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Early start of enzyme replacement therapy in pediatric male patients with classical Fabry disease is associated with attenuated disease progression

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ABSTRACT

Background: Enzyme replacement therapy (ERT) slows disease progression of Fabry disease (FD), especially when initiated before the onset of irreversible organ damage. However, with the clinically asymptomatic progression of renal, cardiac and cerebral disease manifestations spanning decades, optimal timing of ERT initiation remains unclear.

Methods: In this cross-sectional retrospective study, seven male FD patients with a classical disease phenotype (cFD) who started treatment with agalsidase-beta in childhood were evaluated after 10 years of treatment (median age at evaluation 24 years, range 14–26). Cardiac imaging (echocardiography and MRI), electrophysiological and biochemical data of these patients were compared to those of untreated male cFD patients ($n = 23$, median age 22 years, range 13–27).

Results: Albuminuria was less common and less severe in treated patients (albumin to creatinine ratio, ACR 0–8.8 mg/mmol, median 0.4) compared to untreated patients (ACR 0–248 mg/mmol, median 3.7, $p = 0.02$). The treated group had a lower left ventricular mass, measured using echocardiography (median 80 g/m^2 versus 94 g/m^2, p = 0.02) and MRI (median 53 g/m^2 versus 68 g/m^2, p = 0.02). Myocardial fibrosis was absent in all included patients. eGFR was normal in all treated patients whereas 7/23 (30%) of untreated patients had abnormal eGFR. Cerebral manifestations did not differ.

Conclusions: Start of treatment with ERT before age 16, in male cFD patients is associated with reduced occurrence of renal and cardiac manifestations of FD, as assessed by intermediate endpoints. Confirmation that this approach delays or even prevents renal failure and cardiac events requires another decade of follow-up.

1. Introduction

Fabry disease (FD, OMIM 301500) is a rare hereditary lysosomal storage disease (LSD) caused by a mutation in the X chromosome-located *GLA* gene, leading to a deficiency of the enzyme alpha-galactosidase A (αGAL A, EC 3.2.1.22). The accumulation of its substrate, globotriaosylceramide (Gb3), and its deacylated form, globotriaosylsphingosine (lysoGb3), is associated with progressive damage to small nerve fibers, vascular endothelium, renal and cardiac cells [1]. Male FD patients with the classical disease phenotype (cFD), in whom there is absent or very little residual αGAL A activity, are the most severely affected [2]. These patients predominantly present with neuropathic pain in hands and feet in childhood. In this phase of the disease there is increasing tissue accumulation of Gb3, but clinical renal, cardiac and cerebral complications do not yet occur [3,4]. During adolescence and early adulthood, cardiac left ventricular (LV) mass gradually increases and many male cFD patients develop albuminuria [5,6]. Later on, ECG changes become apparent and cerebral white

Abbreviations: ADA, Anti-drug antibodies; αGAL A, Alfa-galactosidase A (enzyme); ERT, Enzyme replacement therapy; FD, Fabry disease; GB3, globotriaosylceramide; GLA, Alfa-galactosidase A (gene); iADA, Inhibiting anti-drug antibodies; LysoGb3, Globotriaosylsphingosine; r- αGAL A, Recombinant Alfa-galactosidase A (enzyme).

