AGALSIDASE ALFA LONG-TERM EFFECT ON LEFT VENTRICULAR HYPERTROPHY IN FABRY DISEASE

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Abstract

Introduction: Fabry disease (FD) is an X-linked lysosomal storage disorder affecting glycosphingolipid metabolism. Most FD patients have cardiac involvement, mainly manifested as left ventricular hypertrophy (LVH), leading to early death due to complications (arrhythmias, valvular disease, vascular involvement). Early initiation of enzyme replacement therapy (ERT) before fibrosis development has been associated with better cardiac outcomes in terms of left ventricular mass index (LVMI) and functional parameters.

Methods: A retrospective observational study was conducted in patients with FD treated with agalsidase alfa for at least 2 years. The primary objectives were: [a] to assess the annual rate of change in LVMI; [b] to define the overall incidence of stability, regression or progression of LVMI.

Results: Forty-nine patients were included in the final analysis, with a median follow-up of 7 years. The overall change in LVMI was 0.38 g/m2.73/year, without significant influence of baseline LVH, gender, age at ERT initiation, LV ejection fraction, body mass index, renal disease, and classical cardiovascular risk factors. Long-term ERT with agalsidase alfa was associated with stabilization of LVMI in 98% of patients with FD and was independent of the same covariables. Conclusion: Our results are in line with previous literature of comparable FD populations and probably represent the first study of its kind in Argentina.

We here highlight the importance of cardiac morphometric stability as a positive outcome of ERT.

Key words: Fabry disease, enzyme replacement therapy, left ventricular hypertrophy

Resumen

Efecto a largo plazo de la agalsidasa alfa sobre la hipertrofia ventricular izquierda en la enfermedad de Fabry

Introducción: La enfermedad de Fabry (EF) es una enfermedad de almacenamiento lisosomal ligada al cromosoma X que afecta el metabolismo de glicoesfingolípidos. La mayoría de pacientes EF tienen afectación cardíaca, manifestada principalmente como hipertrofia ventricular izquierda (HVI), que conduce a muerte prematura secundaria a complicaciones (arritmias, valvulopatías, afectación vascular). El tratamiento de reemplazo enzimático (TRE) precoz, iniciado antes del desarrollo de la fibrosis, se relaciona con mejores resultados cardíacos en términos del índice de masa ventricular izquierda (IMVI) y parámetros funcionales.

Métodos: Se realizó un estudio retrospectivo observacional en que se incluyeron pacientes con EF tratados con agalsidasa alfa por al menos 2 años. Los objetivos primarios fueron: [a] evaluar el cambio anual del IMVI;

[b] definir la incidencia global de estabilidad, regresión o progresión del IMVI.

Resultados: Se incluyeron 49 pacientes, con seguimiento (mediana) de 7 años. El cambio global en el IMVI fue 0.38 g/m2.73/año, sin influencia significativa de HVI basal, sexo, edad de inicio de TRE, fracción de eyección del VI, índice de masa corporal, insuficiencia renal y factores de riesgo cardiovascular clásicos. La TRE a largo plazo con agalsidasa alfa se relacionó con la estabilización del IMVI en el 98% de los pacientes con EF, independientemente de las mismas covariables.

Conclusión: Nuestros resultados están en línea con la bibliografía previa de poblaciones comparables y, probablemente, representan el primer estudio de este tipo en Argentina. Se destaca la importancia de la estabilidad morfométrica cardíaca como resultado positivo de la TRE.

