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Long-term effectiveness of enzyme replacement therapy in Fabry disease with the p.Arg227Ter variant: Fabry disease in Ostrobothnia (FAST) study

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Abstract

Fabry disease (FD) is an X chromosome-linked, life-threatening lysosomal disease caused by one of more than 1000 currently known variants in the α-galactosidase A (GLA) gene. The follow-up part of the Fabry Disease in Ostrobothnia (FAST) study reports the long-term effect of enzyme replacement therapy (ERT) on a prospectively collected cohort of 12 patients, 4 males and 8 females, mean age 46 years (SD 16), with the classical variant c.679C > T p.Arg227Ter, which is one of the most common FD variants worldwide. In the natural history period of the FAST study, half of the patients in both sexes had at least one major event, of which 80% were of cardiac origin. During 5 years of ERT, four patients had a total of six major clinical events consisting of one silent ischemic stroke, three ventricular tachycardias and two increased left ventricular mass indexes. In addition, four patients developed minor cardiac events, four patients minor renal events, and one patient a minor neurological event. ERTs may delay but not prevent the progression of the disease in most patients with the variant Arg227Ter. This variant might be suitable for investigating the efficacy of second-generation ERTs compared to the currently used ERTs regardless of sex.

KEYWORDS
efficacy, enzyme replacement therapy, Fabry disease, follow-up study, sex, variant

1 | INTRODUCTION

Fabry disease (FD) (OMIM # 301500) is caused by pathogenic variants in α-galactosidase A (GLA, OMIM *300644) gene in X-chromosome. An erroneously coded gene produces unstable or functionally inactive enzyme α-galactosidase A (α-GAL A) (OMIM #300644; HGNC 4296; the GenBank reference sequence NM_000169.2). More than 1000 variants in the GLA gene are known today (Stenson et al., 2017) "The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis, and next-generation sequencing studies—PubMed"). Missense variants, which are the most common variants (Stenson et al., 2017 "The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies—PubMed"), cause a different amino acid to be incorporated into α-GAL A resulting in either classical FD with minimal α-GAL A activity or later-onset FD with significant residual α-GAL A activity. Nonsense variants convert

an amino acid-specific codon to a stop codon and results in production of truncated and non-functional enzyme leading to the residual α-GAL A activity <3% of mean normal in males and classical FD (Arends, Wanner, et al., 2017; Brady et al., 1967; Eng et al., 1997; Ishii et al., 2007; Kint, 1970; Nakao et al., 2003; Spada et al., 2006). In FD, neutral sphingolipids, mainly globotriaosylceramide (Gb3) and globotriaosylsphingosine (lysoGb3), accumulate in lysosomes throughout the body. If untreated, classical FD ultimately leads to multiorgan failure and premature death. Later-onset variants cause delayed and generally milder disease with predominantly single organ manifestation (Chien et al., 2012; Desnick et al., 2001; Lavalle et al., 2018; Nakao et al., 2003; von Scheidt et al., 1991). One of the main challenges encountered in former studies is the heterogeneity of material comprising both classical and later-onset variants.

Previous research has established that early treatment is more effective than late treatment (Arends, Wijburg, et al., 2017; Hughes et al., 2020; Hughes et al., 2021; Ortiz et al., 2016; van der Veen et al., 2022). To date, enzyme replacement therapy (ERT) with agalsidase alpha or agalsidase beta and chaperon therapy are the only disease-modifying therapies. Solely ERT can be used regardless of the type of the variant in GLA (Benjamin et al., 2017; Schiffmann et al., 2001; Wilcox et al., 2004). Anti-drug antibodies (ADAs) are one of the most frequently stated problems with ERT. There is still some uncertainty, whether ADAs can have a negative impact on efficacy of ERT (Lenders & Brand, 2018; Lenders, Neußer, et al., 2018; Lenders, Schmitz, et al., 2018; van der Veen et al., 2019).

The nonsense variant c.679C > T p.Arg227Ter [GenBank reference sequence NM_000169.3(GLA)] is one of the most common variants causing classical FD in Finland and worldwide (Giugliani et al., 2019; Pietilä-Effati et al., 2019). The genetic diversity within Sweden and Finland is lower than in central European reference populations and is substantially reduced in eastern Finland. The genetic distance between eastern and western Finns is greater than between the British and northern Germans. In fact, western Finns are genetically equally close to Swedes than to eastern Finns and subjects from the Swedish-speaking region in Finnish Ostrobothnia, in particular, are genetically intermediate between Finns and Swedes (Salmela et al., 2011). The long-term veness of ERT in FD with the p.Arg227Ter variant in Finnish Ostrobothnia aims to overcome the heterogeneity of mutations in the previous ERT efficacy studies using a patient cohort with a single pathological variant in different stages of the FD.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK: 41/1801/2017) and was conducted in accordance with the Declaration of Helsinki.

