Original research

Fabry disease: development and progression of left ventricular hypertrophy despite long-term enzyme replacement therapy

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ABSTRACT

Background Enzyme replacement therapy (ERT) may halt or attenuate disease progression in patients with Anderson-Fabry disease (AFD). However, whether left ventricular hypertrophy (LVH) can be prevented by early therapy or may still progress despite ERT over a long-term follow-up is still unclear.

Methods Consecutive patients with AFD from the Independent Swiss-Fabry Cohort receiving ERT who were at least followed up for 5 years were included. Cardiac progression was defined as an increase of >10 g/m^2 in left ventricular mass index (LVMI) between the first and the last available follow-up transthoracic echocardiography.

Results 60 patients (35 (23–48) years, 39 (65%) men) were followed up for 10.5 (7.2–12.2) years. 22 had LVH at ERT start (LVMI of 150±38 g/m^2). During follow-up, 22 (36%, 34±15 years) had LVMI progression of 12.1 (7–17.6) g/m^2 per 100 patient-years, of these 7 (11%, 29±13 years) with no LVH at baseline. Three of them progressed to LVH. LVMI progression occurred mostly in men (17 of 39 (43%) vs 5 of 21 (24%), p<0.01) and after the age of 30 years (17 of 22 (77%)). LVH at ERT start was associated with LVMI progression (OR 1.3, 95% CI 1.1 to 2.6; p=0.02). A total of 19 (31%) patients experienced a major AFD-related event. They were predominantly men (17 of 19, 89%), older (45±11 vs 32±9 years) with baseline LVH (12 of 19, 63%), and 10 of 19 (52%) presented with LVMI progression.

Conclusions Over a median follow-up of >10 years under ERT, 36% of the patients still had LVMI cardiac progression, and 32%, predominantly older men, experienced major AFD-related events. LVH at treatment initiation was a strong predictor of LVMI progression and adverse events on ERT.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anderson-Fabry disease (AFD) industry-sponsored registry data indicated that enzyme replacement therapy (ERT) may avoid cardiac complications if started early in the disease course. However, limited long-term prospective data are available regarding the optimal timing of ERT initiation, whether early therapy effectively prevents the development of left ventricular hypertrophy (LVH) or limits its progression.

WHAT THIS STUDY ADDS

⇒ Over a period of 10 years of ERT-treated patients with AFD, up to 36% still experienced progression of left ventricular mass index (LVMI) and 32%, predominantly older men, experienced major Fabry disease-related events. LVH at treatment initiation was a strong predictor of LVMI progression and adverse events on ERT.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ On average, LVMI remained stable when ERT was started in young male patients (before age 30 years) and women aged less than 50 years, with minimal AFD-related events, offering the clinician a window of opportunity to timely and effectively start the ERT.

Anderson-Fabry disease (AFD) is a rare X linked lysosomal disorder caused by deficiency of the enzyme α-galactosidase A (*GLA* gene).[1] The natural course of Fabry disease (FD) is characterised by a slow progression, punctuated by variable occurrence and severity of clinical events according to sex, age and type of mutations.[2] If untreated, the disease leads to a reduction of life expectancy of 15–20 years.[3 4] Fabry cardiomyopathy is characterised by progressive left ventricular hypertrophy (LVH), myocardial fibrosis, conduction abnormalities, arrhythmias, and systolic and diastolic dysfunction and represents the leading cause of death in AFD.[1] Since 2001, disease-specific therapies have been developed, including recombinant human enzymes, agalsidase-α derived from human fibroblasts (Replagal) and agalsidase-β (Fabrazyme).[1 5] Current expert consensus recommends enzyme replacement therapy (ERT) initiation as soon as possible in men with the classic form of the disease, before organ involvement, and for women with the classic form and patients with late-onset form at the earliest signs of organ involvement.[6] Registry data indicated that ERT may avoid cardiac complications if started early in the disease course but may be less efficient in more advanced cases.[6–8] This is a crucial aspect,

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as ERT in AFD is expensive and represents a lifelong commitment for the patients. Additionally, long-term prospective data assessing whether early therapy effectively prevents the development of LVH or whether left ventricular (LV) mass still progresses toward LVH despite ERT are still limited.[9–11] Therefore, in the present study, we analysed the evolution of cardiac morphology and function with transthoracic echocardiography (TTE) over a median follow-up (FU) period of 10 years in patients with FD from the Independent Swiss Cohort treated with ERT.

