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MAJOR CARDIOVASCULAR ADVERSE EVENTS IN FABRY DISEASE PATIENTS RECEIVING AGALSIDASE ALFA

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Abstract Cardiovascular mortality (CVM) has become the major contributor to overall Fabry disease (FD) mortality in the enzyme replacement therapy (ERT) era. Our objectives were to describe causes and potential predictors of mortality in FD adult patients in Argentina, and to assess risk of major adverse cardiovascular events (MACE) in the ERT era. We retrospectively studied 93 consecutive patients treated with alpha-galactosidase A (median follow up: 9.5 years from start of ERT). Mean age at ERT starting was 35±16.3 years. Prevalence of cardiomyopathy and renal disease reached 47% and 41%, respectively. Eleven subjects (11.8%, 95%CI: 5-18%) died during follow up (1.24/100 patient-years). Mean overall survival was 71 years (95%CI: 66-75 years). Seven cases were considered as CVM; main causes were sudden death and stroke. Risk of MACE was 14% (95%CI: 6.9-21.1%; 1.47 events/100 patient-years from start of ERT). All but 2 subjects had at least one comorbid cardiovascular risk factor; however, 86% of patients remained free of MACE during follow-up. CVM remained low and our study was underpowered for detection of predictors of mortality, but it is worth noting that age at diagnosis and ERT starting, left ventricular mass index and renal disease trended to correlate with CVM. Prevalence of hypertension, diabetes and dyslipidemia were lower in FD patients when compared to population level data. As in the Argentinean general population, CVM was the leading cause of mortality among this cohort of consecutive FD patients treated with agalsidase alfa.

Key words: Anderson-Fabry disease, cardiomyopathy, cardiovascular mortality, enzyme replacement therapy, agalsidase alfa, Argentina

Resumen ***Eventos cardiovasculares mayores en pacientes con enfermedad de Fabry tratados con agalsidasa alfa.*** La mortalidad cardiovascular (MCV) se ha convertido en el principal contribuyente a la mortalidad general por enfermedad de Fabry (EF) en la era de la terapia de reemplazo enzimático (TRE). Nuestros objetivos fueron describir las causas y posibles predictores de mortalidad en pacientes adultos con EF en la Argentina, y evaluar el riesgo de eventos cardiovasculares mayores (MACE) en la actual era de TRE. Se estudiaron 93 pacientes consecutivos tratados con agalsidasa-alfa por una mediana de 9.5 años tras iniciar TRE. La edad al inicio de TRE fue 35 ± 16.3 años. La prevalencia de cardiomiopatía y enfermedad renal alcanzó 47% y 41%, respectivamente. Once sujetos (11.8%; IC95%: 5-18%) murieron durante el seguimiento (1.24/100 pacientes/año). La supervivencia global fue 71 años (IC95%: 66-75 años). Siete casos fueron considerados como MCV; las principales causas fueron muerte súbita e ictus. El riesgo de MACE fue 14% (IC95%: 6.9-21.1%; 1.47 eventos/100 pacientes/año desde la ERT). Todos menos 2 sujetos tenían al menos un factor de riesgo cardiovascular, pero el 86% permaneció libre de MACE. Los eventos de MCV fueron escasos. El estudio tuvo reducido poder estadístico para detectar predictores de mortalidad, pero la edad al diagnóstico y al iniciar la TRE, índice de masa ventricular izquierda y enfermedad renal tendieron a correlacionarse con MCV. La prevalencia de hipertensión, diabetes y dislipidemia fue menor en comparación con la población general. Como ocurre con la población general en Argentina, los eventos cardiovasculares fueron la principal causa de muerte en esta cohorte de pacientes consecutivos con EF tratados con agalsidasa-alfa.

Palabras clave: enfermedad de Anderson-Fabry, miocardiopatía, mortalidad cardiovascular, terapia de reemplazo enzimático, agalsidasa alfa, Argentina

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KEY POINTS
Current knowledge

- Fabry disease (FD) progression has been linked to major adverse cardiovascular events (MACE) that limit life expectancy of untreated patients.