The Fabry Disease in Ostrobothnia (FAST) study consists of a cohort of 14 patients with FD by variant Arg227Ter in GLA. Two families with this variant were diagnosed in Vaasa Central Hospital and in the Hospital District of Southwest Finland during the years 2013–2014. The natural history of this cohort has previously been described (Pietilä-Effati et al., 2019). Twelve patients, four males and eight females, were considered to benefit from ERT and gave their written informed consent to this prospective, observational, five-year follow-up study (Figure 1).

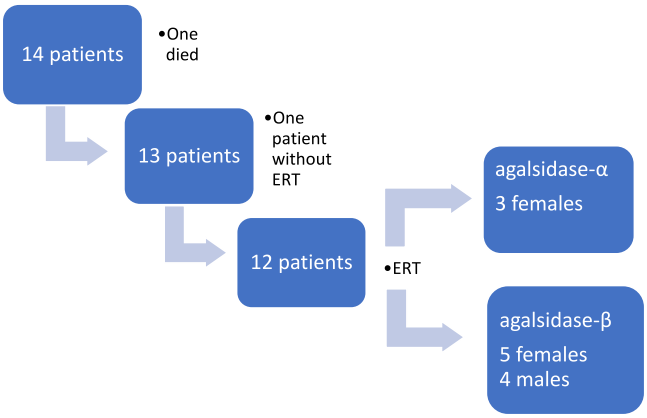

FIGURE 1 Flow chart.

2.2 | Enzyme replacement therapy

Enzyme replacement therapy was initiated with agalsidase alpha at dose 0.2 mg/kg in three patients and with agalsidase beta at dose 1 mg/kg for nine patients and were given intravenously every other week (eow). The discretion of the physician and patients´ preference were the main reasons behind the choice of ERT. The first ERT infusion was given in the hospital ward. Females were transferred to home care starting from the second infusion. Males received 6–10 infusions in the hospital ward; subsequent infusions were given at home by a specialized nurse. All males received some combination of glucocorticoids, antihistamine, and non-steroidal anti-inflammatory drugs as premedication prior to ERT. Females received premedication only if needed. Patients had immediate access to the hospital ward in the event of a severe infusion-related reaction.

2.3 | Clinical follow-up

A comprehensive evaluation was performed annually by a multidisciplinary team comprising a cardiologist (Päivi Pietilä-Effati), internist (Ilkka Kantola) and neurologist (Jukka T. Saarinen). A nephrologist and other specialists were consulted if necessary. Details of the protocol have been described in a previous paper (Pietilä-Effati et al., 2019). In short, laboratory parameters, electrocardiogram (ECG), 24-h continuous ECG, transthoracic ultrasound (TTE), and audiogram were prospectively collected at every visit. Ophthalmological examination and cardiac magnetic resonance imaging (cMRI) were performed at every

other visit, and brain imaging with MRI (bMRI) or with computed tomography (CT) was performed at the end of the follow-up unless there was a clinical need to perform the scan earlier.

Left ventricular mass index (LVMI) was calculated from cMRI excluding papillary muscles in the left ventricular mass. The mean normal values for LV mass indexed by body surface area (BSA) (g/m^2) were age and sex dependent. Upper reference values were calculated mean + 2 SD. The size and location of fibrotic areas in the heart were determined using gadolinium (Dotarem® 279.3 mg/ml) as a contrast agent. These late gadolinium enhancement (LGE) images were acquired 12–17 min after intravenous injection of gadolinium (Hudsmith et al., 2005; Kawel et al., 2012). Images were analyzed using the 17-segment heart model (Cerqueira, 2002).

White matter hyperintensities (WMHs) of presumed vascular origin in bMRI were reported with the use of probably the quickest to apply and among the best validated visual rating scale, the Fazekas scale for bMRI (Fazekas et al., 1987). WMHs that are excessive for age are associated with increased future risk for stroke (Smith et al., 2017).

For kidney assessment, we used the guidelines developed by the Kidney Disease: Improving Global Outcomes (KDIGO) organization in 2012 (Supplementary material 1) (Stevens & Levin, 2013).

High-sensitivity cardiac troponin T (hs-TnT) and N-terminal pro-brain-type natriuretic peptide (NT-Pro-BNP) were measured from plasma. Reference range was <15 ng/L for hs-TnT. For NT-Pro-BNP reference ranges were age and sex dependent (Supplementary material 1). LysoGb3 was measured from a dried blood spot in Centogene AG (Rostock, Germany).

For ADAs, Anti-αGAL IgG antibody titers were assessed by enzyme-linked immunoabsorbent assay at the Genzyme Clinical Specialty Laboratory (Framingham, MA) until the end of 2019, and after that, at LabCorb (Calabasas Hills, CA) for patients using agalsidase beta. Covance Bioanalytical Services (Indianapolis, IN) was used for patients with agalsidase alpha. The reciprocal of the highest dilution of serum sample which gave a positive result was determined.

Performance ability was measured by cardiopulmonary exercise text (spiroergometry) before ERT if possible. If the result was abnormal, spiroergometry was also used in the follow-up at regular intervals. If performance ability was normal or if spiroergometry was unavailable before ERT, a combination of spirometry and 6-minute walking test (6MWT) was used instead.