Palabras clave: enfermedad de Fabry, terapia de reemplazo enzimático, hipertrofia ventricular izquierda

KEY POINTS

- **Current knowledge:** Most Fabry disease (FD) patients have cardiac involvement, mainly manifested as left ventricular hypertrophy (LVH), leading to early death due to complications. Early initiation of enzyme replacement therapy (ERT) before fibrosis development has been associated with better cardiac outcomes in terms of left ventricular mass index (LVMI) and functional parameters.
- **What this manuscript adds:** In an Argentinean, real-world setting, long-term ERT with agalsidase alfa is associated with stabilization of LVMI, independent of age at treatment start, gender, and cardiovascular risk factors, both in subjects with or without baseline LVH. The importance of cardiac morphometric stability as a positive outcome of ERT is highlighted

The Anderson–Fabry disease, also known as Fabry disease (FD), was first described by Johannes Fabry (Germany) and William Anderson (England)[1,2]. FD is an X-linked lysosomal disorder affecting glycosphingolipid metabolism[3,4]. Notably, most heterozygous females are also affected[4]. Over 900 genetic variants in the *GLA* gene are related to the pathogenesis of FD[3], resulting in a deficiency of the lysosomal enzyme α-galactosidase A (AGAL). This alteration leads to the progressive accumulation of globotriaosylceramide (GB_3) in cells of different tissues. The resulting lysosomal dysfunction triggers a combination of mitochondrial alterations, abnormal autophagy, systemic inflammation, and fibrosis, with several multisystemic effects[3,5,6]. FD may affect endothelial, epithelial, smooth muscle cells, cardiomyocytes, nephrons, renal tubular cells, mesangial cells, corneal epithelial cells as well as peripheral nerves[4].

FD has been divided into a severe "classical" phenotype (most commonly described in male subjects and characterized by the absence of residual AGAL activity) and a milder, "non-classical", later-onset phenotype[7]. Patients with classical FD present with characteristic symptoms in childhood or adolescence, including neuropathic pain, gastrointestinal manifestations, neuro-otological symptoms, *cornea verticillata,* and angiokeratomas[8]. Affected individuals may develop cardiac, renal, and cerebrovascular complications, including asymptomatic brain lesions[8,9].

Most FD patients have cardiac involvement, mainly manifested as left ventricular hypertrophy (LVH)[5], fibrosis, valvular disorders, and ischemia that may lead to early death due to heart failure or arrhythmias[10].

Enzyme replacement therapy (ERT) has changed the prognosis of FD. The early introduction of ERT results in a better cardiac response[11,12]. Current goals of ERT in patients with cardiac involvement include: [a] reduction of left ventricular mass (LVM) in patients with LVH; [b] improvement of left ventricular (LV) functional parameters in patients with compromised function; and [c] improvement of arrhythmias in patients with baseline rhythm disturbances[13]. In FD patients without cardiac involvement, ERT can preserve normal cardiac structure and function[14].

Available data about the long-term treatment and evolution of FD patients from Latin America are limited. In the present study, we evaluated the long-term effects of ERT on LVM in FD subjects from AADELFA (*Asociación argentina de estudio y tratamiento de Fabry y otras enfermedades lisosomales*) registries. Our primary objectives were: [a] to assess the mean annual rate of change in left ventricular mass index (LVMI: LVM in grams divided by height in cm) in patients treated with

agalsidase alfa, defined as the difference of annual follow-up LVMI minus baseline LVMI; [b] to estimate the overall incidence of stability, regression or progression of LVMI. Stability was defined as an increase or regression <10% in LVMI over a mean follow-up period; regression was defined as a documented reduction ≥10% in LVMI over a mean follow-up period; progression to LVH was defined as an increase ≥10% in LVMI over a mean follow-up period.

Materials and methods

Study population

A retrospective observational cohort study was performed in consecutively evaluated patients with FD that had started ERT with agalsidase alfa (Replagal®, Takeda) between June 2001 and August 2017. Demographic (age, diagnosis date, anthropometric variables), clinical (cardiovascular risk factors, renal function), echocardiographic (morphometric and functional parameters), and treatment-related data were retrospectively retrieved in AADELFA centers and centrally analyzed in two coordinating sites (*Hospital Británico* for cardiac follow-up and *Sanatorio Urquiza* for overall patient registry).

Eligible patients had a documented diagnosis of FD (enzyme assay in males and/or DNA analysis [males and females]), were aged ≥15 years at treatment initiation and had received uninterrupted ERT with agalsidase alfa at standard doses for at least 2 years. Follow-up was based on the centralized review of medical records. Cardiac magnetic resonance data were not analyzed due to the small number of patients with baseline and follow-up imaging.