What this article adds

- Long-term FD treatment with agalsidase alfa is associated with a low number of deaths and major cardiovascular events in Argentina.
- Even though prevalence of cardiomyopathy and renal disease reached 47% and 41%, respectively, among FD patients, mean overall survival was 71 years (95%CI: 66-75 years) and 86% of patients remained free of MACE during 9.5 years of follow-up.
- Overall prevalence of vascular risk factors in FD was lower than in the general population.
- Age at FD diagnosis and enzyme replacement therapy starting, left ventricular mass index and renal disease trended to correlate with cardiovascular mortality among FD patients.

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by mutations in the gene encoding for alfa-galactosidase A. FD is characterized by progressive lysosomal accumulation of glycosphingolipids in multiple systems and organs including peripheral and autonomic nerves, gastrointestinal tract, skin, heart, kidneys and brain, with a myriad of progressive signs and symptoms including left ventricular hypertrophy (LVH), proteinuria, decreased renal function, neuropathic pain, hypohidrosis, exercise intolerance, gastrointestinal symptoms, stroke, angiokeratoma and corneal dystrophy (*cornea verticillata*)[1-4]. Symptoms usually begin in childhood and adolescence, especially for classical FD phenotype (mainly characterized by gastrointestinal symptoms, anhidrosis, acroparesthesias and kidney dysfunction); however, misdiagnosis is common[5].The long delay between symptoms onset and the definitive diagnosis is probably related with poor recognition of FD's manifestations[5].

FD progression has been linked to end-stage renal disease and major adverse cardiovascular events (MACE) that limit life expectancy of untreated males and females (20 and 10 year reduction, respectively) as compared to the general population[2]. Natural history of FD has changed after the introduction of enzyme replacement therapy (ERT). In adult subjects, agalsidase alfa is administrated at 0.2 mg/kg body weight every other week by intravenous infusion[6], mostly in a home-based schedule.

Data from the Fabry Outcome Survey (FOS), which collects information on the natural history of FD and the long-term efficacy and safety of ERT, suggest that the importance of renal disease as a cause of death in patients with FD is decreasing, while the importance of cardiac disease is highlighted[7]. Improvement in supportive care, greater accessibility to dialysis facilities and improved treatment of hypertension have all probably contributed to the lower mortality due to renal disease among FD patients[7]. ERT has been linked to a slower decline or even stabilization of renal function in patients with relative lesser degrees of renal impairment[7]. As cardiac disease is now the most commonly reported cause of death in FD patients, its treatment has become strikingly important, as ERT improve cardiac structure and function in this population[7]. Likewise, main causes of death among affected relatives of patients in FOS (mostly before 2001 when ERT was made available) were renal failure in males (42%) and cerebrovascular disease in females (25%)[7]. By contrast, cardiac disease was the main cause of death in both male (34%) and female (57%) patients during the 2001 to 2007 period[7].

As well as in the rest of the world, FD is underdiagnosed in Argentina, because of its low prevalence and its infrequent consideration among differential diagnosis by the medical community[8]. Data about mortality and MACE in FD patients are lacking in Argentina. As cardiovascular mortality (CVM) has become the major contributor to overall FD mortality in ERT era, our aims were to assess the risk of MACE during long-term follow up in ERT-treated patients in Argentina and to describe causes and potential predictors of mortality in our patients' cohort.

Materials and methods

An observational, longitudinal cohort study was performed in 93 consecutive patients with FD treated with agalsidase alfa between June 2001 and June 2015. Data were retrospectively retrieved in AADELFA (*Asociación Argentina de Estudio y Tratamiento de Fabry y Otras Enfermedades Lisosomales*) expert centers in eight Argentinean provinces and centrally analyzed in *Hospital Británico* in Buenos Aires, Argentina.

Inclusion criteria were confirmed FD by deficient enzyme activity in leukocytes and pathogenic mutation in *GLA* gene in males and demonstration of pathogenic mutation by genetic test in females; age ≥ 15 years; and patients receiving ERT with agalsidase alfa as recommended in Argentinean guidelines[9]. Patients without at least one documented follow up visit after 12 months of ERT initiation were excluded. Follow up cohort time was based on review of medical records and actual assessment visits from the moment of ERT initiation until the last documented assessment or death.