The whole burden of FD was measured by Mainz Severity Score Index (MSSI), which is a validated scoring system for FD (Whybra et al., 2004). Both performance ability and MSSI were assessed at every visit.

Health-related quality of life (HRQOL) was assessed yearly with a validated Short-form Health Survey (SF-36). Altogether 8 domains and 36 items evaluated physical or mental health and their effect on daily life with ratings from 0 to 100. The scores were combined as mental component score (MCS) and physical component score (PCS). Higher scores indicated better HRQOL (Ware et al., 1995; Ware & Sherbourne, 1992).

2.4 | Definition of major and minor clinical events

The clinically important events were graded as major or minor, and were classified according to origin as cardiac, neurologic, or renal events. Death from any cause was added as a major event during the follow-up (Table 1).

2.5 | Statistics

Categorial variables are summarized with counts and percentages. The results for continuous variables are presented as mean and standard deviation (SD) with range when the variable followed normal distribution, or median and interquartile range (IQR) when the distribution of the variable was skewed. The mean changes during ERT were analyzed using linear mixed models for repeated measures. Kenward-Roger correction was used for degrees of freedom. Only time effect was tested with this model, and time differences between every two time points were also estimated. Logarithmic transformation was done for some variables to fulfill the assumption of normality of studentized residuals. For quality of life, score "mirror" transformation was used by subtracking the 65-QL score and then performing logarithmic transformation (maximum value for QC'L score was approximately 64). This was done because the original distribution was left-skewed. *P*-values less than 0.05 (two-tailed) were considered statistically significant.

The data analysis for this paper was generated using SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC).

3 | RESULTS

Enzyme replacement therapy was started at a mean age of 46 years (SD 16, range 16–68). The mean age of males was 30 years (range 16–39) and that of females 52 years (range 25–68). Three patients received agalsidase alpha as the first ERT while nine patients received agalsidase beta. During the follow-up, one male was successfully switched from agalsidase beta to agalsidase alpha because of a severe infusion-related reaction. Two patients were switched from agalsidase alpha to agalsidase beta. The reason for the switch was insufficient response for neuropathic pain and depression in one patient and progression of cardiomyopathy in one patient (Table 1).

At baseline, all were non-smokers, none had diabetes, and only one had hypertension. Mean BMI was 24.1 kg/m^2 (SD 4.1). Mean blood pressure was 132/82 mmHg (SD 18/14), mean cholesterol was 4.8 mmol/L (SD 1.1), mean low-density cholesterol 2.9 mmol/L (SD 0.9), mean high-density cholesterol 1.7 mmol/L (SD 0.5), and mean triglycerides 0.8 mmol/L (SD 0.4).

As described in the natural history part of the study (Pietilä-Effati et al., 2019), cardiac manifestations predominated among the complications of FD representing 80% of severe clinical manifestations

TABLE 1 Definition of major and minor events.

Events	Major	Minor
Cardiac	Hypertrophic cardiomyopathy caused by Fabry disease defined by IVS in diastole ≥15 mm in TTE	Increase in IVS ≥2 mm in TTE in 5 years
	Heart failure with reduced ejection fraction <50% in TTE	Increase in LVMI ≥ 10 g/m^2 in cardiac magnetic resonance imagining in 5 years
	LVMI above the reference range related to age and sex	The first appearance of LGE
	Atrial arrhythmias: atrial fibrillation, atrial flutter, or supraventricular tachycardia	Increase in hs-TnT above the reference range ≥15 ng/L
	Non-sustained ventricular tachycardia: ≥3 ventricular beats at a rate ≥120 beats per minute, and for a duration <30 s	
	Sustained ventricular tachycardia: ventricular beats at a rate ≥120 beats per minute, and duration ≥30 s	
	Implantation of pacemaker or cardioverter defibrillator	
	Myocardial infarction	
	Percutaneous coronary intervention or cardiac bypass surgery	
Neurologic	Ischemic stroke	Increase in Fazekas score that was not related to the patient's older age
	Transient ischemic attack	
Renal	Dialysis	Decrease in eGFR >2 ml/mmol/1.73 m^2 in patients over 40 years, or >1 mL/mmol/1.73 m^2 in patients 40 years of age or less
	Renal transplantation	A new albuminuria
	Increase in KDIGO albuminuria category	Doubling of U-Alb/Crea if the patient had albuminuria prior to ERT
	Decrease in chronic kidney disease category together with at least 25% change in eGFR	
Other	Death from any cause	

Abbreviations: eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; hs-TnT, high sensitivity troponin T; IVS, intervernticular septum thickness in diastole; KDIGO, the Kidney Disease: Improving Global Outcomes; LGE, late gadolinium enhancement; LVMI, left ventricular mass index; TTE, transthoracic ultrasound; U-Alb/Crea, the ratio of urinary albumin to creatinine.

(Table 2). Only one male had mild albuminuria U-Alb/Crea 13.4 mg/mmol (KDIGO A1) before ERT and angiotensin II receptor blocker (ARB) were initiated.

During 5 years of ERT, four patients had a total of six major clinical events; except for one silent ischemic stroke, all were cardiac events (Table 2). In addition, four patients developed minor cardiac events, four developed minor renal events, and one patient developed a minor neurological event (Table 3).