Values of >50 g/m$^{2.7}$ were considered indicative of LVH[14] as measured by echocardiogram (biplane Simpson's method). The LVMI was calculated using the Deveraux formula[15]. Relative wall thickness (RWT) was defined as 2 times posterior wall thickness divided by the LV diastolic diameter. Renal disease was defined as proteinuria (>150 mg/24 hours) and/or estimated glomerular filtration rate <60 mL/minute/1.73 m^2 using MDRD-4´s equation and/or dialysis/renal transplantation. Hypertension was defined as resting systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 80 mm Hg, according to contemporary guidelines. Diabetes was defined as fasting blood glucose > 126 mg/dl or casual blood glucose > 200 mg/dl in patients with classic symptoms (hyperorexia, polyuria, polydipsia or unexplained weight loss). Dyslipidemia was defined as total cholesterolemia > 240 mg/dl, low-density lipoprotein cholesterol > 130 mg/dl and/or triglyceridemia > 150 mg/dl, according to recommendations at the time of data collection. Data about pain and quality of life were also retrieved for further research.

Ethics

Our study was performed in compliance with national regulations concerning observational studies (Resolution 1480/11 of the Argentinean Ministry of Health) and under the guidelines of Good Pharmacoepidemiology Practices[16]. The study was approved by the Institutional Review Board of *Hospital Británico*.

Statistical analysis

Retrieved data were anonymized before the formal analysis. Data were tabulated in a Microsoft Excel® spreadsheet. For continuous data, mean, median, standard deviation, minimum, maximum, first and third quartiles (Q1 – Q3), and ranges were calculated. For categorical data, frequencies, percentages, and 95% confidence intervals (95% CIs) were calculated. In addition to descriptive analyses, statistical tests were performed to summarize endpoint comparisons between subgroups when relevant strata of patients were observed. Given the descriptive nature of our study, no formal calculations of the sample size were performed. Data were analyzed using Epi Data® version 7.2.2.6 (Centers for Disease Control and Prevention, U.S. Department of Health & Human Services).

Results

Forty-nine FD patients who had started ERT in June 2001 according to AADELFA registries and without relevant missing data were included in our analysis. Median echocardiographic follow-up was 6.71 years (range: 1.75-11.87 years). Key baseline demographic and echocardiographic characteristics of these patients are described in Table 1 and Table 2, respectively. No significant differences were found between genders. The most frequent pathogenic variant was c.463G>C; detailed distribution is described in Figure 1.

Median baseline LVMI (range) was 45.2 g/m$^{2.73}$ (18.5-94) for males and 43.1 g/m$^{2.73}$ (25.61-77.8) for females. The overall annual change in LVMI was 0.38 g/m$^{2.73}$ per each year of follow-up. These results were not influenced by potential confusion variables, including BMI (p = 0.820), renal disease (p = 0.973), diabetes mellitus (p = 0.547), dyslipidemia (p = 0.868), hypertension (p = 0.413) and age at ERT start (p = 0.488).

Tabla 1 | Key baseline demographics (n = 49)

Age at FD diagnosis (years), median (range)	27.8 (5.2–61.5)
Age at ERT initiation (years), median (range)	27.8 (8.2–62.7)
Male gender, n (%)	24 (48.9)
	[34.9–62.9]
Classical phenotype, n (%)	46 (93.87)
Smoking, n (%)	
Current smoker	16 (32.6)
Former smoker	8 (16.3)
Never smoker	25 (51.1)
Overweight/obesity, n (%)	19 (38.8)
	[25.16–52.4]
Chronic kidney disease, n (%)	15 (30.6)
	[17.7–43.5]
Hypertension, n (%)	9 (18.4)
	[7.6–29.2]
Diabetes, n (%)	6 (12.2)
	[3–21.4]
Dyslipidemia, n (%)	6 (12.2)
	[3–21.4]

ERT: enzyme replacement treatment; FD: Fabry disease
Values in square brackets represent 95% confidence intervals