Mutation analysis of *GLA* gene (NM_000169.2) was done using DNA isolated from EDTA blood samples. Polymerase chain reaction amplification of each exon and adjacent intron–exon boundaries by the use of specific primers was carried out. The amplicons were purified and then sequenced in both directions in a DNA sequencing device (Applied Biosystems, California, USA). Interpretation and classification of *GLA* variants were based upon American College of Medical Genetics criteria[10] and recent expert consensus[11]. All patients included in this study presented with pathogenic variants in GLA.

CVM was defined as sudden death (unexpected death within 1 hour of onset of new symptoms, including nocturnal deaths with no history of worsening symptoms); death due

to heart failure, myocardial infarction, stroke or other cardiovascular cause (cardiological procedures, peripheral artery disease and pulmonary embolism).

MACEs have been inconsistently defined in the literature[12]. In this study, MACE were widely defined a composite criterion including cardiovascular death, non-lethal stroke, non-lethal myocardial infarction and coronary revascularization[13].

Cardiovascular death and non-cardiovascular deaths were adjudicated based on review of medical records by a clinical endpoint committee formed by expert medical specialists in cardiology, neurology, nephrology and hematology, all with broad experience in FD.

Renal disease was defined by the presence of proteinuria (> 150 mg/24 hours), decreased estimated glomerular filtration rate (less than 60 ml/minute/1.73 m^2), dialysis or renal transplant at inclusion. Coronary artery disease was defined as history of acute coronary syndrome, coronary angioplasty or coronary artery bypass surgery.

FD cardiomyopathy was defined as presence of left ventricular mass index (LVMI) calculated by the Deveraux formula[14] > 115 g/m^2 in males and > 95 g/m^2 in females or left ventricular systolic dysfunction (ejection fraction < 50%) assessed by echocardiogram (biplane Simpson's method). All echocardiograms were centrally performed in *Hospital Británico*.

The study was approved by the institutional ethics committee of *Hospital Británico* and was performed according to good pharmacoepidemiology practice guidelines[15] and local country regulations for observational clinical research (Resolution 1480/2011 from the Argentinean Ministry of Health)[16], in compliance with the Declaration of Helsinki. Given the retrospective data collection and the anonymization of included data, the Institutional Revision Committee has exempted the investigators from needing informed consents from participants.

Continuous variables were summarized as mean and standard deviation or median and quartiles, depending on distribution. Categorical variables were summarized using percentages and 95% confidence intervals (CI) were calculated. We compared the subgroup of patients without MACE during follow up versus those with MACE by univariate analysis. We used parametric or non-parametric test (depending on the distribution of quantitative variables) and Chi square or Fisher's exact test, as applicable for categorical variables.

Mean cardiovascular survival time and overall survival time were determined by Kaplan Meier survival analysis; all patients were followed until death by any cause or until the last documented clinical evaluation visit that was the censoring moment for patients that did not die during follow up.

Potential predictors of mortality and MACE were evaluated through logistic regression analysis; including eventual variables with $p < 0.2$ in the univariate analysis for logistic regression testing and posteriorly removing covariates with two-sided $p > 0.10$. Statistical significance was considered at $p < 0.05$. Data were tabulated using Microsoft Excel® 2013 and were analyzed using Stata Statistical Software (Release 12, College Station, TX: StataCorp LP)

Results

Ninety-three consecutive patients with FD treated with agalsidase alfa were included in this cohort study. Median follow up was 9.5 years (first and third quartile [Q1-Q3]: 6.5-12 years) from start of ERT.

Our patient population was characterized by a median age at start of ERT of 31 years (Q1-Q3: 23-48), mean 35 ± 16.3 years; 52 were females (56%). General data and prevalence of cardiovascular disease risk factors are summarized in Table 1.

Overall prevalence of FD cardiomyopathy was 47% (95% CI: 37-57), while coronary artery disease was documented in 8% of subjects (4 patients had prior myocardial infarction, 4 coronary artery bypass surgery and/or percutaneous angioplasty). Renal disease was present in 41% (95% CI: 34-54), including 11% of patients with dialysis or renal transplant.

