



Effects of agalsidase- β administration on vascular function and blood pressure in familial Anderson–Fabry disease

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Abstract

Fabry is an X-linked disorder of glycosphingolipid metabolism that is caused by variants of the GLA gene that codes for α -galactosidase A, leading to lysosomal accumulation of globotriaosylceramide in many cell types. As a result, affected patients manifest with an increased risk of developing ischemic stroke, peripheral neuropathy, cardiac dysfunction, and chronic kidney disease. The protective effects of enzyme replacement therapy (ERT), the milestone in Fabry disease treatment, against globotriaosylceramide (GL-3) accumulation and Fabry disease progression are well known. However, the mechanism of action of ERT is not well understood. Since GL-3 also accumulates in the vascular endothelium, we investigated the effects of agalsidase- β , a recombinant human α -Gal enzyme approved for the treatment of Fabry disease. In this study, vascular function and blood pressure in four adult siblings affected by Fabry disease were evaluated upon agalsidase- β . In all patients, agalsidase- β infusion improves flow-mediated dilation and augmentation index. These changes occurred after the first infusion and were then maintained for the whole period of observation, i.e., 1 year, with more pronounced additional increments in flow-mediated dilation after the second agalsidase- β infusion. Blood pressure was also maintained at optimal levels in all of the patients for the whole period of observation. Our findings show that agalsidase- β administration can improve vascular function in patients suffering from Fabry disease. Changes in flow-mediated dilation and augmentation index persisted for the whole period of observation (1 year), thus suggesting that early substitutive therapy should be promoted in order to protect the cardiovascular system.

Introduction

Glycosphingolipids are synthesized by the sequential addition of monosaccharides to ceramide [1, 2]. Globotriaosylceramide (GL-3) synthase catalyzes the addition of α -1,4-galactose to lactosylceramide and leads to the production of GL-3. The enzyme α -Galactosidase (α -Gal) A

removes terminal α -galactose residues from glycosphingolipids, including GL-3. Thus, inherited defects of α -Gal lead to the Fabry–Anderson disorder—usually defined as “Fabry disease”—a progressive, multisystemic lysosomal storage disorder, characterized by GL-3 accumulation [3]. Anderson–Fabry (or Anderson–Fabry) is an X-linked disorder caused by mutation of the α -Gal A (α -Gal A) gene (Reference Sequence accession number NG_007119 (NM_000169.3:c.1117G>A), MIM 300644; numbering like [4, 5]). The partial or complete lack of activity of α -Gal A therefore represents the primary cause of the disease, leading to the progressive accumulation of GL-3 in the vascular endothelium and in other cell types [6].

Under the clinical profile, the Fabry disease is characterized by a markedly increased risk of early ischemic disease that is particularly pronounced at the heart and brain levels [3, 7]. However, the disease also manifests during infancy or early adolescence through symptoms that reflect

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the involvement of the peripheral nervous system and kidney function, with the progressive onset of peripheral neuropathy, proteinuria, and overt renal failure [8]. Despite the fact that transmission of the Fabry disease is X-linked, heterozygous females can also manifest with significant morbidity and premature mortality [7].

Ischemia is undoubtedly not the only pathogenetic mechanism but plays a key role in Fabry disease. Alterations in the vasodilative properties of the arterial bed are generally believed to favor the progression of renal favor and precede later thromboembolic complications, although the exact mechanism leading to ischemic tissue damage is not fully understood [9, 10]. Concordant to this, accumulation of GL-3 begins with the fetal age [11, 12] but patients are usually asymptomatic during the first decades of life [13]. Further, early onset of hypertension is commonly observed in patients affected by the Fabry disease, even in the absence of renal impairment [14], while a significant degree of endothelial dysfunction has been described by several studies, again also in patients still free of cardiovascular, cerebral, and/or renal manifestations [15, 16].

Before the introduction of enzyme replacement therapy (ERT), the treatment of Fabry disease consisted mainly of symptomatic treatments and nonspecific corrective measures, such as the use of analgesics, pharmacological prophylaxis for stroke, cardiac surgery, dialysis and renal transplantation. In contrast, the protective effect of ERT, i.e., the milestone in Fabry disease treatment [17, 18], against GL-3 accumulation and Fabry disease progression [19] is well known. However, the mechanism of action of ERT for treating Fabry disease is not well understood.