Tabla 2 | Key baseline echocardiographic data (n = 49)

Left ventricular diastolic diameter, median (Q1-Q3)	47 mm (43-51)
Left ventricular systolic diameter, median (Q1-Q3)	29 mm (24-31)
Interventricular septum, median (Q1-Q3)	9 mm (9-13)
Posterior wall thickness in diastole, median (Q1-Q3)	9 mm (8-12)
Left atrial area, median (Q1-Q3)	37 cm^2 (32.2-40)
Aortic root, median (Q1-Q3)	29 mm (26-31)
LVM, median (Q1-Q3)	Male: 178.3 g (133.9-247.7)
	Female: 161.2 g (118.9-184.7)
LVMI, range (*)	Male: 45.2 g/ m$^{2.73}$ (18.5-94)
	Female: 43.1 g/m$^{2.73}$ (25.61-77.8)
LVH, n (%)	19 (38.77 %)
	[25.13–52.4%]
Left ventricular shortening fraction, median (Q1-Q3)	39.3% (33.1-44.3)
Left ventricular ejection fraction, median (Q1-Q3)	64.7% (56.7-70.1)
RWT, median (range)	38.3% (24.62-68.29)

LVH: left ventricular hypertrophy; LVM: left ventricular mass; LVMI: left ventricular mass index; Q1: 1st quartile;
Q3: 3rd quartile; RWT: relative wall thickness
Values in square brackets represent 95% confidence intervals
*(*) Normal range <50 g/m$^{2.73}$*

Among male patients, LVMI remained mostly unchanged during follow-up without significative differences from baseline to last follow-up, both in participants with or without baseline LVH (Fig. 2). A non-significant reduction of LVMI was observed in female patients both with or without baseline LVH (Fig. 3). The annual variation in LVMI was not significantly correlated with gender, age at ERT initiation (r = -0.101), basal ejection fraction (r = 0.132), body mass index (r = -0.033), renal disease (r = 0.005), and classical cardiovascular risk factors (smoking: r = 0.087; diabetes mellitus: r = 0.083; dyslipe-mia: r = -0.030; hypertension: r = 0.115, at least one factor: r = -0.013; Spearman test).

Fifteen participants (30.6%) had renal disease, largely due to proteinuria (73.3%); in this subgroup of patients, no statistical differences were observed in the annual rate of LVMI change when compared with FD patients without renal involvement (p = 0.27, Mann-Whitney U test).

Another primary goal of our study was to describe the overall incidence of stability, regression or progression of LVMI, as previously defined. Results are summarized in Figure 4. Ninety-eight percent of our patients showed no

