Enzyme replacement therapy in Fabry disease, towards individualized treatment

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Discontinuation of enzyme replacement therapy in Fabry disease in the Dutch cohort

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Abstract

Fabry disease (FD) is a progressive, multi-organ, lysosomal storage disease. Enzyme replacement therapy (ERT) is available for the treatment of the disease. While the reasons to initiate ERT have been frequently discussed, discontinuation of ERT is rarely reported. In this paper we describe our experiences with stopping ERT in FD. From 1999 through 2015, twenty-one patients discontinued ERT. These patients were generally older and more severely affected in comparison those who continued ERT. The reason to discontinue ERT switched from death or terminal illness in the first years towards treatment failure in more recent years. Three cases are described in more detail. We conclude that discontinuation of ERT should or may be considered in subgroups of FD patients although further studies on the effectiveness of ERT in subgroups of patients and the course of the disease after discontinuation of ERT are needed.

Introduction

Fabry disease (FD) (OMIM 301500) is a rare inherited lysosomal storage disorder caused by a deficiency of α-galactosidase A (enzyme commission number: 3.2.1.22), leading to accumulation of globotriaosylceramide (Gb3) in the lysosomes of various cell types, in particular endothelial and vascular smooth muscle cells.[1,2] Depending on the residual enzyme activity and several other, partly unknown factors, affected individuals may have a clinical course that range from 'classical' disease characterized by early renal failure, premature strokes and severe cardiomyopathy, to mild 'non-classical' disease with less progressive and more limited disease manifestations.[3]

In the EU, two enzyme preparations (enzyme replacement therapy, ERT) are available for the treatment of FD: agalsidase alfa (Replagal, Shire HGT) and agalsidase beta (Fabrazyme, Genzyme, a Sanofi company). Long term effectiveness studies have shown that ERT can postpone some clinical complications of the disease, but cannot prevent these.[4,5] One of the major factors responsible for the absence of a treatment response in a subset of patients is the presence of irreversible organ damage such as glomerular sclerosis, cardiac fibrosis and extensive white matter lesions in the brain or multiple strokes. It is known that the effectiveness of ERT is limited in patients with proteinuria exceeding 1 gr/day, a high number of sclerotic glomeruli on renal biopsy or a low GFR at treatment start.[6-8] Secondly, it has been shown that the presence of cardiac fibrosis has a negative effect on the effectiveness of ERT.[5,9]

As a result of this lack of effectiveness in irreversible disease stages it is expected that discontinuation of ERT will be considered more frequently. However, while the reasons to initiate ERT are subject of continuing debate,[5,10-12] discontinuation of ERT has been given little attention so far. A first step was recently made by the European Fabry Working Group (EFWG) who published consensus based recommendations regarding initiation and cessation of ERT.[12] A major limitation of this consensus procedure is the lack of published reports on the reasons to stop treatment. Hence we describe the characteristics of the Dutch patients who discontinued ERT, including a detailed description of three illustrative cases.

Methods

This is a retrospective study of all patients who are, or have been evaluated at the Academic Medical Center, Amsterdam, The Netherlands, the national referral centre for this disorder. All data of ERT treated patients are prospectively recorded in a designated database. A definite diagnosis of Fabry disease was made according to the criteria published by Smid et al.[13] The α-galactosidase A activity was measured in leucocytes and expressed as percentage of the mean of the reference values. Plasma lysoGb3 was assessed by tandem mass spec-

trometry,[14] with an upper reference limit of 0.5 nmol/l. A value of >45 nmol/l in male patients predicts a classical FD phenotype.[15] The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula.[16] End stage renal disease (ESRD) was defined as renal transplantation, dialysis or an eGFR <15 ml/min/1.73m^2. Left ventricular mass was calculated using the Devereux formula and indexed for height. The upper reference values of the left ventricular mass index (LVMI) in male and female patients were set at 51 and 48 gram/m$^{2.7}$, respectively.[17].

Cardiac complications were defined as: atrial fibrillation, implantation of cardiac defibrillator or pacemaker, coronary bypass graft surgery or percutaneous transluminal coronary angioplasty, rhythm disturbances necessitating hospitalisation or heart failure necessitating hospitalisation. Stroke was considered a clinical event when diagnosed by a neurologist.

