Molecular Genetics and Metabolism 138 (2023) 106967

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Clinical outcomes among young patients with Fabry disease who initiated agalsidase beta treatment before 30 years of age: An analysis from the Fabry Registry

Robert J. Hopkin [a,*], Gustavo H. Cabrera [b], John L. Jefferies [c], Meng Yang [d], Elvira Ponce [e], Eva Brand [f], Ulla Feldt-Rasmussen [g], Dominique P. Germain [h], Nathalie Guffon [i], Ana Jovanovic [j], Ilkka Kantola [k], Amel Karaa [l], Ana M. Martins [m], Camilla Tøndel [n], William R. Wilcox [o], Han-Wook Yoo [p], Alessandro P. Burlina [q], Michael Mauer [r]

[a] Division of Human Genetics, Cincinnati Children's Hospital Medical Center, and Department of Pediatrics University of Cincinnati College of Medicine, Cincinnati, OH, USA
[b] Centro Médico Santa Maria de la Salud, Buenos Aires, Argentina
[c] The Cardiovascular Institute, University of Tennessee Health Science Center, Memphis, TN, USA
[d] Formerly Sanofi, Cambridge, MA, USA
[e] Sanofi, Cambridge, MA, USA
[f] Internal Medicine D, Department of Nephrology, Hypertension and Rheumatology, University Hospital Münster, Münster, Germany
[g] Department of Medical Endocrinology and Metabolism, Rigshospitalet, Copenhagen University Hospital, and Department of Clinical Medicine, Faculty of Health and Clinical Sciences, Copenhagen University, Copenhagen, Denmark
[h] French Referral Center for Fabry disease, Division of Medical Genetics, University of Versailles and APHP – Paris Saclay University, Garches, France
[i] Centre de Référence des Maladies Héréditaires du Métabolisme, Hôpital Femme Mère Enfant, Bron Cedex, France
[j] Mark Holland Metabolic Unit, Salford Royal NHS Foundation Trust, Salford, UK
[k] Division of Medicine, Turku University Hospital, University of Turku, Turku, Finland
[l] Department of Genetics, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[m] Reference Center for Inborn Errors of Metabolism, Federal University of São Paulo, São Paulo, Brazil
[n] Department of Pediatrics, Haukeland University Hospital, Bergen, Norway, and Department of Clinical Science, University of Bergen, Bergen, Norway
[o] Division of Medical Genetics, Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA
[p] Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Republic of Korea
[q] Neurology Unit, St Bassiano Hospital, Bassano del Grappa, Italy
[r] Departments of Pediatrics and Medicine, University of Minnesota, Minneapolis, MN, USA

ARTICLE INFO

Article history:
Received 30 July 2022
Received in revised form 26 November 2022
Accepted 26 November 2022
Available online 30 November 2022

Keywords:
Fabry disease
Agalsidase beta
Pain
Gastrointestinal symptoms
Glomerular filtration rate
Cardiomyopathy

ABSTRACT

Background: Clinical manifestations of classic Fabry disease (α-galactosidase A deficiency) usually occur in childhood, while complications involving major organs typically develop in adulthood. Outcomes of Fabry-specific treatment among young patients have not been extensively reported. Our aim was to analyze clinical outcomes among patients aged 5–30 years at initiation of treatment with agalsidase beta using data from the Fabry Registry (NCT00196742, sponsor: Sanofi).

Methods: Reported *GLA* variants were predicted to be associated with the classic phenotype or not classified in fabry-database.org. Linear mixed models were conducted to assess changes over ≥2-year follow-up in the estimated glomerular filtration rate (eGFR) stratified by low (LRI) and high (HRI) renal involvement (defined by proteinuria/albuminuria levels), and changes in interventricular septal thickness (IVST) and left ventricular posterior wall thickness (LVPWT) *Z*-scores stratified by median age at first treatment. Self-reports ('yes'/'no') of abdominal pain, diarrhea, chronic peripheral pain (denoting neuropathic pain), and acute pain crises at baseline were compared with reports after ≥0.5-year and ≥2.5-year follow-up using McNemar's test.

Results: Male ($n = 117$) and female patients ($n = 59$) with LRI initiated treatment at a median age of 19.9 and 23.6 years, respectively, and were followed for a median of 6.3 and 5.0 years, respectively. The eGFR slopes were −1.18 ($P_{\text{from 0}} < 0.001$) and −0.92 mL/min/1.73 m^2/year ($P_{\text{from 0}} = 0.040$), respectively. Males with HRI

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eow, every other week; eGFR, estimated glomerular filtration rate; FD, Fabry disease; GL-3, globotriaosylceramide; HRI, high renal involvement; IVST, interventricular septal thickness; LRI, low renal involvement; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVPWT, left ventricular posterior wall thickness; mGFR, measured glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio; 95% CI, 95% confidence interval.