METHODS

Study population

Patients with genetically proven AFD consecutively diagnosed at two Swiss reference centres (Lausanne, Zurich) between 2001 and 2019, and treated with ERT (Independent Swiss-Fabry Cohort) were included. Clinical evaluation was carried out at least annually. TTE was performed in all patients at the time after ERT start. In the FU period, TTE was clinically prescribed every 1–5 years, depending on initial clinical involvement, sex and age. Patients with an FU period of at least 5 years were included in the study.

All patients received commercially available and approved recombinant human enzymes: agalsidase-α (Replagal) and agalsidase-β (Fabrazyme).

Echocardiographic examination and endpoints definition

TTE was performed according to clinical standards following the European and American recommendations.[12 13] Myocardial mass was calculated using the American Society of Echocardiography formula and indexed to body surface area. LVH was defined as a left ventricular mass index (LVMI) >95 (normal range 43–95) g/m^2 in women and >115 (49–115) g/m^2 in men. No patients aged <18 years were included and all were Caucasians; therefore, no age or ethnicity-specific cut-off was used.[14] An increase in LVMI >10 g/m^2 between the first and last TTE, considering the variability of measurement (interstudy intraobserver variability of 13.5%, corresponding to ±4.2 g/m^2) and the size of our study population,[15 16] was defined as a significant progression in LVMI. The sample size needed to detect a 10 g/m^2 increase in LVMI, with a null hypothesis of 0 change, using a paired t-test, with a power of 90% and an α error of 0.05, was calculated as 54 patients.[15 16]

Cardiac, renal and cerebrovascular events during the FU were defined as follows:

- Cardiac events: new symptomatic arrhythmia requiring antiarrhythmic medication, pacemaker or defibrillator implantation, congestive heart failure (New York Heart Association class III or IV) and sudden unexpected death of cardiac origin.
- Renal events: start of renal replacement therapy or kidney transplantation.
- Cerebrovascular events: stroke or transient ischaemic attack.

Statistical analysis

Continuous variables, reported as mean with SD or median with IQR for non-normal distribution, were compared between groups with Student's t-test or Wilcoxon test, as appropriate. Categorical variables, reported as counts and percentages, were compared between groups with χ2 or Fisher's exact tests.

Multivariate logistic regression analysis (variable selection method with backward stepwise elimination) was performed to identify the baseline parameters associated with cardiac progression under ERT and corrected for FU duration. The candidate variables included in the analysis were those with a significant (p<0.10) association in univariate analysis. A two-sided p value less than o.05 was considered statistically significant. All analyses were performed using SPSS V.7.0.

RESULTS

Baseline clinical and echocardiographic profile

60 patients (median age 35 (23–48) years), of whom 39 (65%) were men, were included in the study. A total of 51 (85%) patients presented with variants associated with classic phenotype and 9 with late-onset disease (online supplemental table 1).

51 (85%) received agalsidase-α substitution, whereas 9 received agalsidase-β. Indications for treatment initiation were as follows: (1) men with the classic form of the disease (19, 32%), (2) evidence of cardiac involvement at the moment of disease diagnosis (22, 36%), (3) chronic renal disease (9, 15%), and (4) peripheral and/or central neurological manifestations (8, 13%). Baseline clinical and echocardiographic characteristics stratified per sex and age class are summarised in table 1.

22 patients (37%) had LVH at the time of ERT start (mean LVMI 150±38 g/m^2 vs 79±18 g/m^2, p<0.001) (table 2). These patients were significantly older than those without LVH (50±8 (range 44–54) vs 27±9 (range 21–36) years, p<0.001), were predominantly men (82% vs 56%, p=0.03), and had more frequent history of chronic renal failure and hypertension (31% vs 8%, p=0.03) (online supplemental table 2). Among patients with LVH, those with a late-onset variant were older than those with a classic variant (54±11 vs 47±12 years, p=0.03).