Major cardiac events during the follow up were mainly asymptomatic NSVTs on 24-h ambulatory ECG.

CMRI was performed in eight out of 12 patients (67%) before the initiation of ERT. LVMI remained stable in this subgroup ($p = 0.48$). At a patient level, LVMI remained stable or decreased slightly in all patients over 18 years of age. The slight increase in LVMI in the youngest patient can be explained by late adolescence. Another patient whose LVMI was first time above the reference range during the follow-up, had no cMRI before the initiation of ERT (Figure 2). Of note, the two oldest patients with non-MRI compatible pacemakers could not be assessed.

Five out of eight patients (63%) had 1–2 LGE-positive segments in cMRI already in natural history period. LGE increased by 0.5–1 segment in all those five. None of those three patients who were LGE negative before ERT, developed new LGE positive segments during the follow-up.

Despite ERT, median hs-TnT increased from 9.5 ng/L (IQR 5.5–23.5) to 17 ng/L (IQR 10.5–40.5), which is both statistically and clinically significant ($p = 0.04$) (Figure 3). N-terminal pro-brain-type natriuretic peptide (NT-Pro-BNP) remained unchanged, but EF tended to rise from median 65% (IQR 61–75) before ERT to 72% (IQR 66–75) in follow-up ($p = 0.05$).

None of the patients experienced ischemic stroke or TIA with clinical symptoms during the 5 years of follow-up. However, the oldest male, who experienced a stroke at the age of 39 leading to diagnosis of FD, had several new silent lacunar infarcts during the follow-up, and his Fazekas score increased from 0 to 2. In the other patients, no new silent infarcts could be detected in bMRI or CT. Fazekas scores remained unchanged as well.

For renal outcomes, eGFR tended to decrease from mean 95 ml/min/1.73 m^2 (SD 19) to 88 ml/min/1.73 m^2 (SD 22) ($p = 0.06$). Cystatin C remained stable. One patient had mildly increased albuminuria (KDIGO A1) which resolved after initiation of ERT and angiotensin II receptor blocker and remained absent throughout follow-up (Figure 4). None of the patients developed new, persistent albuminuria during the follow-up.

TABLE 2 Major clinical events.

				Major clinical events before ERT			Major clinical events during the 5 years of ERT			
ID	Sex	Age at diagnosis (years)	ERT during the 5 years follow-up	C	R	N	C	R	N	D
1	M	15	Agalsidase beta							
2	M	33	Agalsidase beta	1[a]						
3	M	35	1. Agalsidase beta 2. Agalsidase alpha				2[b,c]			
4	M	39	Agalsidase beta	1[a]		1[d]	2[b,c]		1[d]	
5	F	25	1. Agalsidase alpha 2. Agalsidase beta							
6	F	46	Agalsidase beta							
7	F	48	1. Agalsidase alpha 2. Agalsidase beta	1[e]			1[b]			
8	F	52	Agalsidase beta							
9	F	61	Agalsidase beta	2[a,c]						
10	F	60	Agalsidase beta							
11	F	61	Agalsidase beta	4[a,f–h]						
12	F	66	Agalsidase alpha	3[a,f–h]		2[d,i]				

Abbreviations: C, cardiac event; D, death from any cause; ERT, enzyme replacement therapy; ID, identification number; N, neurological event; R, renal event; Sex, M is male; F is female.

[a]Hypertrophic cardiomyopathy caused by Fabry disease.

[b]Ventricular tachycardia.

[c]Left ventricular mass index.

[d]Clinical or subclinical stroke.

[e]Supraventricular tachycardia.

[f]Atrial fibrillation.

[g]Sick sinus syndrome.

[h]Pacemaker.

[i]Transient ischemic attack.

Before the initiation of ERT, mean LysoGb3 in plasma was 101 μg/L (SD 11.4) in males and 8.3 μg/L (SD 5.2) in females. After 5 years, mean LysoGb3 was 37.8 μg/L (SD 13.6) in males and 7.5 μg/L (SD 3.6) in females ($p = 0.05$ for decrease in the whole group). Details are presented patient-by-patient in Figure 5.

All four males develop ADAs during the ERT and experienced mild infusion-related reactions despite premedication. After 3.5 years of agalsidase beta, one of the four experienced a severe infusion-related reaction and was switched to agalsidase alpha. The infusions of agalsidase alpha were well tolerated, and the patient continued home infusions after the fourth dose. Of note, he already had a decreasing antibody titer when the severe reaction occurred. Low titers of ADA 100–200 could also be detected in females with very low α-Galactosidase A activity but without correlation of infusion-related side effects.

MSSI scores and performance ability did not change during the follow-up. Equally, the frequency of pain and gastrointestinal symptoms varied over time in individual patients, and no change could be observed at group level.

In the quality of life, the mean change over time in MCS was significant ($p = 0.032$), so that there was a significant increase between baseline and 3 years ($p = 0.028$), after which a significant decrease between 3 and 5 years was seen ($p = 0.0020$), ending quite close to baseline level. PCS was stabile during the follow-up.