* Corresponding author at: Division of Human Genetics, Cincinnati Children's Hospital Medical Center, and Department of Pediatrics University of Cincinnati College of Medicine, 3333 Burnet Avenue, Cincinnati, OH, USA.
E-mail address: rob.hopkin@cchmc.org (R.J. Hopkin).

https://doi.org/10.1016/j.ymgme.2022.106967

($n = 23$, median UPCR 1.0 g/g), who started treatment at a median age of 26.7 years, had an eGFR slope of −2.39 mL/min/1.73 m^2/year ($P_{from\ 0} < 0.001$; $P_{difference} = 0.055$, as compared with the slope of −1.18 mL/min/1.73 m^2/year for LRI males) during a median follow-up of 5.6 years. Echocardiographic variables were stable among males, regardless of age, and among young females (median follow-up >5.5 years and ≥4.5 years, respectively). Older females (treatment initiation at median age 27.5 years) had a slope of LVPWT *Z*-scores of 0.18/year ($n = 12$, $P_{from\ 0} = 0.028$), whereas IVST *Z*-scores remained stable ($n = 13$, 0.10/year, $P_{from\ 0} = 0.304$) during a median follow-up of ≥3.7 years. These slopes did not significantly differ from slopes of younger females. Reports of chronic peripheral pain and acute pain crises by males, and of diarrhea and acute pain crises by females, significantly reduced after a median follow-up of ≥4.0 years. After a median follow-up of ≥5.4 years, reports of all four symptoms significantly decreased among males, whereas among females only reports of abdominal pain significantly decreased.

Conclusions: During sustained treatment with agalsidase beta in young Fabry patients with a predicted classic phenotype or with unclassified *GLA* variants with similar characteristics, the decline in eGFR was modest among male and female patients with LRI. The greater decline in eGFR among older, proteinuric (i.e., HRI) males may suggest a benefit of earlier treatment. Overall, echocardiographic variables remained stable, particularly among males and younger females. Significant reductions in symptom reports occurred primarily among males after longer follow-up and were less noticeable among females. These observed trends are suggestive of an overall improvement after treatment in young patients, but warrant larger longitudinal studies.

1. Introduction

Fabry disease (FD, OMIM #301500) is an X-linked lysosomal storage disorder caused by pathogenic *GLA* variants [1,2]. Deficient α-galactosidase A activity leads to accumulation of the enzyme's substrate, globotriaosylceramide (denoted GL-3 or Gb_3), in plasma, urine, and, in many cell types, primarily within the lysosomes, as well as increased levels of deacylated GL-3 (lyso-GL-3 or lyso-Gb_3) in plasma and urine [1–4]. Progressive cellular damage leads to early onset of symptoms and to dysfunction and, ultimately, to fibrosis of vital organs [5].

In males with *GLA* variants associated with the classic phenotype and minimal or no α-galactosidase A activity, progressive GL-3 accumulation presumably starts before birth [6,7] and the first stages of organ injury may begin at a very young age [8,9]. The array of symptoms typically emerging during childhood or adolescence can include repeatedly occurring burning peripheral (neuropathic) pain and episodic, sometimes incapacitating, pain crises, gastrointestinal symptoms (e.g., abdominal pain, diarrhea), impaired sweating, hearing loss, and fatigue, all diminishing quality of life [10–14]. Relatively early diagnostic signs may include cornea verticillata and angiokeratomas. The risk of developing progressive chronic kidney disease, left ventricular hypertrophy (LVH), myocardial fibrosis, arrhythmias, and strokes increases with age, and these reduce life expectancy [1,2,15–17]. Among female patients, the level of residual α-galactosidase A activity varies from within the normal range to virtually absent depending on the *GLA* variant and X-chromosome inactivation profiles [18] and, consequently, the severity of the female clinical phenotype varies widely [15,19]. Onset of first symptoms usually occurs later than among classic male patients, but frequently still at pediatric ages [13,14]. Adult female patients also have a significant risk for clinical organ involvement and decreased quality of life and overall longevity [15,19]. Variability in phenotypic expression of a given *GLA* variant exists, which may be due to the influence of phenotype-modifying factors (e.g., genetic background, epigenetics, and environmental conditions) [20].

Currently available enzyme replacement therapies include agalsidase beta (Fabrazyme®, Sanofi) and agalsidase alfa (Replagal®, Takeda Pharmaceuticals) administered intravenously at 1 mg/kg and 0.2 mg/kg every other week (eow), respectively. Agalsidase beta has been approved for treatment of FD patients aged ≥2 years in the United States (USA) [21] and aged ≥8 years in other countries [22]. Agalsidase alfa has been approved for patients aged ≥7 years in most countries, although it has not been approved by the USA Food and Drug Administration (FDA) [23]. Oral pharmacological chaperone therapy with migalastat (Galafold®, Amicus Therapeutics) is restricted to patients who have amenable pathogenic variants as determined by an in vitro assay [24] and are aged ≥16 years in the USA [25] and ≥12 years in other countries [26].

