241 (91.3)	429 (84.6)	<0.0001
Caucasian	211 (79.9)	507 (100)	<0.0001
Co-morbidities			
Hypertension	145 (54.9)	301 (59.4)	0.021
Diabetes	20 (7.6)	67 (13.2)	<0.0001
TTR genotype			
ATTRv	63 (23.9)	120 (23.7)	0.458
ATTRwt	201 (76.6)	368 (72.6)	0.070
Genetics not performed	0 (0)	19 (3.7)	
Blood pressure (supine) (mmHg)			
SPB	115.4 ± 15.4	130.3 ± 18.7	<0.0001
DPB	70.4 ± 10.3	76.9 ± 10.1	<0.0001
Heart rate (supine) (b.p.m.)	70.7 ± 12.3	73.1 ± 12.7	<0.0001
NYHA class			
I	24 (9.1)	106 (20.9)	<0.0001
II	162 (61.4)	287 (56.6)	0.026
III	78 (29.5)	112 (22.1)	<0.001
IV	0 (0)	2 (0.4)	
NT-proBNP (pg/mL)	2995.9 [1751.5–4861.5]	2547 [1333–4578] (n = 398)[a]	<0.001
BNP (pg/mL) [if NT-proBNP not available]		285 [150–629] (n = 71)[a]	
Creatinine clearance (mL/min)	58.8 ± 17.9	66.5 ± 25.5 (n = 475)[a]	<0.0001
Troponin I (ng/mL)	0.14 [0.09–0.20]	0.02 [0.01–0.07] (n = 294)[a]	<0.0001
Troponin T (ng/L) [if troponin I not available]		54.5 (42.0–88.0) (n = 78)[a]	
Echocardiography			
LA diameter (mm)	43.8 ± 7	46.6 ± 6.5	<0.0001
IVS thickness (mm)	16.7 ± 3.8	16.9 ± 3.0	0.134
LVEF (%)	48.4 ± 10.3	53.4 ± 10.7	<0.0001
Medications			
Diuretics	175 (66.3)	391 (77.1)	<0.0001
Beta-blockers	76 (28.8)	233 (46.0)	<0.0001
ACEi/ARBs	69 (26.1)	251 (49.5)	<0.0001
Antithrombotics	105 (39.8)	199 (39.3)	0.818

Values are given as mean ± standard deviation, number (%), or median [Q1–Q3].
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ATTR-ACT, Transthyretin Amyloidosis Cardiomyopathy Clinical Trial; ATTRv-AC, hereditary variant transthyretin amyloid cardiomyopathy; ATTRwt-AC, wild-type transthyretin amyloid cardiomyopathy; BNP, B-type natriuretic peptide; DBP, diastolic blood pressure; IVS, interventricular septum; LA, left atrial; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TTR, transthyretin.
[a]Number of patients with available data.

diagnosis of the disease.[2] This could also explain the higher proportion of NYHA class I–II patients in our cohort, as already shown in other series.[7] Notably, these characteristics resemble those of ATTR-ACT patients that seemed to benefit the most from the experimental treatment with tafamidis.[3] On the other hand, an ATTR-AC diagnosis may increasingly be reached in individuals already 'on-treatment' for other cardiovascular conditions, such as hypertension and diabetes, which were more prevalent and probably led to a wider usage of cardiac medications in our RW population.

Tafamidis only inhibits further TTR amyloid deposition, thus it is expected to have its greater impact when administered early in the disease course.[3] Accordingly, its benefits on hospitalization and survival were not immediate, but seen after approximately 12 and 18 months of treatment, respectively.[3] Therefore, the possibility, as highlighted by the present report, of diagnosing ATTR-AC in patients mostly with few symptoms may represent a striking opportunity in order to offer tafamidis treatment to a greater number of subjects expected to benefit from it, altering significantly the course of their disease. Medications that silence TTR production have also shown some preliminary positive results, but their investigation so far has been limited to ATTRv-AC patients of younger age and with milder disease as compared to the ATTR-ACT and RW ones analysed here.[4] Interestingly, the pre-defined proportion of ATTRv/ATTRwt-AC of ATTR-ACT was replicated by chance in our RW population,

in which ATTRv-AC was mostly related to Ile68Leu, Val122Ile and Val30Met late-onset mutations.

In the context of cardiovascular medicine, it is very unusual to see a RW population being clinically comparable to (or even more fit than) a trial population; thus, we did not anticipate these results. However, some limitations should be acknowledged. A shorter duration of the ATTR-AC disease could explain the RW milder phenotype; however, this information was neither available from ATTR-ACT nor from our database. In addition, our RW sample may have suffered from substantial referral bias, as ATTR-AC patients with a greater burden of co-morbidities and a lower life expectancy might less likely be referred to dedicated centres for more advanced diagnostics and treatments. Nonetheless, the RW population included in this analysis might represent a sizable indicator of patients suitable for a dedicated specific treatment in our country. Finally, we did not systematically collect important parameters that were considered as exclusion criteria in ATTR-ACT, namely a low modified body mass index and a short 6-min walk test distance.[3] These indicators of poor prognosis should always be assessed before considering a patient for expensive therapies with survival benefits expected only at long-term follow-up.

In conclusion, our findings that RW ATTR-AC patients closely resemble those enrolled in ATTR-ACT have relevant implications, considering that ATTR-AC is still considered a rare condition, and specific treatments will likely become initially available for a small proportion of the affected patients, primarily because of the relevant costs.

Conflict of interest: M.C. served on the Italian scientific advisory board of Pfizer. F.C. served on the Italian scientific advisory board of AKCEA, and received an unrestricted research grant from Pfizer. A.M. received personal fees from Alnylam Pharmaceuticals. C.A. served on the Italian scientific advisory board of Pfizer. F.P. served on the Italian scientific advisory board of Alnylam Pharmaceuticals and Pfizer. C.R. served on the Italian scientific advisory board of Pfizer, received unrestricted research grants and personal fees from Pfizer, and personal fees from Alnylam Pharmaceuticals. S.P. served on the Italian scientific advisory board of Pfizer. The other authors report no conflicts of interest.

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