All patients who discontinued ERT were reviewed. The reasons of discontinuation were categorized as follows: 1) patients who stopped ERT at their own request 2) patients who died while receiving ERT or stopped ERT because of terminal illness (*i.e.* a life expectancy of less than 3 months) 3) patients who stopped ERT because of treatment failure (defined as deterioration of disease manifestations despite ERT treatment to such an extent that no additional benefit is to be expected on any organ system) and 4) patients who stopped for other reasons. In addition, three illustrative cases representing the treatment failure category (patients 1 and 2) and discontinuation at own request category (patient 3) were selected for a more detailed description.

Statistical analysis were performed using SPSS version 22 (IBM, Chicago). Continuous data are expressed as median and interquartile range. Non-parametric tests were used for between group testing: the Mann Whitney U test for continuous variables and the Fisher's exact test for categorical (binary) variables. Two tailed p-values <0.05 were considered statistically significant.

Results

Discontinuation of ERT

In the period from 1999 until November 2015, 75 patients started ERT (initial treatment modality was agalsidase alfa in 41 and agalsidase beta in 56 patients) of whom 21 discontinued ERT. Compared to the patients who continued ERT, the patients who discontinued ERT were significantly older at treatment initiation, more likely to have suffered cardiac complications or a stroke before start of ERT, and more likely to have an eGFR <60 ml/min/1.73m^2. This is especially true for the patients who stopped treatment because they died, were terminally ill or showed treatment failure. In contrast, patients who discontinued ERT at own request were more often young women who had not suffered clinical complications before start of

ERT. Six out of twelve (50%) patients with non-classical FD and 15 out of 70 (18%) patients with classical FD discontinued ERT.

Phenotype was not related to the reason to stop treatment. Details are depicted in table 1 (see supplemental table A for individual patient data).

Eight patients (38%, 6 with a classical phenotype) discontinued ERT at their own request. Reasons for discontinuation were: no (experienced) benefit of ERT (*n=5*), side effects such as flushing, shaking chills, throat tightness (*n=1*) and loss of taste sensation (*n=1*), and perceived misbalance between the burden of the treatment and its benefits (*n=1*) even though most patients generally receive their treatment at home [18]. Another 7 patients (33%, 5 with a classical phenotype) died while receiving treatment (*n*=5) or stopped ERT because of terminal illness (*n=2*). Treatment failure was the main reason for discontinuation of ERT in the remaining 5 patients (24%, 4 with a classical phenotype). These 5 patients were not terminally ill, but all had combined severe renal impairment, cardiac hypertrophy and cerebrovascular disease, and, consequently, no beneficial effect of ERT was to be expected. Finally, one patient stopped ERT because new evidence demonstrated the P60L *GLA* mutation to be non-pathogenic, and, as a result, our team decided to discontinue ERT.

Of interest, the majority of patients (12/21) discontinued ERT in the last 5 years. Moreover, reasons to discontinue ERT shifted from death/terminal illness towards treatment failure (Figure 1). Twelve of the 21 patients who stopped ERT have died. Causes of death were: cardiac disease (n=6), cerebrovascular disease (n=2), ESRD (n=1), other (n=3, meningitis, sepsis, multi-organ failure). Some patients (especially female and non-classical patients who discontinued ERT at their own request) remained stable after cessation of therapy.

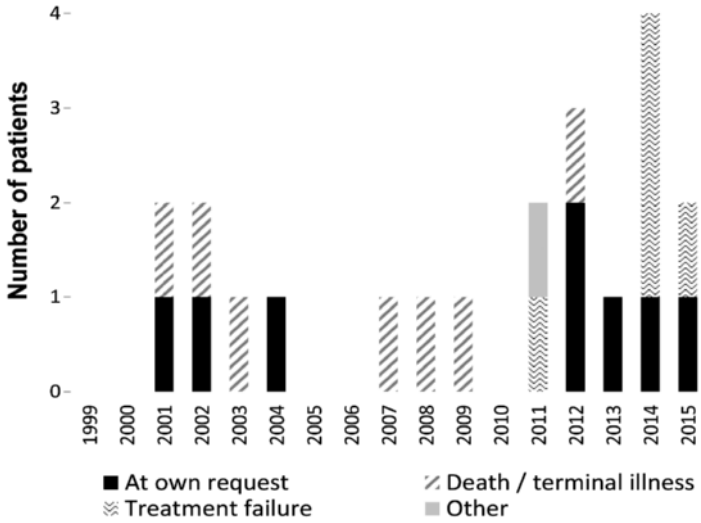

Figure 1 Discontinuation of enzyme replacement per year.