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matter lesions (WML) appear on MRI, this is followed by the development of myocardial- and glomerular sclerosis, during the 3rd and 4th decade of life, leading to cardiac complications and renal failure [7]. Ultimately the cardiac, renal and cerebrovascular complications cause severe morbidity and premature death, in the vast majority of patients before the age of 60 [5]. Almost two decades ago, two recombinant preparations of αGAL A became available for treatment of FD. Agalsidase-alfa (Replagal, Shire/Takeda) registered at a dose of 0.2 mg/kg/every other week (eow) and agalsidase-beta (Fabrazyme, Sanofi-Genzyme) registered at a dose of 1 mg/kg/eow. In the pivotal trials that led to the registration of agalsidase-alfa and -beta it was shown that enzyme-replacement therapy (ERT) resulted in a clear biochemical response with reduction of Gb3 in plasma and urine [8–10]. ERT was shown to clear storage material from endothelial cells and several renal cell types including vascular, interstitial and mesangial cells [11,12]. Podocyte clearance was also observed in several patients, especially in patients treated with agalsidase-beta that started treatment at a young age [13] and in patients that were treated for a longer period of time [14]. In a subset of patients, treatment with ERT resulted in a stabilization of renal function, a reduction of cardiac mass [15] and a delay of clinical events [16], but response to treatment was highly variable and in most patients the disease progressed despite treatment [15]. Especially in patients with declined renal function, proteinuria and/or myocardial fibrosis at the time of treatment initiation, disease markedly progressed despite treatment with ERT [15,17]. Patients that started treatment relatively early in their disease course, that is to say with an estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73 m2 and no significant myocardial fibrosis at the time of treatment initiation, tended to have more favorable outcomes [18–24]. This led to the international clinical consensus [5,25,26] that in male patients with the classical disease phenotype, treatment with ERT should be started early, even before clear clinical disease manifestations in kidney or heart are present. To date, a more precise advice regarding optimal age of treatment initiation in this patient group is not possible, as there are no trials comparing effects of starting treatment in early childhood versus adolescence/young adulthood. Some studies suggested a beneficial effect of starting ERT in childhood, since a more pronounced substrate reduction in podocytes was observed in FD patients that started ERT in early childhood [23]. However, ERT is costly and the biweekly infusions may pose a significant treatment burden, especially for young children. In addition, male cFD patients are at risk to develop infusion related reactions such as hyperthermia, cold chills, skin rashes, dyspnea or in the worst case scenario anaphylactic shock, requiring treatment with immunosuppressive drugs to tolerate the infusions [8,27,28]. Therefore, clinical evidence to guide timing of ERT initiation is clearly needed. In 2019 the results of the FIELD study, evaluating the effect of childhood initiation of low dose ERT (5 years of treatment) were published. The FIELD study showed treatment resulted in reductions in plasma and urine Gb3 levels and a mixed response on histopathological endpoints (e.g. reduction in intracellular Gb3 depositions in most, but not all patients). The downside of this study was that it lacked an untreated control group [12], hampering a solid conclusion on treatment effect. The patients that were originally treated in this study at our centers have now been treated for a decade (continuation after study ended). They form a unique cohort of FD patients that started treatment in childhood and in the current study we compared clinical, imaging, biochemical and electrophysiological parameters of these patients after 10 years of treatment with ERT to a group of untreated Fabry patients with the same phenotype (classical) and of comparable age.

2. Methods

2.1. Patients

All included patients were male and classified as having the classical Fabry disease phenotype based on the residual enzymatic activity (leucocyte α-Gal A activity ≤5% of the median of the reference range) and the presence of one or more characteristic symptoms of FD (Fabry specific neuropathic pain, angiokeratoma, and/or cornea verticillata) [2,29].

2.1.1. Treated group

This group consists of male cFD patients who participated in the FIELD study [12]. The FIELD study was a randomized controlled trial assessing the effect of different dosing regimens of agalsidase-beta in pediatric FD patients. There was no untreated group in the original study. All patients were treated with a lower then registered dose, only the interval differed. One group was treated with 0.5 mg/kg biweekly (3 patients in our study) the other with 1.0 mg/kg once a month (4 patients in our study), no differences in outcome were found between these 2 groups). The study ran from September 2008 to June 2015 (NCT00701415) [12]. All patients that were enrolled in the FIELD study at the Amsterdam University Medical Centers (UMC) Amsterdam, the Netherlands ($n = 5$) and Haukeland University Hospital (UH), Bergen, Norway ($n = 2$) were included in the current analysis. All patients continued treatment on study dose directly after the study ended and had been treated for approximately 10 years at time of assessment. 6/7 patients switched to full dose (1 mg/kg biweekly) after a median treatment duration of 9 years (range 8.3–10).

2.1.2. Untreated group

We conducted a search in the clinical database at the Amsterdam UMC for patients with the same sex and phenotype as the treated patients (male FD patients with the classical disease phenotype), of whom treatment naive data were available between the age of 12 and 27 (±2 years of the age range in the treated group). Twenty-three patients fitted these criteria. If data of more than one time point was available for an individual patient ($n = 3$), the time point was chosen to best match the median age at evaluation of the treated patients. In three untreated patients, reduced renal function or severe proteinuria was present at the time of referral to the Fabry expertise center and the main reason for performing diagnostics. No other reason than FD for kidney disease was found. As we could not rule out potential inclusion bias, we ran two analyses on renal parameters, one including and one excluding these patients.

This retrospective, cross-sectional study compared clinical manifestations of FD in adolescent and young adult classical male Fabry patients after 10 years of treatment with ERT (the treated group) to untreated classical male FD patients in the same age range (untreated group). The study was conducted in accordance with the principles of the Helsinki Declaration, as revised in 2013. All included patients signed informed consent for the use of their data at start of clinical follow up.