In particular, although endothelial dysfunction is a significant predictor of mortality in several patient subsets, with or without renal impairment [20–22], the effects of ERT on flow-mediated dilation (FMD), arterial stiffness, and BP levels are substantially unknown. In this context, agalsidase- β is a recombinant form of human α -Gal A approved for long-term ERT in male patients aged ≥ 8 years and in symptomatic women with Fabry disease [23]. Further, frequent ERT (weekly or biweekly) slows the kidney failure in particular in adult subjects with severe forms as reported in A Prospective 10-year Study [24].

Since GL-3 also accumulates in the vascular endothelium, we investigated the effects of agalsidase- β , a recombinant human α -Gal enzyme approved for the treatment of Fabry disease.

Thus, we designed this cross-over, blinded, placebo-controlled study in order to evaluate short- and long-term effects of agalsidase- β treatment on vascular function and office arterial pressure levels in a family of patients affected by Fabry disease.

Methods and subjects

Case report 1

The first proband is a 49-year-old male with BMI 25.7 kg/m² (Table 1). He suffered from end-stage renal disease since he was 28 years of age and underwent successful kidney transplantation in 2014. Starting from the surgical intervention, patient was treated with standard immunosuppressant therapy. The patient also suffered from hypertension, paroxysmal atrial fibrillation, and hypercholesterolemia and was then treated with antihypertensive drugs and statins.

Despite the evident renal disease, the diagnosis of Fabry disease was made after referral to our Department in 2016 through appropriate genetic testing (Table 1), which revealed the variants “NG_007119 (NM_000169.3: c.1117G>A)” in exon 7 of α -Gal gene (GLA) and the following intronic polymorphisms: –12 G>A; c.89-2A>G; IVS6-22C>T (exons are numbered like in ref. [5]). This variant has been reported to result in classical Fabry disease [25].

Patient urinalysis, estimated glomerular filtration rate, and other laboratory findings are reported in Table 1. Of note, cholesterol levels were elevated, despite statin treatment (Table 1). Plasma lyso Gb3 levels at baseline were 46.8 nMol/L (normal ≤ 0.6 nmol/L) [26].

ERT therapy with intravenous agalsidase- β (Fabrazyme[®], Sanofi Genzyme) was then initiated and led to a strong lyso Gb3 decrement to 16.5 nMol/L (Table 2). The decision to start with agalsidase- β was based on its reported ability to protect against the progression of renal disease and the onset of stroke and myocardial infarction [27].

Case report 2

Patient 2 is a 49-year-old male and the non-homozygous twin of the first proband, with BMI 24.2 kg/m² (Table 1). He has a 10-year history of chronic kidney disease with hypertension and proteinuria (478 mg/L). Genetic testing (Table 1) revealed the variant “NG_007119 (NM_000169.3:c.1117G>A).” Plasma lyso Gb3 levels at baseline were 64.71 nMol/L, urine Gb3 excretion was 2.6 mg/mg creatinine (reference range: <0.2). ERT therapy with intravenous agalsidase- β was initiated and led to a significant lyso Gb3 decrement to 18.4 nMol/L (Table 2).

Case report 3

Patient 3 is a 45-year-old woman and the sister of subjects 1 and 2. She underwent two surgical procedures for otosclerosis in 2008 and 2010. She has no risk factors for cardiovascular disease (see Table 1), but her urinalyses

Table 1 Patients' characteristics at the baseline.

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Male	Male	Female	Female
Age (years)	49	49	45	27
BMI (kg/m ²)	25.7	24.2	26.4	21.8
Current smoker	No	Yes	No	Yes
GLA gene mutation	c.1117G>A	c.1117G>A	c.1117G>A	c.1117G>A
Residual enzymatic activity	0	0	4.9	1
GL-3 (nMol/L)	46.8	64.7	5.8	7.7
SBP	118.7 ± 3.8	120.9 ± 7	116.06 ± 5.5	117 ± 3.2
DBP	73.4 ± 5	69.3 ± 5.3	73 ± 6.7	69.4 ± 2.7
Creatinine (mg/dl)	0.9	2.6	0.8	0.6
eGFR (ml/min)	99.9	27.7	100.1	124.9
Total cholesterol (mg/dl)	244	209	168	130
LDL-cholesterol (mg/dl)	156 ± 5.2	134 ± 6.8	94 ± 4.9	78 ± 5.8
Triglycerides (mg/dl)	167	135	147	129
Albuminuria (mg/24 h)	187	478	566	114
Clinical manifestation	AH, FAP, kidney transplantation	AH	Hypoacusis	Hypoacusis
Therapy	β-blockers, statin, immunosuppressants	ACE-inhibitor, statin	None	None