4 | DISCUSSION

The objective of the FAST follow-up study was to investigate the long-term effect of ERT in different stages of disease in patients with the classical variant Arg227Ter. Nine out of 12 patients received agalsidase beta and three patients agalsidase alpha as the first disease-modifying therapy. Both ERTs have been shown to improve cardiac and renal outcomes and to have a positive effect on quality of life in mixed variant studies (Arends, Wijburg, et al., 2017; Benjamin et al., 2017; Hughes et al., 2020; Lenders, Neußer, et al., 2018; Lenders, Schmitz, et al., 2018; Schiffmann et al., 2001; van der Veen et al., 2019; Wilcox et al., 2004).

In our study, FD progressed in seven out of 12 patients despite a median duration of 5 years of ERT. Four patients experienced their first events, during the follow-up (Tables 2 and 3).

Striking is the lack of traditional risk factors for vascular events, making it unlikely that the events were unrelated to FD. In addition, eight out of 12 patients have been examined with coronary

TABLE 3 Minor clinical events during enzyme replacement therapy.

			Minor clinical events during the 5 years of ERT		
ID	Sex	Age at diagnosis (years)	Cardiac	Renal	Neurological
1	M	15			
2	M	33			
3	M	35			
4	M	39			1[a]
5	F	25			
6	F	46	1[b]	1[c]	
7	F	48		1[c]	
8	F	52	1[b]		
9	F	61			
10	F	60	1[d]	1[c]	
11	F	61			
12	F	66	1[b]	1[c]	

Abbreviations: ERT, enzyme replacement therapy; ID, identification number; sex, M is male; F is female.
[a]Increase in Fazekas score not related to age.
[b]Increase in troponin T above the range 15 ng/L.
[c]Decrease in eGFR ml/mmol/1.73 m^2 more than 10 ml/mmol/1.73 m^2 in 5 years.
[d]Increase in IVS ≥2 mm in 5 years (only patients over 18 years of age).

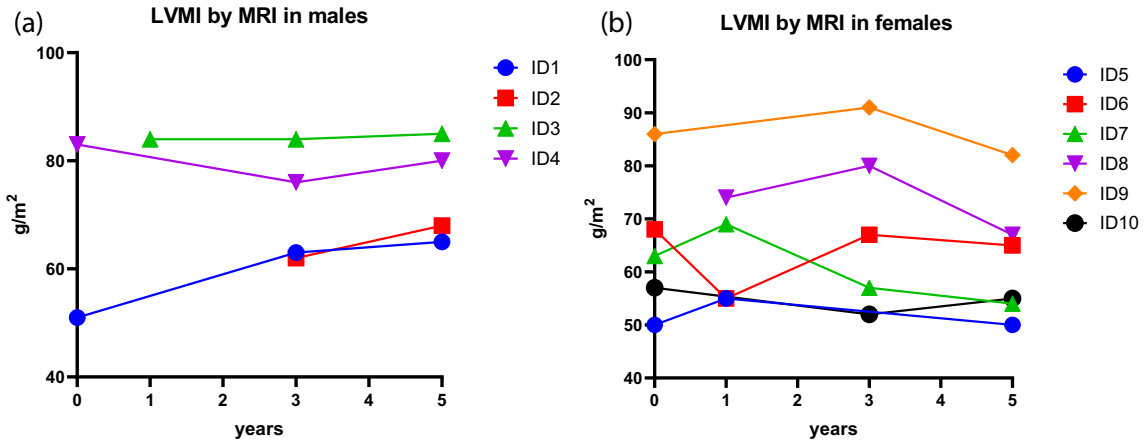

FIGURE 2 The change in 5 years in left ventricular mass index (LVMI) in patient-by-patient defined by cardiac magnetic resonance imagining.

angiography or coronary CT because of angina pectoris and/or positive hs-TnT. No one had coronary artery disease.

Three patients who had major events before ERT remained stable during the follow-up. Only the two youngest patients, a 15-year-old male and 25-year-old female, were free of events at the end of the study. These results reflect those of Lenders et al. (2017) who also found that 50% of patients develop new events during a median 81 months of ERT (Lenders & Brand, 2018). Contrary to their findings and the findings of Arends, Wanner, et al. (2017), patients with normal or mildly reduced eGFR developed several major events in our cohort (Pietilä-Effati et al., 2019). This might be explained by the heterogeneity of variants in those studies, in contrast to the single, classical variant Arg227Ter in our study.

There is a wide consensus that ERT should be initiated before severe disease manifestations occurs (Arends, Wijburg, et al., 2017; Hughes et al., 2020; Hughes et al., 2021; Ortiz et al., 2016; van der Veen et al., 2022). In our study, the mean age was 46 years (SD 16) which is comparable to other studies (Arends, Biegstraaten, et al., 2017; Lenders, Neußer, et al., 2018; Rombach et al., 2013). Only one male and one female, 16 and 25 years of age, respectively, were young enough to be classified as early treated patients. In addition to aging, there is a need to find even earlier markers for disease progression. In part, this led to the inclusion of minor clinical events in addition to the major events when evaluating the effectiveness of the treatment. If the treatment can be intensified or modified, it should be implemented before a new major event and an irreversible organ damage occurs.