2.2. Imaging

2.2.1. Echocardiography

Echocardiography was performed at the Amsterdam UMC (NL) and Haukeland UH (NO). If original images were available (for 20 patients), they were reassessed by a specialized cardiologist (AH) blinded for treatment status. If images were not available, data from the original report were used (6 patients). Echocardiography data were missing from 4 patients. LV mass was estimated with the Devereux and Reichek "cube" formula as recommended by the American Society of Echocardiography's Guidelines [30] and corrected for BSA using the DuBois formula (recommended and best validated according to the American Society of Echocardiography's Guidelines).

2.2.2. Cardiac MRI

Cardiac MRIs were performed at the Amsterdam UMC on a 1.5 T clinical MR system (Magnetom Avanto, Siemens, Erlangen, Germany) and reassessed by a specialized cardiologist (AH) blinded for treatment status. The protocol included a complete cine short-axis stack covering the whole LV from base to apex, acquired using a balanced steady-state free precession sequence. Furthermore, 2-dimensional late gadolinium

enhancement images were performed 10–20 min after contrast and visually scored for the presence or absence of late gadolinium enhancement. For the assessment of LV mass, endocardial and epicardial contours were manually traced in end-diastole and end-systole on the cine short-axis stack according to Society for Cardiovascular Magnetic Resonance guidelines on image post-processing [31]. Papillary muscles were separately traced and included in the LV mass. LV mass was corrected for BSA using the DuBois formula. Analyses were performed using QMass software version 8.1 (Medis Medical Imaging Systems bv). Due to the potential influence of post-processing software, inter-observer variations as well as differences in the in- or exclusion of papillary muscles on LV mass, only patients of whom original images were available for re-evaluation ($n = 17$) were included. Cardiac MRI data were missing for 3 treated patients (no cardiac MRI performed because the patient was either <18 years old or original imaging not available for re-evaluation) and 10 untreated patients (no MRIs were performed before 2008 or in patients <18 years old).

2.2.3. Brain MRI

Brain MRIs were performed locally at the Amsterdam UMC (NL) and Haukeland UH (NO). MRI data from the Amsterdam UMC were obtained using 3 T scanners. Scans before October 2012 on the Philips Intera system (Philips Medical Systems, Best, The Netherlands) and scans after October 2012 on the Philips Ingenia system (Philips Medical Systems, Best, The Netherlands). Data from the original clinical reports were used. White matter lesions (WML), defined as hyper intensities on axial T2-weighed and FLAIR-weighed imaging, were visually scored using the Fazekas scale (ranging from 0, no WMLs to 6, severe confluent WMLs) [32,33]. MRI brain was missing in 1 patient.

2.3. ECGs

If original ECG was available (21 patients), these were analyzed by a specialized cardiologist (AH). If original ECG was not available ($N = 7$), the clinical report of the ECG was checked to see if any anomalies were described. ECG data were missing for one patient.

2.4. Biochemical analyses

To account for the inclusion of both adolescence and adults, the Full Age Spectrum equation for eGFR was used with a correction for age (FASage) to estimate the glomerular filtration rate [34,35]. Serum creatinine values were obtained from the electronic patient records. Full formula and table with age adjusted correction are added to the supplemental material. Normal eGFR range was defined as 90–140 ml/min/1.73 m^2. Albuminuria was depicted as Urinary albumin/creatinine ratio (uACR, mg/mmol) and categorized into A1, A2 and A3 according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [36]. For analyses uACR was included as a continues variable. If the urinary albumin levels were below the level of detection (<3 mg/l), uACR was entered as 0.

Plasma lysoGb3 (nmol/l) was measured with tandem mass spectrometry, as previous described [3,4]. The presence of inhibiting anti-drug-antibodies (iADAs) to r-αGAL A activity was measured as previously described [5]. iADA titers represent the dilution factor of plasma resulting in 50% inhibition of the r-αGAL A activity. Patients are considered iADA-positive if the inhibition titer was >6.

2.5. Statistical analyses

We used R (version 3.4.3) for all statistical analysis. Non-normal distribution was assumed in all analyses due to the small number of observations. Continuous variables were assessed using Mann-Whitney-Wilcoxon test and categorical variables with Fisher exact test. Spearman's rank was used to assess correlations.

Missing values could be explained by known variables in the majority of cases (missing at random) and had no relation to disease severity. Missing values were dealt with through case wise deletion. Reasons for missing data are mentioned in the results.