ACE angiotensin converting enzyme, *AH* arterial hypertension, *BMI* body mass index, *DBP* diastolic arterial pressure, *eGFR* estimated glomerular filtration rate, *FAP* paroxysmal atrial fibrillation, *GL-3* globotriaosylceramide, *LDL* low density lipoprotein; *SBP* systolic arterial pressure.

showed overt proteinuria (566 mg/L). Genetic testing revealed the variant “NG_007119 (NM_000169.3: c.1117G>A)” and ERT therapy with intravenous agalsidase-β was initiated and led to a marked lyso Gb3 decrement (from 5.84 to 2.66 nMol/L) (Table 2).

Case report 4

The last patient was the 27-year-old daughter of subject 3 (Table 1). At the age of 25 she started complaining about progressive hearing loss. She has no cardiovascular risk factors (total cholesterol 130 mg/dl; LDL 78 mg/dl; triglycerides 129 mg/dl) and manifests with a normal level of albuminuria. Genetic testing revealed the same variant of the other family components. Due to the presence of marked hearing loss, i.e., a typical manifestation of Fabry disease [28] and positive genetic findings ERT therapy with intravenous agalsidase-β was initiated and led to a marked lyso Gb3 decrement (from 7.7 to 2.76 nMol/L) (Table 2).

All the other living patient siblings were also evaluated but no GLA variants were found.

Study design

After the diagnosis of Fabry disease but before ERT initiation we asked for a short-track approval by the local Ethics Committee (no. 1037/2019).

All subjects had no previous experience of treatment with agalsidase-β and were asked to continue with the habitual diet, lifestyle, and home drug therapy. They were also asked not to consume tea, red wine, chocolate, and/or

dietary supplements during the different study periods, each lasting 6 weeks (42 days). Office BP and FMD were then evaluated on the day before agalsidase-β infusion (V-1;), 15 min after the infusion (V0), and on days 4 (V4) and 8 (V8) after the infusion. Measurements were performed for three consecutive infusions (each dose administered 2 weeks apart), in the first, the sixth, and the twelfth month of treatment. The investigators blinding performed these analyses.

The same evaluations were performed in all patients before starting the therapy with agalsidase-β by using placebo (50-ml saline, intravenously infused) (Fig. 1).

Measurements

All subjects referred to our Outpatient Unit in a fasted state (from 10.00 p.m. the day before the study) on the visit days. Measurements were performed with participants supine in a quiet, temperature-controlled (22–24 °C) environment and after at least 15 min of rest. Office BP was assessed in triplicate with an oscillometer device (Omron 705 CP, Omron). FMD was measured at the brachial artery level by using the FMD Studio software (QUIPU srl, Pisa, Italia). The arterial diameter was measured by ultrasonography at ~5–10 cm above the elbow. After 1-min baseline measurement, a cuff placed at the forearm below the elbow was inflated at 220 mmHg for 5 min, then deflated, and the maximal dilation of the brachial artery was detected by the software. The SphygmoCor XCEL System (SphygmoCor; AtCorMedical Inc, USA) was used for the clinical assessment of central blood pressure and PWA. The SphygmoCor

Table 2 Lyso Gb3 levels and residual enzymatic activity after 1 year of ERT.

	Patient 1		Patient 2		Patient 3		Patient 4	
	Before ERT	After 1 year of ERT	Before ERT	After 1 year of ERT	Before ERT	After 1 year of ERT	Before ERT	After 1 year of ERT
Residual enzymatic activity	0	0.5	0	0.4	4.9	2.7	1	1.5
GL-3 (mMol/L)	46.8	16.5	64.7	18.4	5.8	2.6	7.7	2.7

ERT enzyme replacement therapy, GL-3 globotriaosylceramide.

XCEL System derived the central aortic pressure waveform from cuff pulsations recorded at the brachial artery; analysis of the waveform provided key parameters including central aortic systolic pressure and indices of arterial stiffness and wave reflection such as augmentation index (Aix). The investigators blinding performed these analyses.