**Figura 1** | *GLA* variant distribution
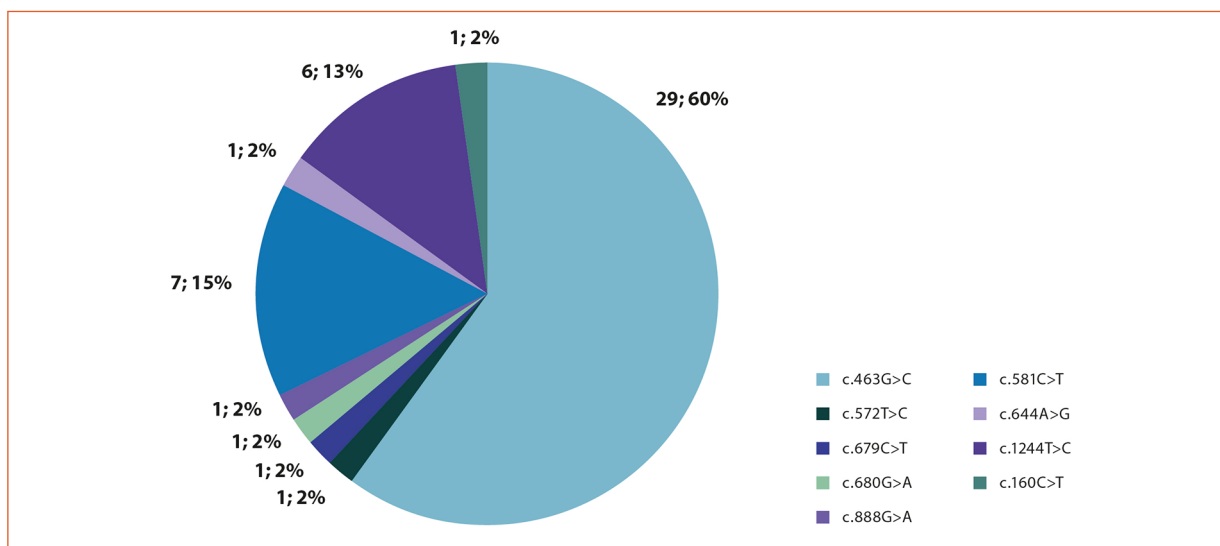
Figura 2 | Mean long-term variation of left ventricular mass index (male patients) according to baseline left ventricular hypertrophy from baseline to end of follow-up. Error bars represent standard deviation
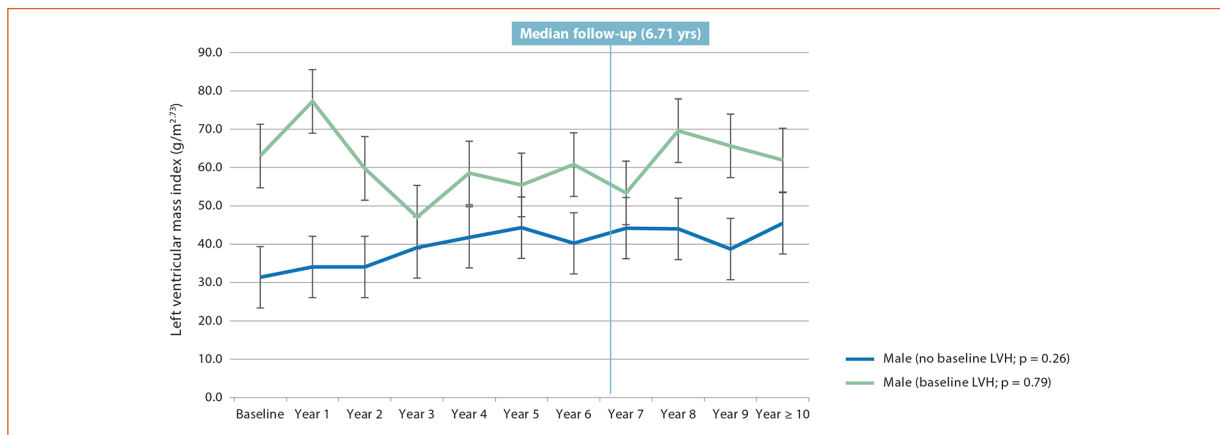

Error bars represent standard deviation

Figura 3 | Mean long-term variation of left ventricular mass index (female patients) according to baseline left ventricular hypertrophy from baseline to end of follow-up. Error bars represent standard deviation
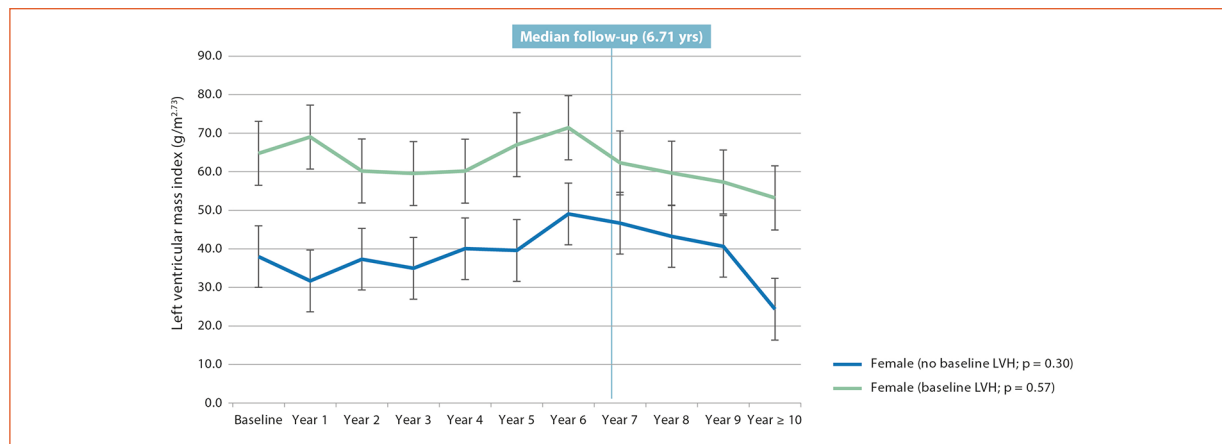
Error bars represent standard deviation