The presence of LVH at baseline was age dependent: 1 of 26 (4%) patients aged <30 years, 10 of 21 (48%) patients between

Table 1 Baseline echocardiographic characteristics stratified per sex and age class

		Age <30 years (n=26)			Age 30–50 years (n=21)			Age >50 years (n=13)			
		All (n=26)	Men (n=18)	Women (n=8)	All (n=21)	Men (n=14)	Women (n=7)	All (n=13)	Men (n=7)	Women (n=6)	P for trend
LV mass index	g/m^2	82±18	86±16	63±8	119±38	129±35	72±14	143±49	171±42	110±31	<0.01*
LV hypertrophy	n	1 (4%)	1	0	10 (45%)	10 (67%)	0	11 (85%)	7	4	<0.01
Septal wall thickness	mm	9±2	9±2	8±1	13±3	14±3	9±2	16±4	18±2	14±3	<0.01*
Relative wall thickness	%	35±6	38±8	28±3	52±14	56±14	38±10	67±20	74±19	55±12	<0.01*
Left atrial diameter	mm	31±4	31±5	30±4	34±7	34±7	34±5	36±6	37±6	35±4	0.09
Mitral E/e' ratio		6.4±1.8	6.8±20	6.3±1.7	10.5±7	10.9±7.2	7.1±1.3	10.8±20	11.8±1.8	9.4±2.4	0.03*
LV ejection fraction	%	62±7	63±7	62±3	68±5	69±6	70±5	68±8	67±9	67±4	0.34

*Wilcoxon rank-sum test used for non-normally distributed variables.
LV, left ventricular.

Table 2 Evolution during long-term follow-up on enzyme replacement therapy of clinical and echocardiographic characteristics

		Baseline (n=60)	At last contact (n=60)	Difference	P value
Age	Years	35±14	44±12	10±7	<0.01*
LVMI	g/m^2	105±43	115±49	10±6	0.04*
LVMI in patients aged <30 years	g/m^2	81±18	82±21	2±3	0.56*
LVMI in patients aged 30–50 years	g/m^2	111±41	124±57	14±9	0.03*
LVMI in patients aged >50 years	g/m^2	143±48	156±45	13±8	0.05*
LVMI in men	g/m^2 (n=39)	131±45	143±58	13±8	0.03*
LVMI in women	g/m^2 (n=21)	83±29	82±30	13±8	0.54*
LV hypertrophy	n (%)	22 (36)	25 (42)	3	0.31*
Septal thickness	mm	11.6±4.2	12.8±5	0.7±4.0	0.23*
Posterior wall thickness	mm	10.4±3.6	11±3.4	0.5±0.4	0.74*
LV diastolic diameter	mm	45.9±4.7	46.4±4.6	0.6±0.1	0.34
Relative wall thickness	%	46±19	48±17	3±2	0.44*
Left atrial diameter	mm	33±6	36±7	3±1	0.96*
LV ejection fraction	%	66±7	63±5	64±7	0.21*
Mitral inflow E/A ratio		1.6±0.8	1.5±0.9	0.1±0.2	0.73*
Mitral annulus e' velocity	cm/s	13±9	9±4	4±2	0.02*
Mitral E/e' ratio		8±5	10±7	3±2	0.16*

*Wilcoxon rank-sum test used for non-normally distributed variables.
LV, left ventricular; LVMI, LV mass index.

30 and 50 years, and 11 of 13 (85%) patients >50 years (p for trend<0.01) (tables 1 and 2).

The presence of LVH was also related to sex. LVH at baseline was identified in 4 of 21 women (19%) vs 18 of 39 (46%) men (p<0.01).

LVMI progression and effect of baseline LVH

The median FU under ERT was 10.5 (7.5–12.2) years, for a total of 612 patient-years and 51 (85%) of patients with at least 6 years of FU. The overall change of LVMI in the entire cohort during the observation time under ERT was 1.2 (−1; 3.2) g/m^2 per 100 patient-years. Significant LVMI progression was observed in 22 (36%) patients, with a median increase of 12.1 (7–17.6) g/m^2 per 100 patient-years.

LVMI progression was significantly more frequent in patients with baseline LVH (68% vs 18%, p<0.01) with an increase in LVMI of 11.1 (0.7–16.8) g/m^2 vs 0.3 (−27.2; 26.1) g/m^2 per 100 person-years (p<0.01), and in relative wall thickness of +12±4% vs +2±1% (p=0.04), compared with the non-progression group (table 3). Nevertheless, seven patients with normal LVMI at baseline (mean age 29±13 years, four men) showed progression with a mean annual LVMI increase of 2.3 g/m^2 per year (1.1–7.1) despite ERT (online supplemental figure 1). They all carried a classic variant of the disease, and the LVMI increase was confirmed by a cardiac magnetic resonance (CMR), available in five of seven patients. Three of them reached the threshold of LVH definition during the FU period. Two men, in their 30s and 50s at therapy initiation, had an increase in LVMI from 73 to 150 g/m^2 in 15 years and from 94 to 119 g/m^2 after 11 years (one on agalsidase-α, the other on agalsidase-β), respectively. A woman, in her 30s at therapy initiation, on agalsidase-α substitution, had an increase in LVMI from 71 to 96 g/m^2 in her 50s. Their enzymatic activity at the start of the therapy was 8%, 10%, and 12%, respectively, and they all presented mutations associated with the classic phenotype. No hypertension was present.