P values < 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Patient characteristics are outlined in Table 1. There were no significant differences in age, mutation type, classical FD features, reason for diagnosis (based on clinical features or through family screening) or height of untreated lysoGb3 concentrations (although there was a trend for higher baseline lysoGb3 in the treated group).

3.2. Renal disease manifestations

Albuminuria (Fig. 1a) occurred at a younger age and was more pronounced in the untreated patients (median: 3.7 mg/mmol, range: 0–248 mg/mmol) compared to treated patients (median: 0.4 mg/mmol, range: 0–8.8 mg/mmol, $p = 0.02$). For three patients in the untreated group renal insufficiency and/or severe proteinuria was the main cause for performing FD diagnostics. To remove the effect of a potential inclusion bias, we ran the test again excluding these patients resulting in a median ACR of 3.3 mg/mmol (range: 0–200 mg/mmol) in untreated patients, with the same distribution in treated patients. Results remained statistically significant ($p = 0.04$). Median eGFR, as a representation of renal function did not differ between groups. The treated group had a median eGFR of 116 ml/min/1.73 m^2 (range: 92–132) while the untreated patients also had a median eGFR of 116 ml/min/1.73 m^2 (range: 46–165 $p = 0.96$). It should be noted however that both reduced renal function (defined as an eGFR <90, $n = 4$) and

Table 1
Patient characteristics. Categorical variables are depicted as number (percentage) and continuous variables as median (range). Missing values (if any): presence of cornea verticillata ($n = 2$), reason unknown.

	Treated	Untreated	*P*-value
No of patients	7	23	
Age at evaluation (years)	24 (14–26)	22 (13–27)	0.7
Treatment duration (years)	10.4 (9.5–10.7)	–	
Mutation type			
Nonsense/Frameshift	4/7 (57%)	10/23 (43%)	1.0
Missense	3/7 (43%)	11/23 (48%)	
Other	0/7 (0%)	2/23 (9%)	
Reason for diagnosis			
Family screening	5/7 (71%)	10/23 (43%)	0.5
Acroparesthesia	2/7 (29%)	10/23 (43%)	
Renal insufficiency or albuminuria[a]	0/7 (0%)	3/23 (13%)	
Untreated plasma lysoGb3 (nmol/l)	118 (89–215)[b]	102 (65–137)	0.07
Clinical features of classical FD (at diagnosis)			
Acroparesthesia	7/7 (100%)	22/23 (96%)	1.0
Angiokeratomas	4/7 (57%)	17/23 (74%)	0.6
Cornea verticillata	6/7 (86%)	17/21 (81%)	1.0
Hypertension	0/7 (0%)	1/23 (4%)[c]	1.0
Use of ACEi or ARB	0/7 (0%)	4/23 (17%)	0.5

[a] Renal insufficiency or albuminuria was the reason for performing Fabry diagnostics in these patients. The presence of renal involvement as the primary reason for Fabry diagnostics was deemed a potential risk factor for bias of patient selection between the treated and untreated patient groups. Therefore all analyses were done with and without inclusion of these patients.

[b] Untreated plasma LysoGb3 levels were used. In the treated group lysoGb3 levels at start of treatment initiation are represented. LysoGb3 levels from Haukeland UH were measured in ng/ml and converted using the formula: (lysoGb3(ng/ml)*1000) / 785,9.

[c] One patient was diagnosed with hypertension, eGFR of this patient was normal (118 ml/min/1.73 m^2). Echocardiography and cardiac MRI data were missing for this patient.