All included patients presented pathogenic mutations in *GLA* gene. A total of 17 mutations were identified in our group. Phenotype was classical type in 80% of patients. Mutations frequencies are detailed in Table 2. Relative distribution of the most frequent mutations was similar in male and female patients (data not shown).

Eleven subjects died during follow up (11.8%, 95% CI: 5-18), equivalent to 1.24 per 100 patient-years. Median age was 53 years (Q1-Q3: 42-58) for these subgroup (male: 63%, *versus* 41.4 % for non-deceased patients; $p = 0.28$). Deceased patients were marginally older ($p < 0.045$) than non-deceased subjects (40 years). Mean overall survival calculated by Kaplan Meier curves from

TABLE 1.– *General and clinical characteristics in the studied patients (n = 93)*

Variable	
Age at diagnosis (years)*	32 ± 16.6 (19-47)
Age at start of ERT (years)*	35 ± 16.3 (23-48)
Male/female	41 (44%) / 52 (56%)
Smoking current/former	30 (32.2%) / 19 (20.3%)
Body mass index (kg/m2)*	26 ± 5.9 (22.4-29)
Hypertension	26 (28%)
Dyslipidemia	15 (16%)
Diabetes	8 (9%)
Obesity	18 (19%)
Familiar history of coronary disease	19 (20%)
Renal disease	38 (41%)
Dialysis or renal transplant	10 (11%)
Cardiomyopathy	44 (47%)
LVMI, male*	143 ± 73 g/m^2 (92-181)
LVMI, female*	96 ± 36 g/m^2 (67-118)
LVEF	66 ± 11%
Atrial fibrillation	7 (7%)
Ventricular tachycardia	2 (2%)
Pacemaker or ICD	5 (5%)

ERT: enzyme replacement therapy; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index

** denotes that corresponding variables are shown as mean ± SD (first and third quartile)*

date of birth was 71 years (95% CI: 66-75). No significant differences were reported in the age at diagnosis, database inclusion or ERT starting among deceased and non-deceased subjects.

Seven of the eleven cases were considered as CVM: sudden death in 4/7, stroke in 2/7 (one ischemic and one hemorrhagic), and heart failure in 1/7. No mortality events were related to medical procedures, peripheral artery disease and pulmonary embolism. All patients that died due to cardiovascular causes had the classical phenotype. No aborted episodes of sudden death due to successful cardiac resuscitation or appropriate internal cardioverter defibrillator shock were described during the follow up period. Detailed data about these patients subset are available in Table 3.

Non-CVM was observed in 4/11 patients, caused by renal transplant complications, metastatic cervical carcinoma, accident and suicide due to depression.

Risk of MACE was observed in 13/93 patients (14%, 95% CI: 6.9-21.1), equivalent to 1.47 events per 100 patient-years according to median follow up from start of ERT. The two patients with no lethal MACE were women with history of hypertension and dyslipidemia; both of them experienced myocardial infarction (one of them with ST elevation). MACE patients were significantly older (median age: 54, Q1-Q3: 46-59) than subjects without MACE (median age: 37, Q1-Q3: 30-49; $p < 0.01$, Mann-Whitney U Test). Male patients represented 54% of this subgroup. Eleven out of 13 MACE subjects had at least one comorbid conventional cardiovascular risk factor; the other two patients suffered from renal failure, attributed to FD.

Due to lack of statistical power (limited number of mortality and MACE events), it was not possible to identify predictors of CVM. However, the subgroup of patients with CVM during follow up was characterized by a trend to older age at diagnosis and at start of ERT ($p = 0.06$ for both comparisons). A non-significant trend of higher prevalence rates of atrial fibrillation, coronary artery disease, renal disease, and a non-significant trend of increased LVMI were also observed (data not shown).

A subset of 44 (47%) patients had at least one cardiac magnetic resonance imaging (MRI), including 4/7 patients with cardiovascular death. Late gadolinium enhancement (LGE) was present in the 4 deceased patients with CVM (100%) and in 38% of the patients without CVM.