Hypertrophic cardiomyopathy caused by Fabry disease (FHCM) was defined from IVS thickness ≥15 mm in diastole measured by TTE because it was possible to perform it in all patients. The average wall

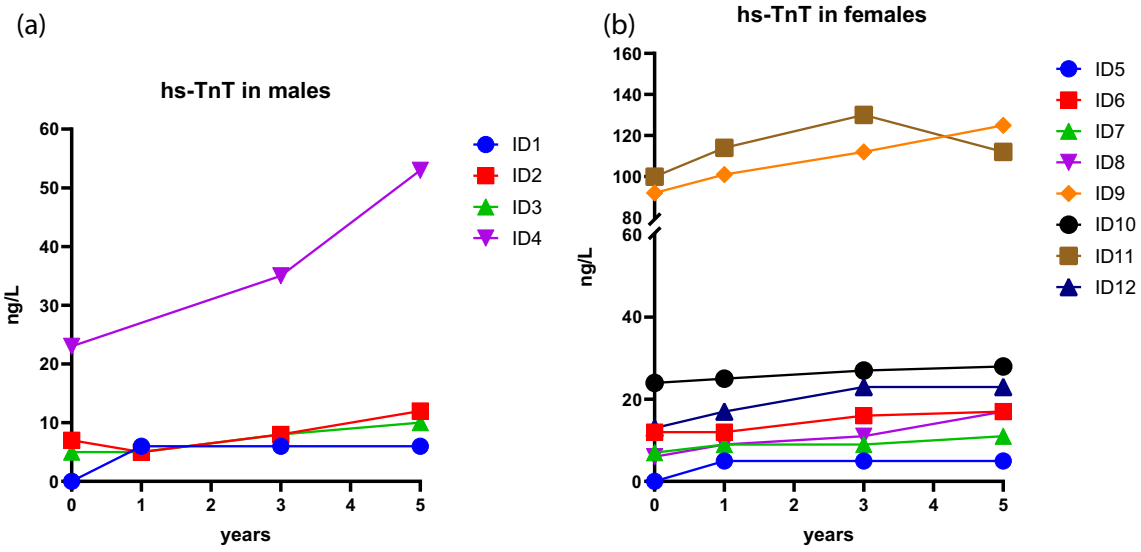

FIGURE 3 The change in 5 years in high-sensitivity cardiac troponin T (hs-TnT) in patient-by-patient.

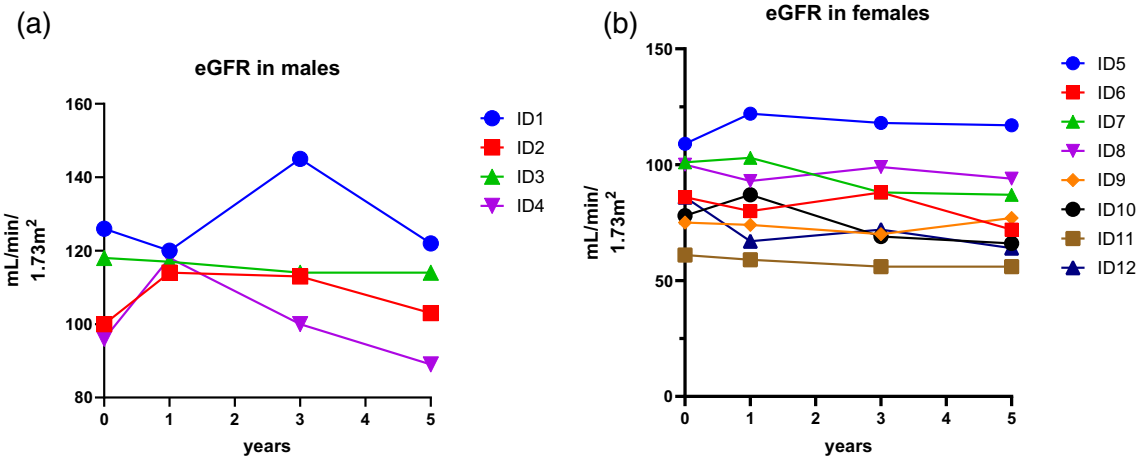

FIGURE 4 The change in 5 years in estimated Glomerular Filtration Rate (eGFR) in patient-by-patient.