Table 1a Patient characteristics at initiation of ERT

	Patients who continued ERT	Patients who discontinued ERT
Number of patients	76	21
Male	39 (51%)	14 (67%)
Age (years) at start of ERT	41 (21-49)	50 (31-61)†
Classical FD	70 (92%)	15 (71%)†
eGFR <60 ml/min/1.73m²	10 (13%)	8 (38%)†
ESRD	1 (1%)	1 (5%)
Increased LVMI	27 (36%)	11 (52%)
Cardiac complications	6 (8%)	7 (33%)†
Stroke	3 (4%)	4 (19%)†
Duration of ERT	7.5 (5.0-11.3)	2.3 (1.5-10.1)

Continuous variables are presented as median and interquartile range, categorical variables are presented as number of patients and percentage.

† *indicates a statistically significant difference (p < .05).*

Table 1b Patient characteristics at initiation of ERT

	Patients who discontinued ERT			
	At own request	Death / terminal illness	Treatment failure	Other
Number of patients	8/21	7/21	5/21	1/21
Male	3 (38%)	7 (100%)	4 (80%)	0 (0%)
Age (years) at start of ERT	39 (22-63)	53 (47-62)	52 (38-62)	65
Classical FD	6 (75%)	5 (71%)	4 (80%)	0 (0%)
eGFR <60 ml/min/1.73m2	0 (0%)	5 (71%)	2 (40%)	1(100%)
ESRD	0 (0%)	1 (14%)	0 (0%)	0 (0%)
Increased LVMI	2 (25%)	4 (57%)	4 (80%)	1 (100%)
Cardiac complications	2 (25%)	4 (57%)	1 (20%)	0 (0%)
Stroke	1 (13%)	2 (29%)	1 (20%)	0 (0%)
Duration of ERT	2.1 (1.6-8.5)	2.1 (0.5-7.3)	9.7 (6.6-13.8)	6.5

Continuous variables are presented as median and interquartile range, categorical variables are presented as number of patients and percentage.

Case series

Patient 1

This male patient (genotype R227Q, enzyme activity: 0,2%, lysoGb3: 96.2 nmol/l) was diagnosed with FD at the age of 11 during an episode of fever with painful acroparesthesia. At age 46, ERT was started (agalsidase alfa, 0.2 mg per kilogram every other week). At that time he had renal failure (chronic kidney disease (CKD) stage: G4A3, measured glomerular filtration rate: 22 ml/min/1.73m^2), left ventricular hypertrophy (LVH) (LVMI: 67.7 gram/m$^{2.7}$) and multiple white matter lesions (WMLs) and lacunar infarctions on brain magnetic resonance imaging (MRI). Neuropsychological evaluation showed a decreased performance capacity, delayed information processing and emotional instability. In addition to ERT, adjunctive treatment with ACE-i/ARB, anti-platelet drug, statins and anti-hypertensive medication was provided in agreement with local guidelines. After one year, ERT was switched to agalsidase beta 1.0 mg per kilogram every other week because of progressive disease despite treatment. Four years later he reached end stage renal disease and subsequently started with dialysis, followed by a renal transplant one year later. In 2010, he switched to agalsidase alfa again, because of a shortage of agalsidase beta.

At age 57, 11 years after start of ERT, he was admitted to hospital because of an infection of his artificial knee replacement, implanted three years earlier because of arthrosis. This admission was complicated by a psychosis. He recovered but the subsequent annual evaluation showed neurological deterioration: the number of lacunar infarctions had increased and the WMLs had become confluent. Both he and his family noticed cognitive decline, including behavioural changes and memory deficits. During ERT, the LVH was stable as assessed by ultrasound, but cardiac MRI showed fibrosis of 57% of the basal posterolateral wall. Interpretation of the time of onset of cardiac fibrosis was difficult since no pre-treat-

ment cardiac MRI was available. Our team concluded that there was disease progression and no further beneficial effect of ERT was expected on heart and brain. In addition, ERT was not considered to be beneficial to the kidneys either, as he had received a renal transplant 5 years before. In close consultation with the patient and his family the decision was made to stop ERT. Three months later the patient died from a medial cerebral artery stroke.