On the contrary, seven patients (mean age 52±7 years, five men) with baseline LVH did not present with significant LVMI progression. Three of them had a late-onset variant of the disease.

Effect of sex and age on LVMI progression

Patients who presented with LVMI progression under ERT were older than non-progressors (41±12 vs 32±13 years, p<0.01). In the age group <30 years, there was no significant overall LVMI progression (81±18 g/m^2 to 82±21 g/m^2, p=0.56). In the age group between 30 and 50 years, 10 of 21 (47%) had LVMI progression, with an average increase in LVMI from 111±41 g/m^2 to 124±57 g/m^2 (p=0.03). Finally, among patients >50 years, 7 of 13 (54%) had LVMI progression with an increase in LVMI from 143±48 g/m^2 to 156±45 g/m^2 (p=0.05) (table 2).

On average, there was a significant increase in LVMI during the FU in men (progression in 17 of 39 (43%), increase in LVMI from 131±45 g/m^2 to 143±58 g/m^2 p=0.03) but not in women (5 of 21, 24%, 83±29 g/m^2 to 82±30 g/m^2, p=0.54) (table 2). In men, cardiac progression was age dependent: in those <30 years only, 4 of 18 (22%) progressed, but on average, no significant increase in LV mass was observed (87±16 g/m^2 to 87±19 g/m^2, p=0.85); in the age group 30–50 years, 9 of 14 (60%) progressed to LVMI from 129±35 g/m^2 to 149±51 g/m^2 (p=0.02); in the age group above 50 years, cardiac progression was observed in 4 of 7 (57%) but the increase in LVMI was not significant on average (171±42 g/m^2 vs 185±29 g/m^2, p=0.26) (figure 1 and table 2).

Of the five (24%) women who presented with an increase in LVMI, one (5%) was aged less than 30 years, one (5%) in the age group 30–50 years and three (14%) aged more than 50 years (table 1 and figure 2).

LVMI progression and parameters of cardiac function

In patients with LVMI progression, there was a significant increase in LV ejection fraction (+5±2% vs −1±3, p<0.01) and a reduction in diastolic function (E/e' ratio +3±1 vs −2±2, p=0.03).

Clinical and echocardiographic characteristics associated with LVMI progression in univariate analysis are summarised in

Table 3 Baseline clinical and echocardiographic characteristics at enzyme replacement therapy initiation stratified among progressors and non-progressors

			All (n=60)	LV mass progression (n=22)	No LV mass progression (n=38)	P value
Clinical						
	Age	Years	35±14	41±12	32±13	<0.01*
	BMI	kg/m^2	22±3	21±4	22±5	0.32*
	Men	n (%)	39 (65)	17 (77)	23 (59)	<0.01
	Arterial hypertension	n (%)	10 (17)	5 (23)	5 (13)	0.76
	Creatinine	mmol/L	114±69	138±86	105±59	0.05*
	eGFR	mL/min/1.73 m^2	90±23	84±26	93±23	0.07*
	Agalsidase-α	n (%)	52 (85)	18 (81)	34 (87)	0.38
	Agalsidase-β	n (%)	9 (15)	4 (19)	5 (13)	0.22
	Classic form	n (%)	51 (92)	19 (86)	32 (84)	0.56
	Late-onset form	n (%)	9 (8)	4 (14)	5 (16)	0.86
	Enzymatic activity	%	15.8±7.5	11.1±6.7	17.3±9.5	0.11*
Echocardiography						
	Septal thickness	mm	11.6±4.2	13.2±4	10.7±4.0	0.01*
	Posterior wall thickness	mm	10.4±3.6	11.5±3.7	9.5±3.2	0.02*
	LV diastolic diameter	mm	45.9±4.7	44.8±4.7	46.6±4.3	0.09*
	Relative wall thickness	%	46±19	52±19	41±17	0.02*
	LV mass index (LVMI)	g/m^2	105±43	151±48	100±42	<0.01*
	Aortic root diameter	mm	34±6	35±6	33±6	0.53
	Left atrial diameter	mm	33±6	33±7	32±5	0.96
	LV ejection fraction	%	66±7	70±6	64±	<0.01*
	Mitral inflow E/A ratio		1.6±0.8	1.3±0.6	1.7±0.8	0.73*
	Mitral annulus e' velocity	cm/s	13±9	13±12	12±4	0.99*
	Mitral E/e' ratio		8±5	10±7	6±2	0.02*
	LV hypertrophy	n (%)	22 (36)	15 (68)	7 (18)	<0.01