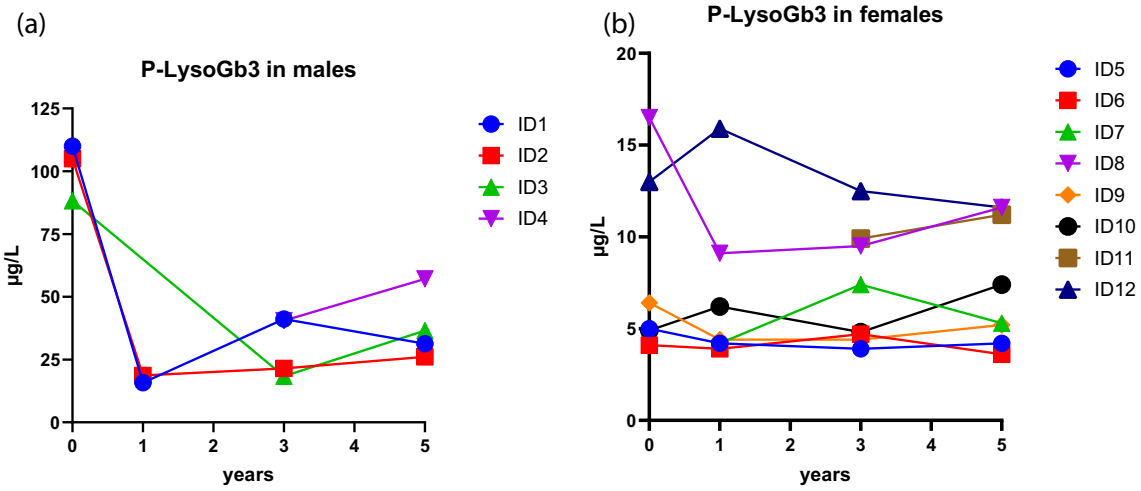

FIGURE 5 The change in 5 years in globotriaosylsphingosine (LysoGb3) in patient-by-patient.

thickness would have been inappropriate because posterior wall thickness is a double-edged sword: Normal wall thickness may represent normal myocardium in non-cardiac disease or scar in advanced disease (Kawano et al., 2007; Teraguchi et al., 2004). To distinguish reliably between the two, cMRI with gadolinium would have been required, but it could not be performed for all patients due to contraindications to MRI which was an inevitable limitation in our study.

To assess LMVI, cMRI is more accurate and reproducible compared to TTE (Armstrong et al., 2012; Hazari et al., 2018). We chose to use only cMRI for these measurements and recorded the increase in LMVI as a minor event rather than a major event because cMRI was not feasible in all patients.

Cardiac troponins are known markers of unfavorable prognosis in several inflammatory and non-inflammatory diseases, including FD (de Lemos et al., 2010; Feustel et al., 2014; Kandolin et al., 2015; Saunders et al., 2011; Seydelmann et al., 2016). Further, The PREDICT-FD modified Delphi consensus initiative considered elevated serum cardiac troponin to be one of the most important early indicators of cardiac damage in FD. The two other main indicators were reduced myocardial T1 relaxation time on cMRI and NT-ProBNP (Hughes et al., 2020). Plasma hs-TnT is cost-effective and widely available method to evaluate the progression of FHCM, and the correlation with the amount of LGE is linear (Seydelmann et al., 2016).

Male patient with new silent ischemic strokes and increase in WMLs did not have cardiovascular risk factors (Saarinen et al., 2015). This is in line with previous finding that in Fabry patients ischemic stroke seemed to be related to WMLs regardless of cerebrovascular risk factors and ERT (Körver et al., 2018). Not even ERT initiation before age 30 has diminished the progression risk of the Fazekas scale and infarctions (Körver et al., 2020).

The decline in eGFR during ERT has been questioned in several studies especially in females (Madsen et al., 2019; Mehta et al., 2009; Nowak et al., 2017; Wanner et al., 2020). It should be emphasized that in those mixed mutation studies comprising mainly missense mutations with significant α-GAL A activity, the disease course in FD can be expected to be more favorable than in our study, in which the single nonsense mutation results in zero residual α-GAL A activity in males (Madsen et al., 2019; Mehta et al., 2009; Nowak et al., 2017; Wanner et al., 2020).

It can be questioned whether annual decrease in eGFR ≥2 ml/min/1.73 m^2 is clinically meaningful and deserves to be counted as an event, even a minor one. However, the annual decline in eGFR in healthy Caucasian population over 40 years of age is about 1 ml/min/1.73 m^2 (Grewal & Blake, 2005; Madsen et al., 2019). In our cohort, concomitant contributing diseases were scarce. None of the patients had diabetes and only one had regular medication for hypertension. Mean eGFR before ERT was normal, 95 ml/min/1.73 m^2, and only one patient had mild albuminuria. Therefore, an eGFR limit of ≥2 ml/min/1.73 m^2 was chosen, which is twice the expected decline depending on aging. In patients below 40 years of age, eGFR is expected to be stable in healthy population. Therefore, a lower eGFR limit ≥1 ml/min/1.73 m^2 was chosen for this age group (Grewal & Blake, 2005; Madsen et al., 2019).

The formation on ADAs with neutralizing property might attenuate the effect of treatment response (Lenders & Brand, 2018; Lenders, Neußer, et al., 2018; Lenders, Schmitz, et al., 2018; van der Veen et al., 2019). Even if the formation of ADAs is more common with agalsidase beta, a fivefold dose of 1 mg/kg eow compared to agalsidase alpha 0.2 mg/kg eow seems to overcome this problem (Arends et al., 2018; Lenders, Neußer, et al., 2018; Lenders, Schmitz, et al., 2018). ADAs might explain the progression of the disease in two out of the four males. However, the youngest male developed antibodies but remained free of events. The fourth male with low ADAs did not develop major or minor events despite his LVH (IVS 16 mm) prior to ERT. Furthermore, his mild albuminuria (KDIGO A1) resolved with the combination of ERT and ARB which has been shown to be effective in Fabry nephropathy (Kantola, 2019; Warnock et al., 2015).