Patient 2

This 46-year-old male patient (genotype R342Q, enzyme activity: 2%, lysoGb3: 124.3 nmol/l) with classical FD participated in the pivotal agalsidase beta trial at age 30.[19] Ten years later he temporarily received a lower dose due to the shortage of agalsidase beta. At start of therapy, he had severe neuropathic pain in hands and feet, albuminuria and mildly reduced renal function (eGFR: 74 ml/min/1.73m^2, CKD stage: G2A2), borderline LVH (LVMI: 45.4 gram/m$^{2.7}$), and multiple lacunar infarctions on brain MRI. ERT had a positive effect on the neuropathic pain. In addition to ERT, adjunctive treatment in the form of ACE-i/ARB, anti-platelet drug and anti-hypertensive medication was provided in agreement with local guidelines. However, in the next 16 years he gradually demonstrated disease progression. The eGFR dropped to 35 ml/min/1.73m^2 with proteinuria of > 1 gram a day (CKD stage: G3bA3). The left ventricular mass remained stable but diffuse fibrosis and a left bundle branch block had developed. In particular, his neurological condition and cognitive capacities severely deteriorated. Repeated brain MRIs showed an increasing number of solitary and confluent WMLs as well as (lacunar) infarctions. In addition, he suffered a stroke with permanent paresis at age 43 (13 years after initiation of ERT). Two years later, neuropsychological evaluation showed delayed information processing as well as severe memory impairment. At that moment he was no longer capable of independent living and a guardianship was established. Because of the extensive disease manifestations, and the expectation that ERT would have no beneficial effects, the medical team and the patient decided to cease ERT almost 16 years after the initiation of treatment. One year later his clinical condition is unchanged.

Patient 3

This 62-year-old female patient (genotype: heterozygous T134*, enzyme activity: 45%, lysoGb3: 12.6 nmol/l) with classical FD discontinued ERT at own request after 12 years of treatment. At baseline some small WMLs and LVH (LVMI: 61.7 gram/m$^{2.7}$) were present. She suffered from treatment resistant symptomatic ventricular extrasystoles with brief ventricular tachycardias. In addition to ERT (agalsidase beta, 1.0 mg per kilogram every other week), adjunctive treatment in the form of ACE-i/ARB, anti-platelet drug and anti-hypertensive medication was provided in agreement with local guidelines. After 3 years of ERT she developed paroxysmal atrial fibrillation necessitating the implantation of a pacemaker. In the next couple of years, her exercise tolerance deteriorated, possibly due to progressive diastolic dysfunction. Renal function remained stable with a GFR of 70 ml/min/1.73m^2 and mild albuminuria (CKD stage: G2A1/2). No new WMLs developed. Since our team concluded that her most burdensome symptoms (*i.e.* angina pectoris, exercise intolerance and oedema) were

not likely to improve upon ERT, she decided to stop therapy after 12 years of treatment. Since it was deemed unlikely that her renal function would decline to such an extent that she would need dialysis or a renal transplant during life, we agreed to discontinue ERT. One year after discontinuation the patient has recurrent episodes of rhythm disturbances. A cardiac catheterization did not reveal significant stenosis and her renal function is unchanged.

Discussion

With the current study we show that the number of patients who discontinue ERT has increased in the Netherlands, especially in the last 5 years. The reasons for stopping ERT changed from terminal illness or death in the first years to disease progression with irreversible organ damage in more recent years.

Despite high expectations and the first positive results from the pivotal studies on the effect of ERT in FD,[19,20] subsequent studies have shown that ERT may not benefit all FD patients, in particular not those with severe disease demonstrated by irreversible organ involvement such as severe proteinuria, a high number of sclerotic glomeruli, severely decreased GFR or cardiac fibrosis.[5-9] Studies demonstrating limited effectiveness of ERT in patients with irreversible organ damage resulted in the EU consensus recommendation that in case of end stage renal disease (without an option for renal transplant) in combination with advanced heart failure cessation of ERT may be considered.[12] Notably, the effect of ERT on the progression rate of WMLs or the risk of TIAs or strokes is not well established,[4,11,21,22] while cerebral disease manifestations play an important role in the final phase of FD; 2 patients from our cohort died from stroke and several other patients had severe cognitive decline. Heart failure or myocardial infarction was the cause of death in 6 out of the 12 patients who died. Only 1 patient died from end stage renal disease, while end stage renal disease was one of the most important causes of death among untreated patients from a historical cohort.[23] With ERT, optimal adjunctive treatment and improved dialysis and renal transplant options, the final disease phase of FD which was first mainly characterised by renal failure seems now to be dominated by cardiac and cerebral disease manifestations.[24]