Statistical analysis

The relationship between FMD or Aix and ERT treatment was evaluated with linear regression, analyzed by Prism 8.0 software. BP data are expressed as means \pm SDs. Database repository is publicly available in Figshare, Dataset. <https://doi.org/10.6084/m9.figshare.12753470.v1>.

Results

ERT is known to change the natural history of Fabry disease by slowing down the progression of renal disease and reducing the incidence of its cardiac and neurologic sequelae [27, 29]. A multicenter, randomized, controlled, double-blind study showed that agalsidase- β treatment reduces GL-3 storage in the endothelial cells of patients affected by Fabry disease [30]. In agreement with these findings, all of the four patients enrolled in this study showed a marked ERT-related reduction in GL-3 values (Table 2) and a consequent improvement in the endothelial function after ERT with agalsidase- β . Similarly, constant and lasting increments in FMD and reductions in Aix were observed (Fig. 1). In addition, it is possible to appreciate in the graphs (Fig. 1) almost a sinusoidal periodicity, in particular in those related to male patients, in which ERT response is more evident sooner after ERT infusion than 2 weeks just before the next infusion.

Upon agalsidase- β both systolic and diastolic BP were maintained at optimal levels (Table 1) [31, 32]. Of note, FMD changes were more evident in women than in men, probably due to the more modest Fabry disease progression that was present at baseline. Indeed, our female patients manifested with relatively modest organ damage and no cardiovascular risk factors and both were still in the fertile age before ERT therapy. In contrast, the two men had a long history of undiagnosed disease with advanced chronic kidney disease, hypertension, and/or arrhythmias. At the beginning of the study, patient 1 also had increased LDL-cholesterol levels, undertreated with moderate-intensity statin and with persistent dyslipidemia. Thus, the increased efficacy of ERT observed in our female patients is very likely to reflect the close to normal clinical conditions manifested before ERT initiation. More than these divergent responses to ERT, it is worth to note that decrements in plasma GL-3 levels were accompanied by significant changes FMD levels with modulation of Aix, able