There is increasing clinical recognition of the critical importance of earlier diagnosis of patients with the classic FD phenotype and initiation of FD-specific treatment to better moderate the impact of the disease [27–30]. However, the evidence available for various clinical outcomes among young patients, who are expected to increasingly develop signs and symptoms of FD if they remain untreated, is still relatively limited [31–33]. The objectives of our study were to evaluate kidney function, echocardiographic variables of cardiomyopathy, and self-reported outcomes of typical gastrointestinal and peripheral pain symptoms of FD among male and female patients aged 5–30 years at initiation of treatment with agalsidase beta.

2. Methods

2.1. Fabry Registry

We used data from the Fabry Registry (NCT00196742, sponsor: Sanofi) as of March 4, 2022. The Fabry Registry was initiated in 2001 as a multicenter, international, longitudinal, observational program designed to monitor the natural history and treatment outcomes of patients with FD. Participation of patients and investigators is voluntary. Recommended schedules of clinical assessments are available, but treating physicians determine the frequency of assessments. Each site is independent and is responsible for obtaining informed written consent from patients to submit their health data to the Fabry Registry and use their anonymized data in analyses. The protocol, informed consent form, and any locally required authorization documents needed for entering patient information are reviewed and approved by the local Institutional Review Board or Independent Ethics Committee unless the site provides documentation that approval is not required or has been waived.

2.2. Patients

Male and female patients in the Fabry Registry aged 5–30 years at initiation of agalsidase beta treatment as their first FD-specific therapy were included in the analyses. Only patients who had received an average dose at or near the licensed dose of 1 mg/kg (range 0.9–1.1 mg/kg) eow were included. The current analysis was restricted to patients with a *GLA* variant categorized in the fabry-database.org database as predicted to be associated with the classic FD phenotype (herein referred

to as classic patients, or patients with classic *GLA* variants) or unclassified variants (not entered in fabry-database.org, or entered but not classified). Thus, we excluded patients with variants classified as pathogenic with a later-onset phenotype, (likely) benign or as a genetic variant of uncertain significance, as well as patients whose genotype had not been reported to the Fabry Registry.

Patients with a measurement at −12 to +3 months of first treatment (baseline data) and ≥1 follow-up measurement ≥2 years apart were included for longitudinal analysis of continuous variables. Patients on dialysis or with a kidney transplant before baseline were excluded.

For categorical variables, a baseline assessment (within −12 to +1 month of first treatment) and an on-treatment follow-up assessment (≥0.5-year or ≥2.5-year follow-up) were required.

2.3. Clinical outcome assessments

Kidney function was assessed by eGFR and calculated using the creatinine-based bedside Schwartz equation, which has been reported as less biased and showing higher precision and accuracy than the Chronic Kidney Disease Epidemiology Collaboration equation for estimating GFR in children and adolescents, regardless of the level of eGFR, and in adults aged ≤40 years with mild-to-moderate kidney impairment [34–36].

Echocardiographic assessments (either two-dimensional or M-mode) included interventricular septal thickness (IVST) and left ventricular posterior wall thickness (LVPWT). Height and weight were acquired within −3/+3 months of each echocardiographic assessment for patients aged <18 years. For patients aged ≥18 years, the same time window (−3/+3 months from each echocardiographic assessment) was used for weight measurements only, since height attained by the age of 18 would not vary. Body surface area (BSA) was then calculated as the square root of weight (in kg) multiplied by height (in cm), divided by 3600.

Self-reported outcome assessments included symptoms of (symptom terminology as used by the Fabry Registry) 'abdominal pain', 'diarrhea', 'peripheral Fabry pain' (herein referred to as 'chronic peripheral pain' denoting chronic neuropathic pain), and 'acute pain crises requiring narcotics and/or bed rest' (herein referred to as 'acute pain crises'). Binary responses ('yes' if present, or 'no' if absent) to the assessment of each symptom were analyzed. All assessments occurring after discontinuation of agalsidase beta treatment were excluded from analyses.

2.4. Statistical methods

Descriptive statistics were calculated for total patients by sex, and between patients with classic or unclassified *GLA* variants within each of the sexes. Baseline characteristics are reported as counts and percentages, or as mean (standard deviation [SD]) and medians (25th, 75th percentiles), as appropriate. *P*-values were calculated using a chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables.