Figura 4 | Prevalence of stability, regression or progression of left ventricular mass index. Progression to left ventricular hypertrophy was defined as an increase ≥10% in left ventricular mass index over a mean follow-up period. Regression was defined as a documented reduction ≥10% in left ventricular mass index over a mean follow-up period. Stability was defined as an increase or regression <10% in left ventricular mass index over a mean follow-up period
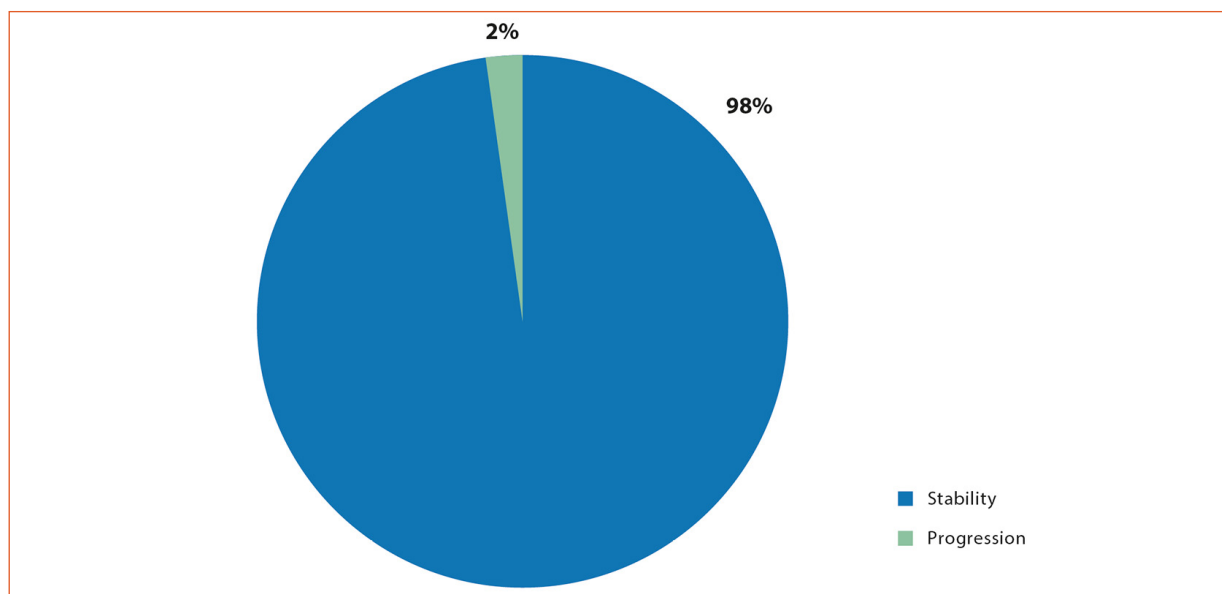
Progression to LVH was defined asan increase ≥10% in LVMI overa mean follow-up period. Regression was defined as a documented reduction ≥10% in LVMI over a mean follow-up period. Stability was defined as an increase or regression <10% in LVMI overa mean follow-up period.

changes in LVMI during the follow-up period. These results were not influenced by the prevalence of baseline LVH.