An increase in LVMI >10 g between the first and last TTE, taking into account the variability of measurement and the size of our study population defined as a significant progression in LVMI.
*Wilcoxon rank-sum test used for non-normally distributed variables.
BMI, body mass index; eGFR, estimated glomerular filtration rate; LV, left ventricular; TTE, transthoracic echocardiography.

table 4 (2 of 9 (22%) patients with variants associated with late-onset disease, 20 of 51 (39%) with classic phenotype variants). The type of replacement therapy was not associated with LVMI progression. Multivariate analysis identified LVH at the start of ERT as the only independent baseline parameter significantly associated with cardiac progression during follow-up (OR 1.3, 95% CI 1.1-2.6; p=0.02) (table 4).

Clinical adverse events during FU

A total of 19 (32%) patients experienced an FD-related adverse event during the FU under ERT, and 17 (89%) of them were men (table 5). Patients who had an event were older (45±11 vs 32±9 years, p<0.01) and more frequently had LVH at baseline (12 of 19, 63% vs 10 of 41, 24%, p<0.01) and 10 of 19 (58%) presented with LVMI progression.

A total of eight (13%, six men) patients experienced atrial fibrillation (AF), at a mean age of 49±7 years. AF was exclusively observed in patients with LVH and was more common in those who had an LVMI progression during ERT (six vs two patients, p<0.01).

Cardiac adverse events occurred in nine (15%, 1.5 per 100 patient-years) patients at a mean age of 47±12 years. Five (8%) had pacemaker implantation, four (6%) received an implantable cardioverter defibrillator (ICD) in primary prevention and one (0.2 per 100 patient-years) patient experienced sudden cardiac death due to mechanical dissociation with pulseless electrical activity despite the presence of an ICD without secondary causes.

Nine (15%, 1.5 per 100 patient-years) patients underwent renal replacement therapy (mean age 43±15 years), and 10 (17%, 1.6 per 100 patient-years) experienced a neurological event (mean age 43±14 years).

Overall, the occurrence of any FD-related event was more common in patients who had an LVMI progression under ERT. The presence of baseline LVH was independently associated with any AFD adverse event (OR 1.3; 1.1 to 2.6, p=0.02).

DISCUSSION

Over a median FU of 10 years, progression in LVMI still occurs in 68% of the patients with baseline LVH. LVMI progression was more common in men, and on average, a significant increase in LV mass was observed in men but not in women over the FU period. In younger patients <30 years, only 20% had a progression of LVMI under ERT, but this proportion increased to 45% in those aged 30–50 years and 100% in those older than 50 years. Moreover, in seven patients (18%) without baseline LVH, we observed an increase in LVMI under ERT.

Previous histological studies showed that ERT partially cleared Gb_3 deposits from cardiomyocytes[17] and that this effect was associated with LVMI regression.[1] However, clinical evidence supporting these histological findings is controversial and mainly based on small cohorts with relatively short FU periods.[7 10] Using CMR, Weidemann *et al* reported a significant reduction in LV mass in 10 patients after 12 months of ERT, providing the treatment was started early in the course of the disease (ie, before the