Linear mixed models were used to estimate changes over time in eGFR or *Z*-scores of IVST and LVPWT. Follow-up time was calculated from the date of each baseline clinical measurement to the time of discontinuation of agalsidase beta treatment, first post-treatment renal event (dialysis, transplant), or date of last assessment, whichever came first. The intercept and time were considered as random effect, and unstructured covariance matrix was selected based on the optimal goodness of fit indices, and the Akaike's information and Bayesian information criteria [37]. Estimated slopes for subgroups and corresponding *P*-values indicated whether the slopes were different from zero ($P_{\text{from 0}}$). $P_{\text{difference}}$ compared the slopes between subgroups by including a product term of follow-up time and subgroup indicators. Predicted intercepts and slopes were used to generate individual lines in figures.

The level of renal involvement was determined by using the urine protein-to-creatinine ratio (UPCR) or, if not available, the urine albumin-to-creatinine ratio (UACR) reported at treatment initiation or the median of ratios during follow-up if baseline data were not available. Low renal involvement (LRI) was defined as UPCR ≤0.5 g/g or UACR ≤0.3 g/g, and high renal involvement (HRI) as UPCR >0.5 g/g or UACR >0.3 g/g [38,39]. eGFR slopes were determined for both LRI and HRI subgroups if data were sufficient. As an additional exploratory analysis, patients were stratified based on baseline eGFR >135 and eGFR ≤135 mL/min/1.73 m^2, with 135 mL/min/1.73 m^2 representing the center of the 130–140 mL/min/1.73 m^2 range of most reported cut-offs used for glomerular 'hyperfiltration' in the medical literature [40]. A small number of LRI patients were included in this eGFR slope analysis that used a model adjusted for sex and included an interaction term between sex and time.

IVSTs and LVPWTs were converted to *Z*-scores based on BSA captured within the time frame mentioned above [41,42]. The presence of a *Z*-score ≥2 was considered abnormal. Estimated slopes of IVST and LVPWT *Z*-scores were stratified by the group's median age at treatment initiation. Additional adjustment of the model intercepts for potential confounding by age at first treatment, renal involvement, and use of angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARBs) did not, overall, change the results and, therefore, these variables were not included in the main analyses (modeling data for male patients are shown in Supplementary Table 1).

Usable responses to gastrointestinal and pain symptoms were defined as 'yes' or 'no' responses, excluding 'unknown' or missing answers. *P*-values were calculated from McNemar's test to compare proportions of patients reporting symptoms at last follow-up with proportions at baseline.

For all analyses, a two-sided *P*-value of <0.05 was considered to represent statistical significance. Statistical analyses were performed using SAS statistical software 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient demographics and clinical characteristics at treatment baseline

The demographics and baseline clinical characteristics of the 524 male and 261 female patients who started agalsidase beta treatment at ages 5–30 years and had *any* available data of interest are summarized in Supplementary Table 2. There were neither notable differences between the males with classic ($n = 261$, 49.8%) or unclassified *GLA* variants ($n = 263$, 50.2%), nor between the females with classic ($n = 128$, 49.0%) or unclassified variants ($n = 133$, 51.0%). While treated males were younger at onset of any FD symptom compared with treated females (median 8.3 vs 10.3 years, $P < 0.001$), the age at diagnosis was similar for males and females (median 14.9 vs 15.0 years, $P = 0.660$). Males had a shorter time from diagnosis to first agalsidase beta treatment (median 1.2 vs 2.5 years, $P < 0.001$) and were younger at treatment start than females (median 18.0 vs 19.6 years, $P = 0.027$). Among males, eGFR at baseline was lower compared with females (median 91.7 vs 102.3 mL/min/1.73 m^2, $P < 0.001$), and *Z*-scores of IVST (median 1.0 vs 0.5, $P < 0.001$) and LVPWT (median 1.0 vs 0.4, $P < 0.001$) were higher. Chronic peripheral pain was the most frequently reported symptom at baseline by males and females who had data available (87.8% vs 83.8%, $P = 0.302$), followed by abdominal pain (49.0% vs 58.2%, $P = 0.090$) and diarrhea (42.1% vs 44.5%, $P = 0.659$). Acute pain crises were least frequently reported (24.9% vs 13.5%, $P = 0.010$).

3.2. Kidney function

Of the 524 males in the overall population, 140 (26.7%) males had the required eGFR assessments and renal involvement classification criteria and were included in eGFR slope estimations (Table 1, Supplementary Table 3). Of the 140 males, 117 (83.6%) had LRI and 23 (16.4%) had HRI. LRI males were younger at diagnosis (median age 16.1 vs 20.1 years, $P = 0.041$), at first treatment (median age 19.9 vs

Table 1
Patient demographics and estimated slopes of eGFR and IVST/LVPWT *Z*-scores in male and female Fabry patients aged 5–30 years at the start of agalsidase beta treatment who were included in subgroup analyses.