Seven deaths were reported during follow-up (sudden death [n = 2]; dialysis catheter-related sepsis [n = 1]; non-FD causes [n = 4]). No statistical differences were identified in LVMI variations between alive or dead FD patients (p = 0.11, Mann-Whitney U test, after removing one outlier in each subgroup). The proportion of patients

with unchanged LVMI was not modified after censoring deceased participants from the analysis. No deaths were deemed to be related to ERT.

Discussion

Our study represents one of the longest-term assessments of cardiomyopathy progression in FD patients in Latin America. LVMI remained mainly unchanged in our agalsidase alfa cohort, thereby suggesting cardiac morphometric stability.

Cardiac manifestations are highly common in FD and have been described in up to 60% of patients[17]. Cardiac complications include LVH (about one-half and one-third of FD untreated men and women, respectively), conduction abnormalities, chronotropic incompetence, arrhythmias, myocardial fibrosis, and valve disease[18]. Pathological mechanisms are fibrotic tissue augmentation, vacuolization of both cardiomyocytes and endothelial cells, and increased cell proliferation mediated by endothelial growth factors[19]. The severity of cardiac abnormalities increases with age. In addition to renal disease, cardiac complications are a significant cause of morbidity and a leading cause of death among male and female patients with FD[20].

ERT is the first disease-specific therapy that has changed the natural history of FD[21], due to its effectiveness in eliminating GB_3 that has accumulated in plasma or tissues[5]. Even though it is advisable to start ERT before myocardial fibrosis in order to achieve long-term improvement in myocardial morphology and function[4], reduction in LVH has also been reported in FD patients with myocardial fibrosis[5]. Mechanisms of LVH regression are not completely understood, but it is hypothesized that clearance of cardiomyocyte GB_3 deposits and reduction of trophic stimuli are involved[12].

Early diagnosis of FD is essential for a better outcome and echocardiography is a useful tool for screening, diagnosis, and follow-up evaluation[22]. In our multicentric study in 49 FD patients with a median echocardiographic follow-up of 7 years, the baseline prevalence of LVH was 38.77% (95% CI: 25.13 – 52.4%), generally with preserved systolic function. In this cohort of FD subjects receiving ERT, the overall annual change in LVMI was 0.38 $g/m^{2.73}$; this variation was not influenced by demographic (gender, classical cardiovascular risk factors, body mass index), echocardiographic, and treatment-related (age at ERT initiation) factors. In addition, this annual variation in LVMI was similar among patients with baseline LVH or normal ventricular mass. LVMI remained unchanged during follow-up in a striking proportion of our patients and only one subject experienced progression of cardiac disease.

Our results are consistent with those reported in other large cohorts with similar baseline LVH prevalence. Kampmann et al carried out a single-center retrospective series using prospectively collected data from the medical records of 45 FD patients (21 men and 24 women). Subjects were treated with agalsidase alfa and followed up for 10 years. During treatment, no patients without LVH at treatment initiation developed this complication and no participants with baseline LVH showed progression in LVM. The investigators concluded that agalsidase alfa is associated with long-term benefits for FD cardiomyopathy, regardless of gender and severity of cardiac symptoms. This absence of cardiomyopathy progression largely resembles our results, even though our multicentric data might probably be more representative of the local FD population[19].

Beck *et al* presented a descriptive analysis of 677 patients followed for a median of 3 years with a baseline LVH prevalence of 43.3%, with stable or improved cardiac parameters in FD subjects receiving ERT with agalsidase alfa[23]. Of note, our patients were followed for a longer period and long-term stability of cardiac parameters remained unchanged.

In the large study of Mehta et al, including 181 FD patients enrolled in the FOS database, the investigators also confirmed the benefits of ERT with agalsidase alfa on cardiac mass and function, in addition to other FD manifestations. They reported sustained benefits of agalsidase alfa during 5 years of follow-up; subjects with baseline LVH showed a clinically significant reduction in LVH and an improvement in myocardial contractility during the first 3 years of treatment.