Being an X chromosome-linked disease, FD results in severe disease course in males. Females with two X chromosomes have a more variable disease course, depending, at least in part, on the skewed X chromosome inactivation (XCI) (Echevarria et al., 2016). We did not have the possibility to measure the XCI pattern, which may be a limitation in our study. However, analysis of XCI in leucocytes is not useful for predicting the phenotype in Fabry carriers (Viggiano & Politano, 2021). With a small sample size, caution must be applied, as the findings might be casual in females.

Second limitation of our study is the inability to measure native myocardial T1 or T2 relaxation times in our hospital. Low T1 values reflects accumulation of sphingolipids in myocardium in prehypertrophic state (Camporeale et al., 2019) and T2 mapping has a strong correlation with LVH, LGE and hs-TnT (Seydelmann et al., 2016; Tanislav et al., 2016). These would have been useful tools to monitor disease progression especially in patients with rising hs-TnT levels.

The small sample is the third limitation in our study, even if all Finnish patients with Arg227Ter variant and ERT were included. We analyzed the data in the whole cohort and separately by sex. As the small sample size limited the potential for statistical analysis between sexes, we decided to report results from the whole cohort and patient-by patient manner. The differences in between sexes can be seen in figures and tables, which are presented patient-by-patient manner.

An additional limitation in our study is that polygenic genetic architecture of cardiovascular diseases is not studied. This is particularly relevant in older patients with FD, since most of the late cardiac, cerebrovascular, and renal complications of FD overlap with common complex disorders in the general population. In a recent review (Al Rifai et al., 2022), among patients with absent coronary artery calcium in coronary CT, polygenic risk score for stroke may have a role in predicting future atherosclerotic events in women and non-Whites.

Limiting the study to one homogeneous cohort minimizes confounding genetic factors to modify the effect of the variant in GLA. In future investigations, we recommend conducting a multinational study in people with Arg227Ter in a different genetic background. If our results can be confirmed, it implies that Arg227Ter could be an appropriate variant to test the efficacy of new therapies for FD regardless of sex.

To receive a full picture of progression of FD, early markers of progression should be used in further studies in conjunction with major events in monitoring the disease course. Detecting minor events signifying the progression of the disease should lead to intensify the medical treatment. The prompt ERT initiation together with cardioprotective and renoprotective agents, angiotensin converting enzyme inhibitors or ARBs, is essential in protecting patients of major complications.

5 | CONCLUSIONS

Arg227Ter variant causes severe FD manifestations during ERT in both sexes in Finnish patients without traditional cardiovascular risk factors. If these results can be confirmed in a multinational study, Arg227Ter might be a suitable variant for studies of second-generation ERTs. The inclusion of minor clinical events in addition to the major events should be used in the further studies investigating the efficacy of ERTs.

AUTHOR CONTRIBUTIONS

Päivi Pietilä-Effati was involved in the study design, data collection, data analysis, and manuscript drafting. Jukka T. Saarinen was involved in the study design, data interpretation and drafting and revising the manuscript for intellectual content. Eliisa Löyttyniemi was involved in the statistical analysis and revising the manuscript for intellectual content. Maria Saarenhovi was involved in the analysis and interpretation of the data and revising the manuscript for intellectual content. Reijo Autio was involved in the analysis and interpretation of the data and revising the manuscript for intellectual content. Ilkka Kantola was involved in data analysis and drafting and revising the manuscript. All authors have read, edited, and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Päivi Pietilä-Effati has served on advisory committees for Amicus, Chiesi, Sanofi-Genzyme, and Takeda. She has participated in a clinical study sponsored by Sanofi-Genzyme, has received research support from Sanofi-Genzyme, has received speaker fees from Sanofi-Genzyme and Takeda, and has received travel support from Sanofi-Genzyme and Takeda. Jukka T. Saarinen has received speaker honoraria from Sanofi-Genzyme and Takeda, funding for travel from Sanofi-Genzyme and Takeda, and research support from Sanofi-Genzyme and has participated in the scientific advisory board of Amicus, Chiesi and Sanofi-Genzyme. Eliisa Löyttyniemi, Maria Saarenhovi, and Reijo Autio declares no conflicts of interest. Ilkka Kantola has received speaker honoraria from Amicus, Sanofi-Genzyme and Takeda; funding for travel from Amicus, Sanofi-Genzyme and Takeda; research support from Sanofi-Genzyme and Takeda; and has participated in the scientific advisory board of Amicus, Chiesi and Sanofi-Genzyme.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

PATIENT CONSENT STATEMENT

All patients gave their written informed consent for this 5-year follow-up study.

CLINICAL TRIAL REGISTRATION

The FAST trial is a prospective observational study that does not need to be registered in the clinical trials database.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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