Subgroup: n	Predicted classic phenotype, %	Age at first treatment[a]	Follow-up[a,b]	Age at last assessment[a]	Slope post treatment (95% CI)[c]	$P_{\text{from 0}}$[d]	$P_{\text{difference}}$[e]
Male patients							
eGFR slope by renal involvement[f]							
Low renal involvement: 117	52.9	19.9 (14.6, 24.2)	6.3 (4.1, 10.7)	27.1 (21.5, 31.4)	−1.18 (−1.66, −0.71)	<0.001	0.055
High renal involvement: 23	39.1	26.7 (19.5, 28.8)	5.6 (3.8, 8.3)	33.2 (23.8, 36.4)	−2.39 (−3.53, −1.25)	<0.001	
IVST *Z*-score slope by median age at treatment initiation							
<20.8 years: 33	57.6	16.9 (13.3, 18.5)	5.5 (3.9, 8.1)	21.9 (17.1, 25.2)	−0.08 (−0.15, −0.02)	0.014	0.199
≥20.8 years: 33	63.6	25.2 (22.4, 28.4)	5.8 (4.6, 9.0)	31.5 (29.0, 34.9)	−0.03 (−0.09, 0.04)	0.420	
LVPWT *Z*-score slope by median age at treatment initiation							
<21.4 years: 34	55.9	17.5 (13.7, 19.5)	5.5 (3.8, 8.3)	22.5 (18.6, 26.5)	−0.03 (−0.08, 0.01)	0.156	0.161
≥21.4 years: 34	61.8	25.3 (23.0, 28.4)	5.5 (3.8, 7.4)	30.8 (28.1, 34.9)	0.02 (−0.06, 0.10)	0.478	
Female patients							
eGFR slope by renal involvement[f,g]							
Low renal involvement: 59	59.3	23.6 (14.8, 26.8)	5.0 (3.7, 7.2)	28.4 (18.7, 32.6)	−0.92 (−1.81, −0.04)	0.040	
IVST *Z*-score slope by median age at treatment initiation							
<23.4 years: 12	50.0	14.0 (1.8, 18.8)	4.5 (3.7, 5.9)	18.8 (15.6, 22.7)	0.003 (−0.19, 0.20)	0.977	0.469
≥23.4 years: 13	46.2	26.5 (25.9, 28.3)	4.1 (2.7, 4.9)	30.1 (28.5, 31.9)	0.10 (−0.10, 0.29)	0.304	
LVPWT *Z*-score slope by median age at treatment initiation							
<21.7 years: 10	40.0	14.0 (12.3, 16.7)	4.6 (3.7, 7.1)	18.8 (17.0, 20.5)	−0.03 (−0.20, 0.14)	0.684	0.066
≥21.7 years: 12	58.3	27.5 (25.9, 28.3)	3.7 (3.0, 4.9)	30.8 (28.9, 31.9)	0.18 (0.02, 0.35)	0.028	

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; IVST, interventricular septal thickness; LVPWT, left ventricular posterior wall thickness; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.
[a] Median in years (25th, 75th percentile).
[b] Follow-up defined as time of baseline assessment (within −12 to +3 months of first agalsidase beta treatment) to last assessment.
[c] mL/min/1.73 m^2/year for eGFR and change in *Z*-score/year for echocardiographic variables.
[d] *P*-value calculated to test whether the post-treatment slope is different from zero.
[e] *P*-value calculated to test the post-treatment slope difference between subgroups.
[f] Renal involvement was defined as low (UPCR ≤0.5 g/g or UACR ≤0.3 g/g) or high (UPCR >0.5 g/g or UACR >0.3 g/g) using available data collected at treatment initiation or during follow-up. eGFR as mL/min/1.73 m^2. Baseline defined as within −12 to +3 months of first agalsidase beta treatment.
[g] Data from high renal involvement females ($n = 7$) were insufficient for eGFR slope analysis.

26.7 years, $P < 0.001$), and at last eGFR assessment (median age 27.1 vs 33.2 years, $P = 0.028$) than males with HRI. The eGFR slopes for these subgroups were −1.18 (95% confidence interval [CI] −1.66, −0.71; $P_{\text{from 0}} < 0.001$) vs −2.39 (95% CI −3.53, −1.25; $P_{\text{from 0}} < 0.001$) mL/min/1.73 m^2/year ($P_{\text{difference}} = 0.055$) during a median follow-up of 6.3 vs 5.6 years.