TABLE 2.– *GLA mutations frequencies in the studied population*

Mutation	Relative proportion (n = 93)
c.463G>C	38.2
c.1244T>C	23.6
c.581C>T	10.1
c.680G>A	4.5
c.281G>A	3.4
c.644A>G	3.4
c.ins902_905TGTC	3.4
c.658C>T	2.3
c.888G>A	2.3
c.160C>T	1.1
c.335G>A	1.1
c.520 T>G	1.1
c.572T>C	1.1
c.679C>T	1.1
c.718_719delAA	1.1
c.772G>T	1.1
c.902G>A	1.1

Discussion

Our research describes the epidemiology of MACE and causes of mortality among a large cohort of con-

TABLE 3.– *Selected characteristics of FD patients with cardiovascular mortality*

Mutation	Age*	Gender	Dialysis	LVMI (g/m^2)	CAD	AF	MRI/ LGE	Cause of death
c.463G>C	39	Female	No	152	No	No	N/A	Sudden death
c.463G>C	62	Female	No	129	Yes	No	Yes	Stroke
c.1244T>C	46	Male	Yes	256	No	Yes	Yes	Heart failure
c.1244T>C	43	Male	No	102	Yes	No	Yes	Sudden death
c.728T>G	59	Male	Yes	150	Yes	No	Yes	Sudden death
c.581C>T	52	Male	Yes	114	Yes	Yes	N/A	Stroke
c.281G>A	61	Male	Yes	315	No	No	N/A	Sudden death

AF: atrial fibrillation; CAD: coronary artery disease; FD: Fabry disease; LVMI: left ventricular mass index. MRI/LGE: magnetic resonance imaging with late gadolinium enhancement; N/A: not available

*Age at moment of death

secutive FD patients treated with agalsidase alfa in Argentina.

CVM was approximately 1% per year of median follow up from ERT initiation and represented the main cause of overall mortality. Sudden death and stroke were the two principal causes of cardiovascular death in our series. In previous reports, life expectancy in cohorts of FD patients (both untreated and treated with ERT) reaches between 50-57 years in males and 64-72 years in females[7, 17-21]. However, results from those studies should be interpreted with caution, considering their heterogeneity in terms of inclusion criteria, participation of patients from different regions and differences in age at diagnosis or starting ERT. Besides, some studies do not include consecutive patients with complete follow up and both prevalence of cardiac and renal involvement and proportion of patients treated with ERT vary among the different cohorts. Moreover, FD patients from Latin America were not usually included in previous studies; therefore, local epidemiological information is scarce, despite the fact that 10% of FD patients live in this region[22]. By contrast, our study included consecutive patients with complete follow up over a decade from starting of ERT with no patient was lost and showed a high prevalence of cardiomyopathy and renal disease (including dialysis and/or renal transplantation). Our population was at higher risk for morbidity and mortality, compared with previous reports that described lower mortality rates, but with less severe renal and cardiac affection[23].

Recent data from the FOS showed that treatment with agalsidase alfa has a positive effect on mortality, with a median survival time of 77.5 years in 360 treated male patients, versus 60 years in historic control patients with a similar FD severity in the era prior to ERT[24]. By contrast, in a study including 40 patients with genetically proven FD (mean age 40 ± 9 years; 31 male) treated prospectively with agalsidase beta during a median follow-up of 6 years, 15 “hard” events were informed in 13 patients (including 6 sudden deaths and 4 strokes)[25]. The event rate was not different between the agalsidase beta treated group and an untreated matched-control group of the Fabry Registry. Our overall estimated survival of 71 years is only slightly lower than in previous studies using agalsidase alfa, which may be attributable to epidemiological differences; however, no evaluation was done in this study.

Cardiovascular deaths events in our cohort remained small and our study was underpowered for detection of predictors of mortality. However, it is worth noting that several variables (age at diagnosis and starting of ERT, LVMI, and renal disease) have shown at least a positive trend of relationship with CVM, as previously observed[7,17-21,23]. It is interesting to note that a subset of our cohort had cardiac MRI, showing a prevalence rate of LGE reaching 100% in patients with cardiovascular death. However, this finding may be affected by selection bias since we only obtained cardiac MRI in 44% of participants.