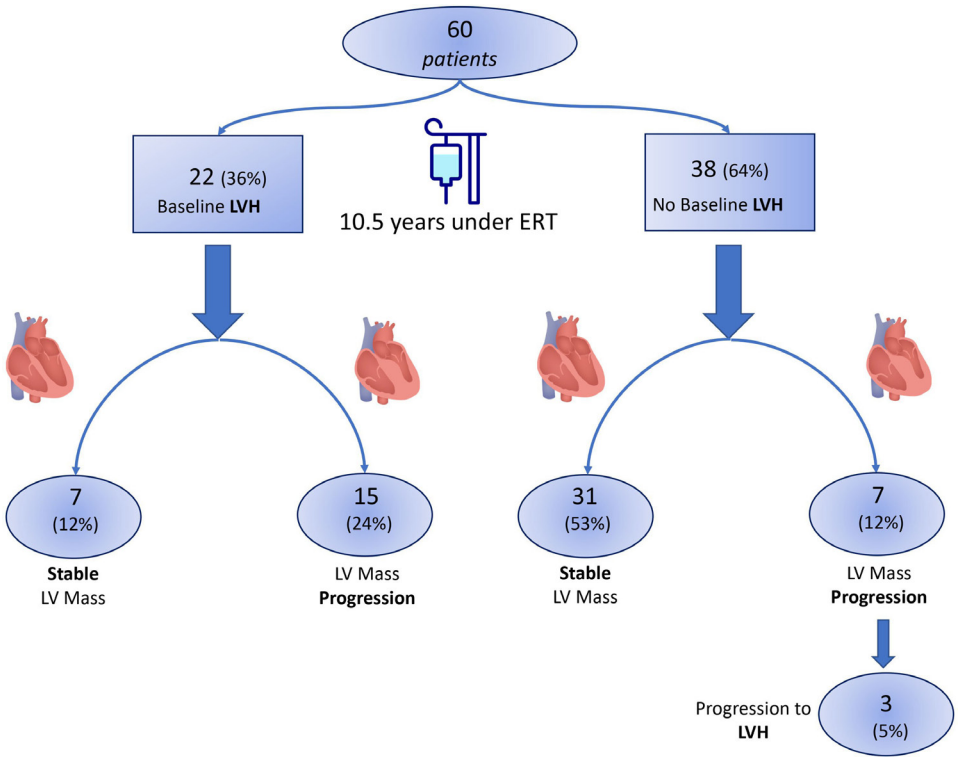

Figure 1 Long-term evolution of left ventricular (LV) mass under ERT. ERT, enzyme replacement therapy; LVH, LV hypertrophy.

development of myocardial fibrosis).[8] Moreover, a retrospective analysis of patients with LVH receiving ERT from the multicentre FOS registry showed a sustained reduction in LVMI after 5 years of treatment.[18] However, these studies may be biased by the nature of their design. Registries often included patients at very low risk of FD-related complications, including women without LVH (ie, up to 49% of young women with classic or late-onset form),[19–21] potentially overestimating the actual effectiveness of ERT. Our findings show that LVMI continues to progress despite ERT in a significant proportion of patients with baseline