Of the 261 females in the overall population, 59 (22.6%) females with LRI had sufficient eGFR assessments for slope analysis (Table 1, Supplementary Table 3). Data from female patients with HRI ($n = 7$) were insufficient to reliably estimate the eGFR slope (data not shown). The 59 LRI females had an eGFR slope of −0.92 (95% CI −1.81, −0.04) mL/min/1.73 m^2/year ($P_{\text{from 0}} = 0.040$) during a median follow-up of 5.0 years. The median ages at first treatment and last eGFR assessment were 23.6 vs 28.4 years.

eGFR slope estimates for patients with a baseline eGFR >135 mL/min/1.73 m^2 were based on small numbers of patients with LRI. Only one patient (female) with HRI had a baseline eGFR above this threshold and was excluded from the analysis. The eGFR slopes among the seven male and six female LRI patients were −2.95 (95% CI −6.01, 0.12; $P_{\text{from 0}} = 0.057$) vs −3.20 mL/min/1.73 m^2/year (95% CI −9.71, 3.32; $P_{\text{from 0}} = 0.140$) ($P_{\text{difference}} = 0.893$) during a median follow-up of 4.9 vs 5.8 years. The median baseline eGFRs were 148.4 vs 138.0 mL/min/1.73 m^2, and the patients had started treatment at a median age of 15.5 vs 12.9 years. For the male patients, the patient demographics and clinical characteristics (other than baseline eGFR) did not significantly differ from data for LRI males with a baseline eGFR ≤135 mL/min/1.73 m^2 (Supplementary Table 4). The LRI females with a baseline eGFR >135 mL/min/1.73 m^2 were younger at diagnosis (median 7.3 vs 15.5 years, $P = 0.019$) and at initiation of treatment (median 12.9 vs 23.7 years, $P = 0.006$) compared with LRI females with a baseline eGFR ≤135 mL/min/1.73 m^2.

The individual eGFR simple regression slopes for the male and female patients are plotted against patient age in Supplementary Fig. 1.

3.3. Echocardiographic variables of cardiomyopathy

The analysis of IVST *Z*-scores for male patients included 33 males who were younger and 33 males who were older than the overall group's median age of 20.8 years at treatment initiation (median age 16.9 vs 25.2 years, $P < 0.001$). The slopes of *Z*-scores of IVST were −0.08 (95% CI −0.15, −0.02; $P_{\text{from 0}} = 0.014$) vs −0.03 (95% CI −0.09, 0.04; $P_{\text{from 0}} = 0.420$) per year ($P_{\text{difference}} = 0.199$) (Table 1). The IVST *Z*-scores at baseline were similar (median 1.2 vs 1.0, $P = 0.622$). Nine younger and six older patients had a *Z*-score of ≥2 at baseline. The follow-up durations were similar (median 5.5 vs 5.8 years, $P = 0.489$) and the last IVST assessment was performed at median ages 21.9 vs 31.5 years ($P < 0.001$) (Supplementary Table 5A).

The slopes of *Z*-scores of LVPWT for younger males (<21.4 years, $n = 34$) and older males (≥21.4 years, $n = 34$) were −0.03 (95% CI −0.08, 0.01; $P_{\text{from 0}} = 0.156$) vs −0.02 (95% CI −0.06, 0.10; $P_{\text{from 0}} = 0.478$) per year ($P_{\text{difference}} = 0.161$) (Table 1). The median ages at first treatment, follow-up durations, and the ages at last assessment were comparable to those for IVST *Z*-score assessments. The LVPWT *Z*-scores at baseline for younger and older males were similar (median 1.1 vs 1.3, $P = 0.961$) (Supplementary Table 5A). Six younger and two older patients had a *Z*-score of ≥2 at baseline.

Compared with male patients, fewer females had IVST and LVPWT *Z*-score data available. The slopes of IVST *Z*-scores for younger (<23.4 years, median age 14.0 years, $n = 12$) and older females (≥23.4 years, median age 26.5 years, $n = 13$) were 0.003 (95% CI −0.19, 0.20; $P_{\text{from 0}} = 0.977$) vs 0.10 (95% CI −0.10, 0.29; $P_{\text{from 0}} = 0.304$) per year ($P_{\text{difference}} = 0.469$) (Table 1). The median IVST *Z*-scores at baseline were 0.7 vs −0.2 ($P = 0.034$). None of the females had a *Z*-score of ≥2 at baseline. Follow-up durations were similar (median 4.5 vs 4.1 years, $P = 0.568$) and the median ages at last IVST assessment were 18.8 vs 30.1 years ($P < 0.001$) (Supplementary Table 5B).

The slopes of *Z*-scores of LVPWT for younger (<21.7 years, $n = 10$) and older females (≥21.7 years, $n = 12$) were − 0.03 (95% CI −0.20,

0.14; $P_{\text{from 0}} = 0.684$) vs 0.18 (95% CI 0.02, 0.35; $P_{\text{from 0}} = 0.028$) per year ($P_{\text{difference}} = 0.066$) (Table 1). The median LVPWT *Z*-scores at baseline were 0.3 vs −0.6 ($P = 0.065$). One older patient had a *Z*-score of ≥2 at baseline. The median ages at first treatment, follow-up durations, and ages at last assessment were similar to those for IVST assessments (Supplementary Table 5B).