Among our ERT-treated FD patients, risk of MACE was equivalent to 1.47 events per 100 patient-years from start of ERT, with 86% of our patients remained free of MACE during the follow-up period. All MACE patients had at least one comorbid conventional cardiovascular risk factor, including renal failure[26]. Interestingly, prevalence of hypertension (28%), diabetes (8%) and dyslipidemia (16%) were lower in our FD cohort in comparison with general adult population in Argentina (36%, 10% and 30%, respectively)[27-29]. This is most likely due to strict control of cardiovascular risk factors in every patient of our group upon FD diagnosis.

Importance of renal failure in the epidemiology of MACE in this population is highlighted. Dialysis or renal transplant may represent the first relevant clinical event in the natural history of patients with FD. In the Fabry Disease Registry, 55% of deceased patients experienced a first renal event (dialysis or transplant) versus 8% of living patients[17]. In FD patients, renal involvement has been linked to cardiovascular disease progression including LVMI, sudden death, arrhythmia and pacing device insertion[30,31]. Chronic kidney disease is a known independent risk factor for coronary artery disease, the leading cause of morbidity and mortality in patients with chronic renal disease[32]. In our cohort, all patients with MACE had at least one CV risk factor, including renal failure.

FD cardiomyopathy is characterized by diffuse vacuolization of myocytes, endotheliocytes and smooth muscle cells due to glycosphingolipid accumulation. Additionally, extracellular glycosphingolipids accumulate due to death of severely affected cells with later myocardial fibrosis[33]. Cascade of myocardial changes in FD involves a broad range of pathological mechanisms, including toxic metabolites, cytokine activation, autophagy and fibrosis[34-37]. These deleterious mechanisms may be potentiated in FD patients with concomitant chronic kidney disease and coronary artery disease, leading to primary or secondary arrhythmic death due to acute coronary events[30,33].

In addition, stroke (one ischemic and one hemorrhagic) was the second cause of cardiovascular death in our study. FD is characterized by stroke at young ages, basilar dolichoectasia and white matter hyperintensities[1-3]. According to previous research, a relevant proportion of young FD patients may present evidence of small vessel disease on brain magnetic resonance imaging, even without a history of stroke[38]. We found a trend towards larger prevalence of atrial fibrillation in deceased patients, which may be a contributor to potential cardioembolic stroke. This merits further research, since early detection and treatment with adequate anticoagulation therapy may potentially impact the incidence of stroke[39].

Our study has several limitations, including its retrospective observational design, and low number of deaths that underpower a potential in-depth analysis of potential mortality predictors. The lack of a control group is a rel-

evant limitation, but ethical consideration regarding the indication of a treatment with proven efficacy needs to be taken into account. However, FD patients have been historically considered a subgroup with early mortality; by contrast, the mortality rates in our cohort seem similar to general Argentinean population data.

We consider our evidence, combined with that of other similar cohorts, adds relevant clinical data to the better understanding of the natural history of high risk in treated FD patients. This is especially important in a context of scarce data for FD patients from Latin America.

Besides, cardiac MRI was obtained only from a subset of our cohort, considering the growing, but yet reduced availability, of this imaging method in Argentina[40]. We recognize that, in addition to the diagnostic contribution of cardiac MRI in terms of different patterns of fibrosis, increasing evidence is accumulating regarding the role of LGE in defining prognosis and treatment in FD patients[41]. However, echocardiography remains the cornerstone for first evaluation and follow-up in FD patients[41]; all echocardiographic examinations of our cohort were obtained in a centrally laboratory, reducing risks of operator-linked bias.

In conclusion, long-term FD treatment with agalsidase alfa was associated with a low number of deaths and MACE. CVM (mainly due to sudden death and stroke) was the leading cause of death. Overall prevalence of vascular risk factors was lower than in the general populations, most likely to early preventive measures implemented and their benefits in our population. Potential impact of these modifiable factors in FD patients' morbidity and mortality warrants a high degree of awareness for prevention, detection and treatment.

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