Among those FD patients with normal baseline LVM, cardiac mass remained stable, with

LVMI within normal limits in over 90% of patients[24]. The mortality rate during follow-up in Mehta's cohort was 17.6%, slightly higher that our reported rate (13.2%).

In contrast, in a retrospective analysis of FOS data by Ramaswami *et al* including agalsidase alfa-treated patients, LVMI had relatively small increases among patients with baseline LVH, but remained stable in patients without LVH at baseline. In addition, participants with decreased kidney function or LVH at baseline experienced modest declines in renal function and/or increases in LVMI[25]. Differences in gender distribution and median age may account for these dissimilarities when compared with our prospective data.

It is worth noting that our results are closely similar to an international large sample retrieved from FOS data by Beck *et al*, including 591 FD patients receiving agalsidase alfa for up to 20 years. In that cohort, the annual rate of change in LVMI was 0.42 $g/m^{2.7}$ for agalsidase alfa-treated patients. This rate of increase was greater for males than females (0.49 vs. 0.34 $g/m^{2.7}$, respectively). Nevertheless, male patients had higher glomerular filtration rates at baseline compared with females, probably due to bias related to age differences between these subpopulations[26]. In our cohort, no differences in median age were described.

In previous models, a younger age at ERT initiation with agalsidase beta has been linked to better morphometric cardiac outcomes, including LVM, interventricular septal thickness and left posterior wall thickness[22]. However, in our analysis, treatment with agalsidase alfa was related to similar results irrespective of age at ERT initiation, suggesting that older patients would benefit from treatment at least in terms of cardiac stability.

Therapeutic goals for morbimortality in FD subjects with both early-stage and advanced cardiomyopathy are reducing morbidity and preventing premature mortality[18]. The optimal objective of FD treatment is to achieve normalization of LVH[18]. However, this is probably unfeasible in most cases, particularly in patients with established myocardial fibrosis[12,18]. Preventing LVH progression might be a more realistic goal based on the proposed assumption that this

would translate into improved patient outcome. When compared with other lysosomal disorders, like Gaucher disease, the evaluation of response to ERT in FD is clearly more complex, because no evident morphological visceral changes occur in response to treatment and no ideal biomarkers correlating with FD severity or clinical response are available[14]. Cardiomyopathy may remain asymptomatic until more advanced disease stages; in absence of regular monitoring, it may be difficult to determine the clinical response to ERT[19]. We emphasize that stability may represent an important sign of response to ERT, rather than the improvement of morphometric parameters or the reversal of clinical symptoms of FD. This approach has been described in kidney disease, in which the stability of the glomerular filtration rate during ERT for FD is considered a positive outcome, by delaying the onset of renal failure or the time to dialysis[27].

Our analysis has several limitations. First, this is an observational retrospective study subject to potential biases inherent to its epidemiological design. However, we highlight its value in relation to the external validity of the results in the real-world setting. Second, echocardiograms were not performed by the same laboratories or operators due to the multicentric design. Still, more than two thirds of the echocardiograms were performed by the same two echo laboratories in the coordinating sites, thus minimizing the risk of operator- or center-related biases. Third, several patients were excluded from our analysis due to missing data; it is worth noting that individual follow-up was performed by local physicians throughout the country, without patients returning to *Hospital Británico*. Fourth, most patients were lost after ≥ 10 years of follow-up, reducing statistical power of our analysis. Nevertheless, at median follow-up, statistical trend for LVMI variation was similar in all subgroups defined by gender and baseline LVH. In addition, high dropout rates are frequent in clinical practice, reflecting real medical conditions.

A major strength of our study is the prolonged follow-up period and we consider that this may represent the first study of its kind in the local FD population.

In conclusion, long-term ERT with agalsidase alfa is associated with stabilization of LVMI in

FD patients, independent of gender, and cardiovascular risk factors. Overall change in LVMI was 0.38 g/m$^{2.73}$ per each year of follow-up.

Our results are similar in subjects with or without baseline LVH and emphasize the importance of cardiac morphometric stability as a positive outcome of ERT.

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