3.4. Self-reported symptoms of Fabry disease

Among male patients with ≥0.5-year follow-up (specific symptom median follow-up range 4.0–4.6 years), reports of chronic peripheral pain (−6.9%, $P = 0.028$) and acute pain crises (−9.5%, $P < 0.008$) significantly reduced, compared with baseline. The changes in 'yes' reports of abdominal pain (−7.5%, $P = 0.101$) and diarrhea (−7.5%, $P = 0.071$) were not significant. After longer (≥2.5-year) follow-up (median follow-up range 5.4–6.1 years), all observed reductions in symptom reports were statistically significant (abdominal pain −13.9%, $P = 0.011$; diarrhea −11.1%, $P = 0.029$; chronic peripheral pain −8.7%, $P = 0.025$; acute pain crises −12.3%, $P = 0.005$) (Table 2).

Among female patients with ≥0.5-year follow-up (specific symptom median follow-up range 3.9–4.4 years), significant reductions in reports of diarrhea (−12.5%, $P = 0.035$) and acute pain crises (−6.6%, $P = 0.046$) were documented. The changes in reports of abdominal pain (−9.1%, $P = 0.114$) and chronic peripheral pain (−6.5%, $P = 0.194$) were not statistically significant. After longer follow-up (median follow-up range 5.4–6.1 years), reports of abdominal pain significantly reduced (−14.0%, $P = 0.034$), whereas other changes were not significant (diarrhea −10.3%, $P = 0.128$; chronic peripheral pain −8.7%, $P = 0.144$; acute pain crises −6.6%, $P = 0.109$) (Table 2).

The vast majority of the males and females with 'no' responses for abdominal pain, diarrhea, and acute pain at treatment baseline also reported absence of these symptoms at last follow-up (Supplementary Fig. 2).

4. Discussion

This longitudinal Fabry Registry analysis examined important clinical outcomes among male and female patients with FD aged 5–30 years at initiation of agalsidase beta treatment and *GLA* variants associated with the classic phenotype of FD or unclassified variants. We assessed changes in kidney function and echocardiographic variables of cardiomyopathy following long-term treatment. In addition, we evaluated self-reported outcomes (binary 'yes'/'no' responses) of selected hallmark symptoms of FD. Our findings suggest that sustained treatment with agalsidase beta in male and female patients with LRI was associated with a modest decline in eGFR. A greater decline was observed for older proteinuric (HRI) males. Overall, echocardiographic variables remained stable, particularly among males and younger females. Significant reductions in reports of FD symptoms were particularly observed among males; after longer follow-up, reports of all analyzed FD symptoms were significantly reduced. There were fewer changes in symptom reports by female patients.

Clinical experience with FD-specific treatments now exceeds 20 years, but most studies report clinical outcomes after relatively late initiation of treatment when substantial irreversible pathological changes in major organs may already have developed [32,33]. Moreover, a very limited number of studies have evaluated outcomes after early initiation of agalsidase beta treatment at 1 mg/kg eow or at lower doses in pediatric patients [31,43,44]. The findings emerging from this comprehensive analysis of clinical outcomes substantially contribute to bridging the gap in understanding the clinical outcomes associated with agalsidase beta treatment among pediatric, adolescent, and young adult patients with this complex genetic disorder, which is progressive if left untreated [15,45].

In classically affected children with FD, early and substantial accumulation of GL-3 in multiple kidney cell types (e.g., vascular, glomerular, interstitial, and tubular cells, podocytes) progressively leads to cellular damage and secondary injury to kidney tissues [43,46–48]. Pathologic kidney damage is typically present before onset of

Table 2
Changes in self-reported Fabry disease symptoms after ≥0.5 and ≥2.5 years of follow-up in male and female Fabry patients aged 5–30 years at the start of agalsidase beta treatment.