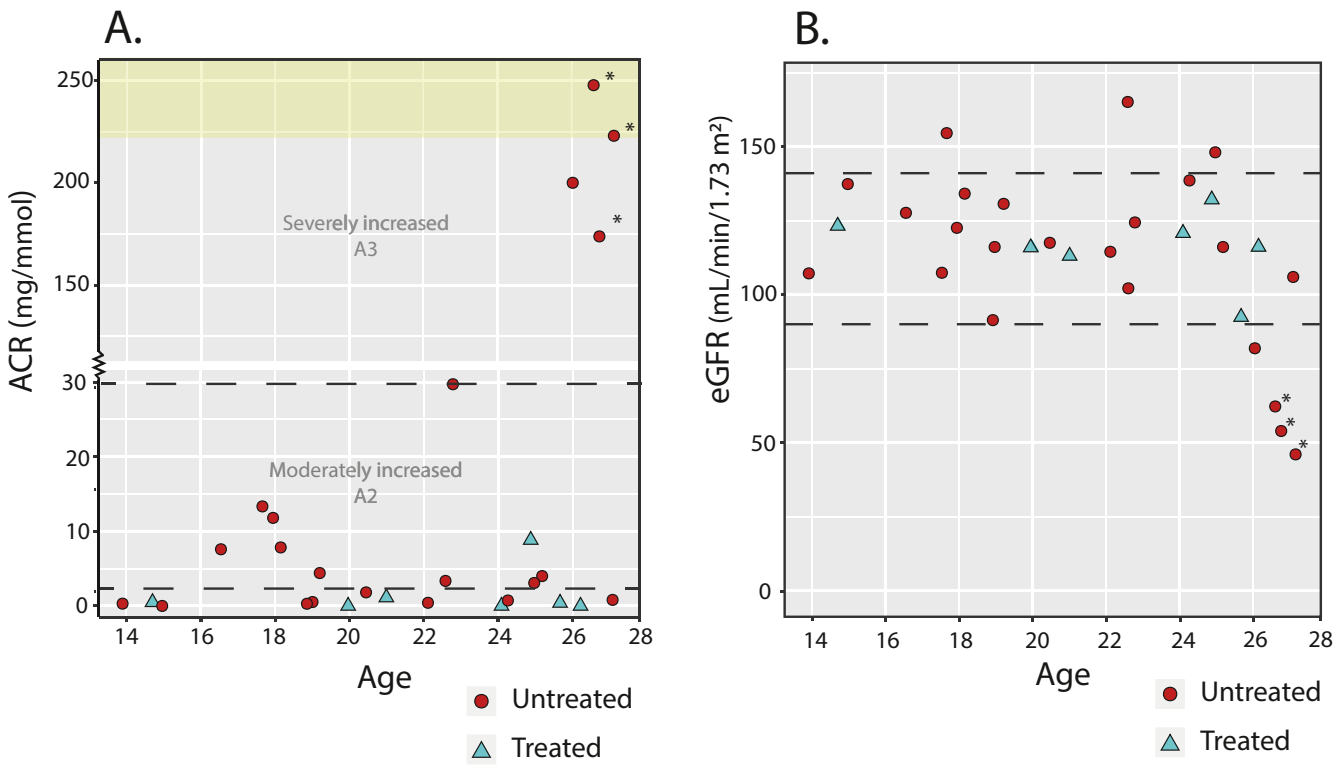

Fig. 1. Renal disease manifestations. (a) albumin to creatinine ratio (ACR) in urine in mg albumin/mmol creatinine ($p = 0.02$). Dashed lines represent the shifts in classification of albuminuria; A1 (<3 mg/mmol, normal to mildly increased), A2 (3-30mg/mmol, moderately increased) and A3 (>30 mg/mmol, severely increased). ACR >220 mg/mmol (arced in yellow) falls within the nephrotic range. (b) eGFR calculated by FASage ($p = 0.96$). Dashed lines represent upper (140 ml/min/1.73 m^2) and lower (90 ml/min/1.73 m^2) limit of normal eGFR. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
* For three patients, renal disease was the presenting symptom leading to the FD diagnosis. Analyses were performed with and without inclusion of these patients. Excluding these patients did not significantly change the outcome of the analyses.

hyperfiltration (defined as an eGFR >140, $n = 3$) only occurred in the untreated group (Fig. 1b). Exclusion of patients that were diagnosed because of renal involvement had no significant effect on the results.

ACR was missing in 1 patient (untreated group, no urine sample at time of evaluation).

Additional disease influencing renal function were excluded in all 3 patients that were diagnosed due to renal involvement.

3.3. Cardiac disease manifestations

Estimated median LV mass based on echocardiography measurements was 94 g/m^2 (59–149 g/m^2) in the untreated group versus 80 g/m^2 (67–84 g/m^2) in the treated group ($p = 0.02$) (Fig. 2a). Median LV mass measured by MRI (including papillary muscles) was 68 g/m^2 (53–99 g/m^2) in the untreated group versus 53 g/m^2 (46–59 g/m^2) in the treated group (Fig. 2b, p = 0.02). Analyses were repeated after excluding patients diagnosed due to renal involvement, this did not change the outcome. Mass measured by echocardiography and MRI correlated well ($\varrho = 0.72$, $p = 0.002$). None of the patients had late gadolinium enhancement on MRI. Cardiac MRIs were missing in 13 patients. Reason for missing were a) original data not available for re-evaluation ($n = 2$) or b) analyses performed before 2008 ($n = 11$) since cardiac MRI as part of the routine follow-up of FD patients was introduced in 2008 at the Amsterdam UMC.