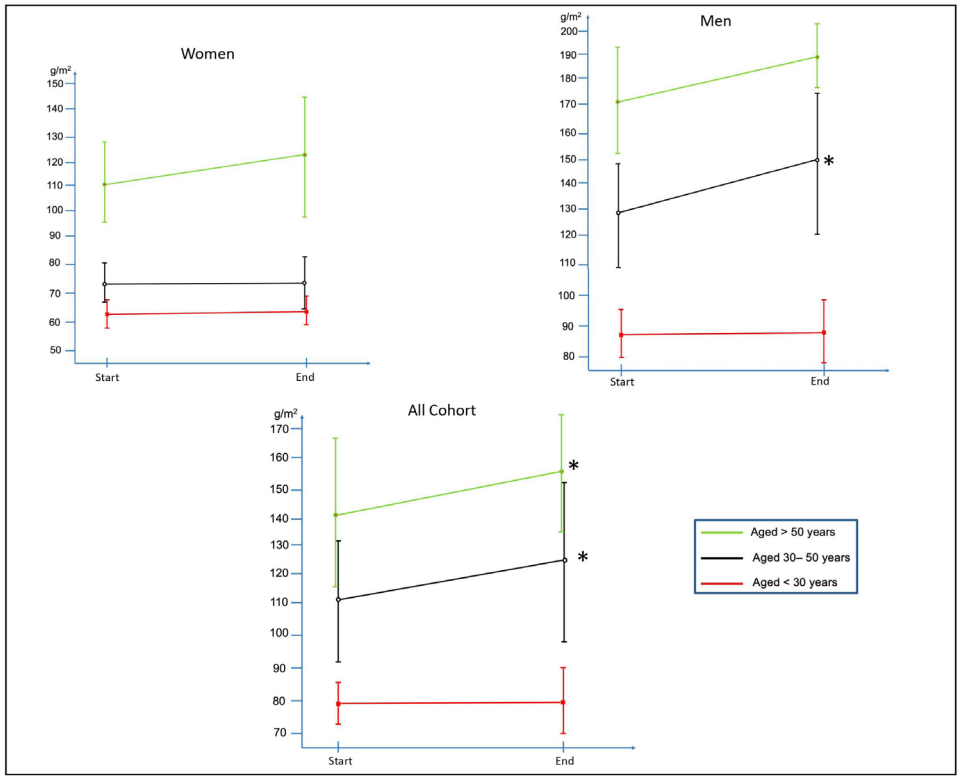

Figure 2 Indexed mass evolution during the follow-up stratified per age class. *Significance difference, p<0.05.

Table 4 Associations of baseline characteristics with increase in left ventricular mass during enzyme replacement therapy (ERT)

	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Men (n)	1.2	0.7 to 1.5	0.06			
Age per 10 increase (years)	1.2	0.6 to 3.1	0.03			
Creatinine per 10 increase	0.7	0.4 to 1.4	0.23			
LVH at ERT start (n)	2.1	1.3 to 5.5	<0.001	1.3	1.1 to 2.6	0.02
E/e' per 2 increase (n)	1.3	0.6 to 3.7	0.03			

LVH, left ventricular hypertrophy.

LVH (figure 3). These are in accordance with Germain *et al*,[22] who reported an age-related development of LVH. They showed that in patients aged <40 years receiving agalsidase-β, left posterior wall thickness (LPWT) and interventricular septal thickness (IVST) remained stable, while in patients aged >40 years at first infusion, LPWT and IVST significantly progressed from baseline to the last FU at 10 years. These findings are consistent with other research showing that patients initiated on agalsidase-β at a younger age had a more favourable cardiac response to treatment.[11 20–25] The absence of an increase in LVMI is usually interpreted as an effect of ERT. However, a significant proportion of patients are probably too young at the time of inclusion to develop LVH over a 10-year FU. In addition, the majority of young women with variants associated with the classic or the late-onset form of the disease are at much lower risk and may rarely develop LVH, independently of ERT administration. Due to the prolonged progression of the disease, even longer FU periods may be warranted to confirm ERT's effectiveness.

Interestingly, because of the limited progression of men aged <30 years with the classic form and women <50 years with the classic or late-onset form, our results suggest that this age frame is a potential and actionable window of opportunity for echocardiographic screening to identify potential progressors who might benefit the most from ERT (figure 3). These findings might have relevant clinical implications since the intensification of cardiological evaluation should be focused around these two age cut-offs.

Importantly, three (5%) patients with no LVH at baseline developed LVH during the FU period despite ERT. Two of the three patients already had an LV mass close to the upper normal limit at baseline, suggesting that once the cardiac remodelling process has started, the efficacy of ERT is limited. LVH appears, therefore, as a relatively late biomarker of cardiac involvement. Interestingly, the third patient who developed new LVH was a woman with a mutation associated with the classic form of the disease. Historically, heterozygous women demonstrate a more variable and attenuated phenotype. However, certain patients may present an inefficient cross-correction between healthy and affected cells in heterozygotes or skewed X-chromosome inactivation, presenting a more severe phenotype similar to men.[26]

19 (31%) patients experienced a significant disease-related complication during the 10 years of treatment. Specifically, the rate of cardiac adverse events was 1.5 per 100 patient-years, in accordance with previous studies.[10 19 27] As expected, they were predominantly men (89%) and older. More frequently, they had LVH at ERT initiation and LVMI progression during the FU. LVMI progression during FU reflects the global progression of the disease, and in our study, it was significantly associated with cardiac, renal and neurological complications. Those findings demonstrate that ERT was ineffective in preventing major FD-related complications in those patients, where treatment was started late in the disease course.