During the last 5 years, one or two patients per year discontinued ERT at their own request. Most often the advantages did not outweigh the disadvantages, being the lack of benefit, side effects or the burden of 2-weekly infusions. In these cases, a thorough discussion with the patient should take place to ensure that an informed decision is made, even though it might be hard for patients and physicians to estimate the risk of developing complications when stopping ERT. With the limited effectiveness of ERT and the less progressive disease course in female patients and patients with the non-classical phenotype we expect that more patients will choose to discontinue ERT in the coming years. To be able to inform the patients as well as possible, additional studies on the effectiveness of ERT in these sub-

groups of patients are needed as well as studies on the course of disease after cessation of ERT. Our results indicate that some patients remain stable after discontinuation of ERT, but there is hardly any literature on this topic, neither in Fabry disease, nor in other lysosomal storage diseases where ERT is employed.[25-30]

In conclusion, our study reveals that some patients show disease progression or die while receiving ERT, especially those patients who had already suffered clinical complications before start of treatment. Based on our experiences as well as literature, we argue that those patients who have progressed to a disease stage with combined end stage renal disease and heart failure despite ERT, should discontinue ERT. Stopping ERT may be considered in female and non-classical patients if there is a perceived misbalance between the advantages and disadvantages. Although our experiences show that some of these patients remain stable after discontinuation of ERT, additional data are needed to make recommendations. We emphasize that decisions to stop ERT should always be made on an individual basis, taking into account the patient's disease severity and preferences.

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Supplemental table A

Supplemental table A Patients who discontinued enzyme replacement therapy

	Phenotype	Gender	Age at start of ERT (years)	eGFR <60	ESRD	Increased LV mass	Cardiac complication	Stroke	Duration of ERT (years)	Reason of discontinuation	Follow up after discontinuation (years)	Course of disease after discontinuation of ERT
1	Classical	M	17						2.1	At own request	13.5	Limited progression, developed ankle oedema and mild albuminuria
2	Classical	F	50			+			12.0	At own request	1.1	Progression, suffered from a minor (haemorrhagic) stroke and later she developed atrial fibrillation
3	Classical	M	47						0.7	At own request	0.7	Died within 1 year after discontinuation of ERT from a myocardial infarction
4	Non classical	F	30						2.2	At own request	2.2	Stable
5	Non classical	M	68				+	+	2.1	At own request	2.2	Stable
6	Classical	F	71			+	+		10.6	At own request	0.3	Stable (stopped <1y ago)
7	Classical	F	20						2.3	At own request	2.6	Stable
8	Classical	F	33						1.5	At own request	10.7	Limited progression, developed mild albuminuria
9	Classical	M	25						1.2	Death	n/a	Cause of death: probably meningitis
10	Non classical	M	64	+		+	+		0.4	Death	n/a	Cause of death: heart failure
11	Classical	M	54	+		+		+	1.7	Death	n/a	Cause of death: severe disease progression with renal, cardiac and cerebral disease complications.
12	Classical	M	48	+			+		0.1	Death	n/a	Died after a systemic infection following urethral catheterization Cause of death: myocardial infarction

Supplemental table A Patients who discontinued enzyme replacement therapy (Continued)

	Phenotype	Gender	Age at start of ERT (years)	eGFR <60	ESRD	Increased LV mass	Cardiac complication	Stroke	Duration of ERT (years)	Reason of discontinuation	Follow up after discontinuation (years)	Course of disease after discontinuation of ERT
13	Classical	M	47	+					10.7	Death	n/a	Cause of death: sepsis after coronary artery bypass graft
14	Classical	M	58			+	+		7.3	Terminal illness	0.1	Died from heart failure within 1 month after discontinuation of ERT
15	Uncertain	M	62	+	+	+	+	+	1.6	Terminal illness	0.2	Died from end stage renal disease within 2 months after discontinuation of ERT
16	Classical	F	60			+			9.2	Treatment failure	0.9	Stable; ERT was discontinued after a stroke with paresis, delirium and speech difficulties, which all improved over the next two years
17	Classical	M	45	+		+			12.2	Treatment failure	0.5	Progression of disease, died from stroke within 6 months after discontinuation of ERT
18	Classical	M	52			+		+	9.7	Treatment failure	0.7	Progression of disease, developed a stroke and cardiac asthma. Died 9 months after discontinuation of ERT
19	Non classical	M	63	+		+	+		4.0	Treatment failure	0.3	Progression of disease, died within 3 months after discontinuation of ERT from end stage renal disease/ heart failure
20	Classical	M	30						15.4	Treatment failure	0.9	Stable (stopped <1y ago)
21	No FD	F	59	+		+			6.5	Other	n/a	P60L GLA mutation considered to be non-pathogenic