All ECGs that were reevaluated ($n = 21$) showed sinus rhythm and normal PR-, QRS- and QTc-intervals were observed. An incomplete right bundle branch block was present in five of 16 patients (31%) in the untreated group and in 0 of 5 patients (0%) in the treated group ($p = 0.3$). Sinus bradycardia (defined as a resting heart rate below 60 bpm) was present in 1 of 7 patients (14%) in the treated group, compared to 11 of 21 patients (52%) in the untreated group. Median heart rate did not differ between groups ($p = 1$). No anomalies were described in the clinical reports from patients of whom original ECG was not available for reevaluation.

3.4. Cerebral disease manifestations

Cerebral involvement was minimal in both groups. Six out of 22 untreated patients had white matter lesions (all Fazekas 1). In the treated group one out of seven patients had white matter lesions (Fazekas 1) (p = 0.6). In one patient (untreated group) a lacunar infarction was described, in another patient (untreated group) microbleeds were found. Cerebral MRI was missing in one patient (reason unknown).

3.5. Adverse events of treatment with ERT

Four of the seven treated patients developed inhibiting anti-drug antibodies (iADA) during treatment. These patients showed a trend for higher plasma lysoGb3 levels during treatment compared to the three treated patients without iADAs (p = 0.06). In one of these patients treatment with ERT caused serious infusion related reactions with pyrexia and cold chills, requiring treatment with antihistamines and corticosteroids prior to infusions to continue treatment.

4. Discussion

This study shows that young adult male cFD patients that have been treated with ERT for 10 years have significantly less albuminuria and a lower cardiac mass compared to untreated patients from the same age group. No difference was found in median eGFR between the treated

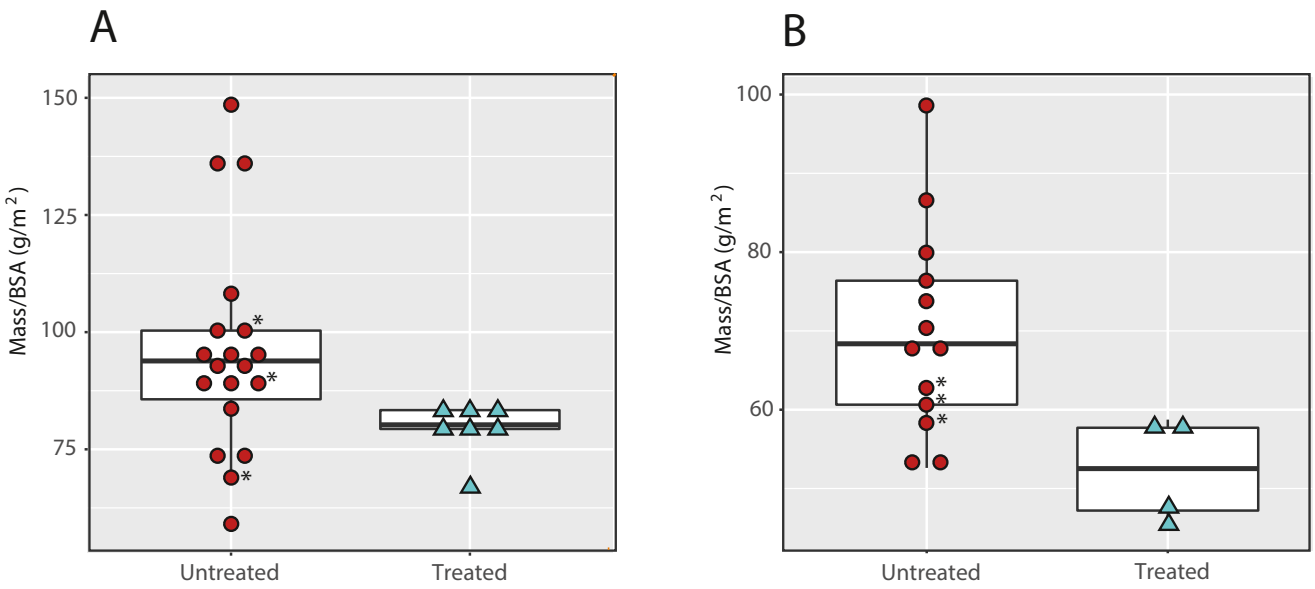

Fig. 2. Cardiac mass measured by echocardiography (A) and MRI (B), in both panels corrected for BSA. Differences between untreated and treated patient groups were significant in both comparisons (A: $p = 0.02$, B: $p = 0.02$).
* For three patients, marked in the figure, renal disease was the presenting symptom leading to the FD diagnosis. Analyses were performed with and without inclusion of these patients. Excluding these patients did not significantly change the outcome of the analyses.