The only independent predictor of cardiac progression over the extended FU was the presence of LVH at the first ERT infusion. This is of most clinical relevance since the current expert consensus recommends ERT initiation in all patients at the earliest signs of organ involvement.[2] However, the presence of LVH represents a relatively late marker of cardiac involvement. Indeed, our data showed that 18% of the patients with no baseline LVH still had LVMI progression despite ERT, suggesting that the cardiac remodelling process already started in those patients. Therefore, earlier markers of cardiac involvement are much needed to calibrate treatment initiation at the pre-hypertrophic stage of the disease, such as low myocardial T1-relaxation in CMR.[28]

Limitations

The number of patients in this study is appreciated to be small, so results must be interpreted cautiously. However, this is an inherent problem when dealing with a rare disease, and this is a relatively large cohort compared with other reported studies.[11 20–25] Because of the long FU, CMR was not available for all patients at baseline; therefore, a systematic comparison with CMR could not be performed in this cohort to confirm the diagnosis of LVH and to correlate the disease course with the presence or not of myocardial fibrosis. No LV strain analysis was present for baseline echocardiography because of the low availability of this technique at the beginning of the study. However, the latter forms the basis of future work in a specifically designed study. Lastly, migalastat was not evaluated since it was commercialised only in 2016, substantially after the study enrolment period.

CONCLUSIONS

Over more than 10 years under ERT, 36% of the patients still experienced cardiac progression, and 32%, predominantly older

Table 5 Events at follow-up as stratified between progressors and non-progressors

		All (n=60)	LV mass progression (n=22)	No LV mass progression (n=38)	P value
Any AFD-related adverse event	(n)	19 (32%)	11 (45%)	9 (24%)	0.03
Pacemaker implantation	(n)	5 (8%)	4 (18%)	1 (3%)	<0.01
ICD implantation	(n)	4 (6%)	4 (18%)	0	<0.01
Sudden cardiac death	(n)	1 (2%)	1 (5%)	0	0.56
Renal replacement therapy	(n)	9 (15%)	6 (28%)	3 (8%)	<0.01
Stroke or TIA	(n)	10 (17%)	5 (23%)	4 (10%)	0.09
Death for all cause	(n)	3 (5%)	2 (9%)	1 (3%)	0.76
Follow-up duration	(years)	10.5 (7.2–12.2)	11.2 (7.3–12.7)	10.1 (7.1–11.0)	0.32

AFD, Anderson-Fabry disease; ICD, implantable cardioverter defibrillator; LV, left ventricular; TIA, transient ischaemic attack.

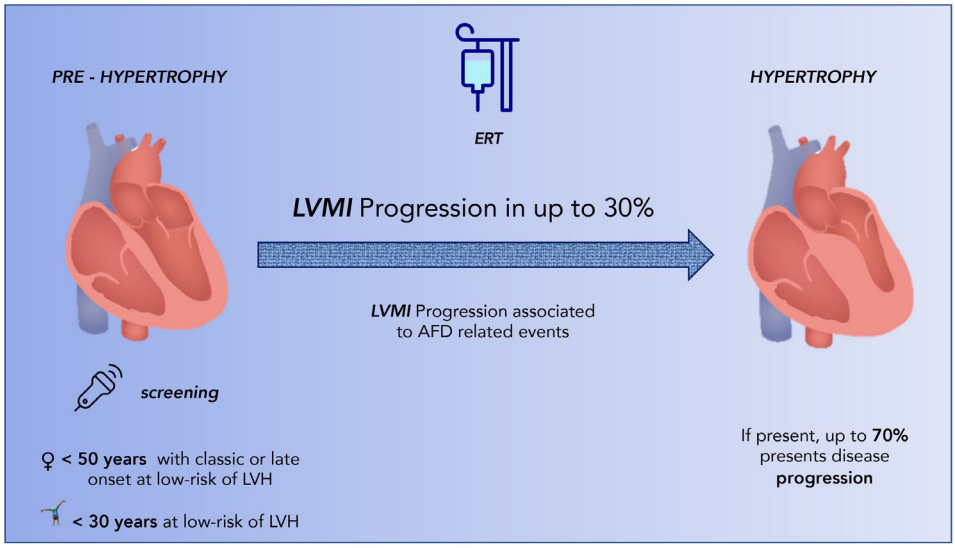

Figure 3 Central illustration: clinical significance of development and progression of left ventricular mass during enzyme replacement therapy (ERT) in Fabry disease. AFD, Anderson-Fabry disease; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index.

men, major FD-related events. LVH at treatment initiation was a strong predictor of LVMI progression and adverse events. On average, LVMI remained stable when ERT was started in young male patients (before age 30 years) and women aged less than 50 years. FD-related events were rare in those groups. LVH appears as a late marker of cardiac involvement, and further studies are needed to validate novel biomarkers of pre-hypertrophic cardiac involvement to optimise the timing of treatment initiation.

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Patient consent for publication Consent obtained directly from patient(s).

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