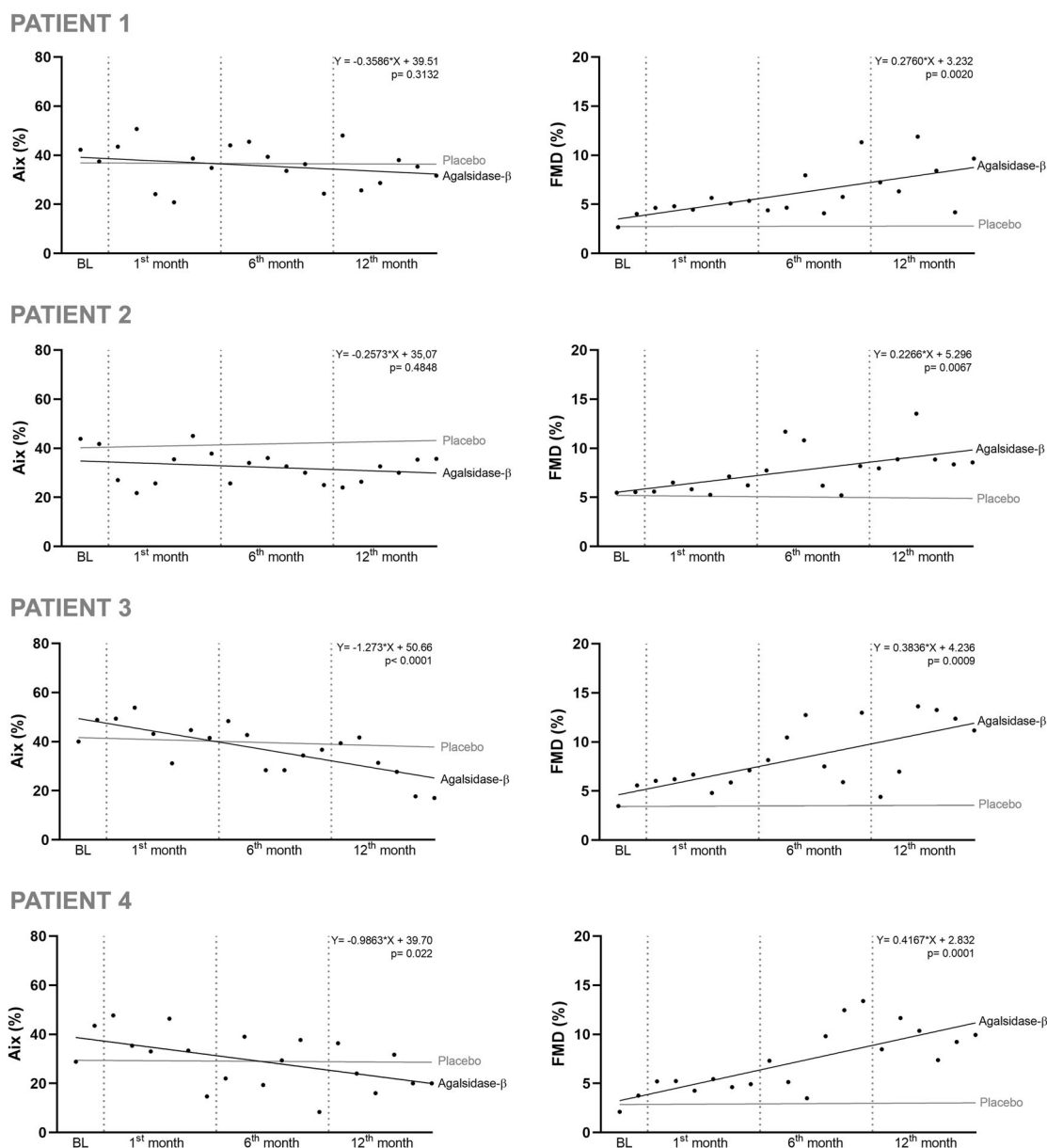


Fig. 1 Aix and FMD data for all the four Fabry patients. It is possible to observe an amelioration of the vascular function upon agalsidase- β administration compared to placebo, persisting for the whole period of observation (1 year).

to further protect against cardiovascular and cerebrovascular events [19, 33] as well as the onset or progression of renal failure [34].

Discussion

Since GL-3 also accumulates in the vascular endothelium, we investigated in a family group the effects of agalsidase- β , a recombinant human α -Gal enzyme approved for the treatment of Fabry disease.

Thus, we designed a cross-over, blinded, placebo-controlled study in order to evaluate short- and long-term

effects of agalsidase- β treatment on vascular function and office arterial pressure levels in this family. Our study confirms that ERT with agalsidase- β reduces significantly circulating GL-3 levels and improves endothelial function. The effects of ERT on FMD, arterial stiffness, and BP levels are substantially unknown. Agalsidase- β treatment showed positive effects on vascular function, and these protective changes were still observable after 1 year of ERT, suggesting that the treatment is able to reduce the global cardiovascular risk in Fabry disease patients with.

Notably, we noticed that male patients showed a conspicuous reduction in lyso Gb3, while in females is less marked.

Gb3 inclusion differences may depend on genotype and inactivation of the Barr body, an X chromosome in female somatic cell. Further, the male patients present inclusions in most of the cells, while female patients have a mosaic pattern, thus only half of the cells are involved.

Although no randomized trials on cardiovascular prevention have never been conducted in patients with Fabry disease, the amelioration in vascular function must be considered as further indications to the earliest initiation of ERT therapy.

In this context, it is relevant to note that—particularly in the two male brethren—clinical manifestations of Fabry disease were accompanied by a marked delay in diagnosis and then ERT initiation. Delayed diagnoses have been often reported in Fabry disease [35] and the study of this affected family represents a further stimulus in seeking rare disorders when not otherwise explainable renal and/or neurological and/or cardiac disorders occur in patients during the first decades of life.

Conclusions

Overall, our study confirms that ERT with agalsidase- β reduces significantly circulating GL-3 levels and showed positive effects on vascular function in patients suffering from Fabry disease. The effects of ERT on these parameters are substantially unknown. In particular, we observed changes in FMD and Aix persisted for the whole period of observation (1 year), thus suggesting that early substitutive therapy should be promoted in order to protect the cardiovascular system. This conclusion may be consistent with the improved clinical observations.

This study was limited because of the small number of patients examined and because it was not designed to evaluate the impact of concomitant therapies. Moreover, future directions will be devoted to check the parameters analyzed in this study in the same patients, indeed, a longer-term follow-up is necessary to show the real benefit of agalsidase- β administration in preventing cardiovascular events. Continued observation will allow further delineation of the long-term perspective of these patients.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent to participate All authors consent to the publication of the manuscript.

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