and untreated group. However, it deserves to be mentioned that seven out of 23 patients (30%) in the untreated group had eGFR values outside the normal reference range (e.g. 90–140 ml/min/1.73 m^2) versus none of the patients in the treated group. Three of these patients had hyperfiltration at the time of evaluation and four had reduced renal function. It should be mentioned, however, that for 3 of the 4 patients with reduced renal function, renal manifestations were the reason for referral and Fabry diagnostics. To reduce potential inclusion bias, all analyses were repeated excluding these patients. This did not affect the outcome.

Previous studies showed that higher uACR is the strongest risk factor for the development of renal failure in FD [6]. For nephropathy caused by more common disorders, such as diabetes and hypertension, positive effects of early interventions (e.g. normalization of blood glucose and blood pressure) are well established. Most nephropathies have a 'point of no return', after which renal decline progresses despite adequate treatment of the underlying condition [37]. This is in concordance with the observation in FD that ERT has a limited benefit on renal decline in patients with reduced eGFR at start of ERT (Fig. 3) [15]. Renal biopsy studies suggest that higher doses and a younger age at start of ERT are related to more sustained reduction of Gb3 in podocytes [13,23]. This may be clinically relevant since podocyte Gb3 inclusions in male cFD patients correlate with albuminuria, progressive podocytes loss and worse renal outcome [4,38] and a greater reduction of podocyte inclusions is related to a reduction in microalbuminuria [13]. In other nephropathies albuminuria is also strongly related to an accelerated renal decline and a reduction of albuminuria after treatment with antiproteinuric drugs generally correlates with the preservation of renal function [39]. Finally, the occurrence of hyperfiltration may represent another early FD disease manifestation [40] and has been found to predispose for renal decline in other nephropathies [41], but in FD this has not been evaluated yet. In summary, the previous mentioned findings in literature combined with the observations from our study, demonstrate a beneficial effect of starting ERT in childhood on albuminuria, with a funded expectation for preservation of, or less decline in, renal function.

Evaluation of the benefit of early treatment initiation on cardiac manifestations of FD is more complicated for several reasons. Most importantly, although cardiac LV mass was on average higher in the untreated group, for most included patients, cardiac mass was still within the reference ranges of normal [30,42–44]. Up to date there are no long-term longitudinal studies showing the prognostic value of (mildly) increased left ventricular mass on the occurrence of cardiac complications in FD. However, both in the general population [45] and in FD, LVH is an independent short term predictor for cardiac events such as arrhythmias, heart failure and cardiac death [46]. But the fact that female patients can still develop cardiac fibrosis and complications despite having a normal LV mass indicates that maintenance of a normal cardiac mass does not automatically means protection from the development of fibrosis and/or the occurrence of clinical complications [47].

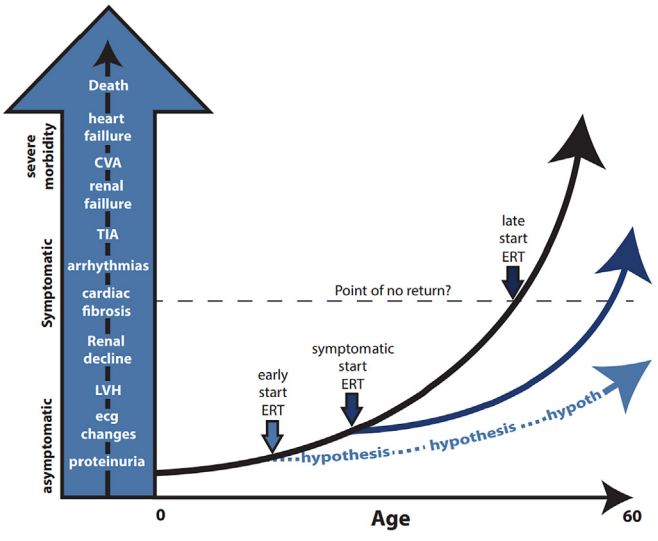

Fig. 3. Influence of treatment with ERT on disease course. From previous studies we know that treatment initiation after the onset of irreversible organ damage does not alter disease course. Starting treatment in an early symptomatic phase (e.g. first signs of organ involvement) slows disease progression. Based on the findings in this study combined with published results of early treatment on histopathological endpoints, we expect that earlier start of treatment (e.g. before the age of 16) in male FD patients with the classical disease phenotype will lead to a more pronounced inhibition of disease progression.

Furthermore, the effect of ERT on cardiac fibrosis formation is not yet known. In patients with fibrosis at start of treatment, its formation progresses despite treatment [17]. Whether or not ERT slows down the progression of fibrosis or prevents it in patients without detectable fibrosis at treatment initiation, is yet unknown. Finally, cardiac biopsies showed no clear reduction of Gb3 inclusions in cardiomyocytes in response to ERT [48], questioning the accessibility of these cells for recombinant enzyme. However, Gb3 accumulation alone does not explain all aspects of the pathophysiology in FD cardiomyopathy [49]. Circulating lysoGb3, for example, has been shown to promote inflammation [50] and hypertrophy [51–53] and is effectively lowered upon treatment with ERT. As secondary disease processes are set in motion well before they lead to clinical manifestations [49], we hypothesize that earlier intervention will modify progression, leading to a more attenuated disease course (Fig. 3). Nonetheless, to confirm the effect of early treatment on the development clinical endpoints of FD such as conduction disorders, arrhythmias and heart failure, validation of intermediate endpoints and longer follow-up are required [54].

The development of anti-drug antibodies (ADAs) against recombinant αGAL A can limit the effect of ERT. ADAs limit cellular uptake of the recombinant enzyme [55], reduce cellular Gb3 clearance [12] and result in an accelerated renal decline [56]. In addition, ADAs are responsible for the majority of adverse reaction to ERT [14] and may even result in anaphylactic reactions. The risk of ADA development and potential infusion reactions should also be taken into account when weighing the pros and cons of ERT, especially in pediatric patients. Future studies assessing different approaches to minimize ADA risks may also help in this regard.

This study was not without its limitations: a relatively small number of early treated patients are included and patients were treated with a lower than registered dose at the time of treatment initiation (e.g. 0.5 mg/kg/biweekly or 1 mg/kg/month). However, the fact that these results were found whilst the treated group received a suboptimal dose, does not weaken the conclusion. In fact, based on earlier studies showing a better effect of higher dosed ERT [57], using the full registered dose can be expected to lead to a more pronounced treatment effect. Potential reasons for (selection) bias were reduced as much as possible by comparing all known variables that could be related to disease severity (a.o. untreated plasma lysoGb3, mutation type, the presence of classical symptoms etc.) and by having original imaging reassessed by a blinded physician. Unfortunately we could not assess the effect of early treatment initiation on native T1 values [58], as most cardiac MRIs in the untreated group were conducted before the routine native T1 assessment was implemented at our site.

Strengths of the study are the precise phenotyping of the patients, making them as comparable as possible, the long treatment duration (10 years) and the standardized analysis of disease manifestations in both patient groups.

Overall, this study is the first to provide clinical evidence that treatment of male cFD patients before the age of 16 has a beneficial impact on progression of clinical renal and cardiac manifestations of FD, as assessed by intermediate endpoints.

Author contributions

Conceptualization, SVDV, SK, CH and ML; data collection, SVDV, SK, CT; methodology and analysis SVDV and SK; re-evaluation of imaging AH; writing—original draft preparation, SVDV.; writing—review and editing, ML, SK, CH, AVK, AH, FW, CT, MB; visualization, SVDV.; supervision, AVK, CH and ML. All authors have read and agreed to the published version of the manuscript.

Disclosures

M. Langeveld and C.E. Hollak are involved in pre-marketing studies with Sanofi-Genzyme, Protalix and Idorsia. Financial arrangements are made through AMC Research BV. S. van der Veen is involved in a pre-marketing study with Protalix. Financial arrangements are made through AMC Research BV. F. Wijburg has received speaker honoraria and travel support from Sanofi/Genzyme and Shire; has participated in studies supported by Sanofi Genzyme and Shire. A. Hirsch has received a speaker fee and travel support from Sanovi-Genzyme. C. Tøndel has received honoraria and travel support from Sanofi Genzyme, Amicus and Shire; has participated in studies supported by Protalix, Sanofi Genzyme, Idorsia, Freeline, Amicus and Shire. S. Korver, M.M. Brands and A.B.P. van Kuilenburg declare that they have no conflict of interest. No fees, travel support or grants are obtained from Pharmaceutical Industry in relation to the submitted work.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2021.12.004.

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