Parameters[a]	Baseline	≥0.5-year follow-up	% Change[b]	*P*[c]	Baseline	≥2.5-year follow-up	% Change[b]	*P*[c]
Male patients								
Abdominal pain								
'Yes' response, n/N (%)	66/146 (45.2)	55/146 (37.7)	−7.5	0.101	54/108 (50.0)	39/108 (36.1)	−13.9	0.011
Follow-up, years	–	4.4 (2.3, 7.9)	–	–	–	6.0 (4.0, 10.2)	–	–
Diarrhea								
'Yes' response, n/N (%)	62/147 (42.2)	51/147 (34.7)	−7.5	0.071	50/108 (46.3)	38/108 (35.2)	−11.1	0.029
Follow-up, years	–	4.6 (2.0, 8.0)	–	–	–	6.1 (4.0, 10.4)	–	–
Chronic peripheral pain								
'Yes' response, n/N (%)	143/160 (89.4)	132/160 (82.5)	−6.9	0.028	103/115 (89.6)	93/115 (80.9)	−8.7	0.025
Follow-up, years	–	4.0 (1.9, 7.4)	–	–	–	5.4 (3.7, 10.6)	–	–
Acute pain crises								
'Yes' response, n/N (%)	42/168 (25.0)	26/168 (15.5)	−9.5	0.008	29/122 (23.8)	14/122 (11.5)	−12.3	0.005
Follow-up, years	–	4.3 (2.0, 8.2)	–	–	–	6.1 (3.9, 10.6)	–	–
Female patients								
Abdominal pain								
'Yes' response, n/N (%)	62/110 (54.4)	52/110 (47.3)	−7.1	0.114	51/86 (59.3)	39/86 (45.3)	−14.0	0.034
Follow-up, years	–	4.2 (2.7, 6.3)	–	–	–	5.4 (3.7, 6.8)	–	–
Diarrhea								
'Yes' response, n/N (%)	50/112 (44.6)	36/112 (32.1)	−12.5	0.035	39/87 (44.8)	30/87 (34.5)	−10.3	0.128
Follow-up, years	–	4.1 (2.7, 6.3)	–	–	–	5.4 (3.7, 6.8)	–	–
Chronic peripheral pain								
'Yes' response, n/N (%)	93/108 (86.1)	86/108 (79.6)	−6.5	0.194	69/81 (85.2)	62/81 (76.5)	−8.7	0.144
Follow-up, years	–	3.9 (2.5, 6.3)	–	–	–	5.3 (3.6, 7.0)	–	–
Acute pain crises								
'Yes' response, n/N (%)	16/121 (13.2)	8/121 (6.6)	−6.6	0.046	13/91 (14.3)	7/91 (7.7)	−6.6	0.109
Follow-up, years	–	4.4 (2.6, 6.5)	–	–	–	5.4 (3.8, 7.1)	–	–

[a] Only patients with usable responses defined as 'yes' or 'no' to the symptom assessment were included in analysis; patients with 'unknown' or missing answers were excluded. Follow-up as median (25th, 75th percentile).
[b] Percent change in the proportion of patients reporting presence of abdominal pain after ≥0.5 and ≥2.5 years of follow-up, compared with baseline.
[c] *P*-value calculated from McNemar's test to compare the last reported values with baseline values.

progressive decline in GFR and increasing proteinuria. The initial renal functional abnormality, microalbuminuria, has also been reported for children with FD [49]. A study in untreated FD patients has demonstrated an association between eGFR and age among males aged ≥18 years with a predicted classic FD phenotype [15]. Among untreated classic female patients, this relationship was also present, although less strong.

We evaluated kidney function according to the extent of renal involvement (i.e., LRI or HRI) primarily defined by the level of proteinuria reported at treatment initiation or during follow-up, as this is a strong and independent risk factor for progression of chronic kidney disease in patients with and without FD [45,50–53]. For LRI patients, we found a modest eGFR decline among 117 males and 59 females (1.18 vs 0.92 mL/min/1.73 m^2/year). These patients were followed till the median ages of 27.1 vs 28.4 years. Compared with LRI males, treatment with agalsidase beta was initiated at significantly older age in the 23 HRI males (median age 19.9 vs 26.7 years). The HRI males had a median UPCR (1.0 g/g), indicative of significant kidney dysfunction [54], and an increased rate of eGFR decline of 2.39 mL/min/1.73 m^2/year (last assessments at median age 33.2 years) without a significant difference compared with the slope among LRI males. Previous studies of agalsidase beta have reported a statistically significantly more rapid decline among adult HRI patients compared with adult LRI patients [55,56]. One of these studies evaluated 10-year (median) agalsidase beta treatment outcomes among 52 classic adult FD patients (50 males, two females) classified as LRI or HRI based on the UPCR and on the percentage of sclerotic glomeruli on kidney biopsy [55]. LRI males had a marginally higher age at first treatment (median 22.5 vs 19.9 years) and a higher rate of eGFR decline (1.89 vs 1.18 mL/min/1.73 m^2/year) compared with LRI males in the current study. HRI males in the previous study were considerably older at first treatment (median 36.6 vs 26.7 years) and eGFR decline was more rapid (6.82 vs 2.39 mL/min/1.73 m^2/year) compared with HRI males in the present study.

A Fabry Outcome Survey study reported a significant decline in eGFR of 1.12 mL/min/1.73 m^2/year among 84 male patients aged 18–30 years at start of agalsidase alfa treatment who had a normal mean eGFR (118.6 mL/min/1.73 m^2) at baseline [57]. However, the analysis did not stratify patients by the level of renal involvement and predicted phenotype. Another study in mostly classic FD patients reported a mean decline in eGFR of 1.5 mL/min/1.73 m^2/year among 21 patients (males and females) aged 18–29 years at the start of either agalsidase alfa or agalsidase beta treatment, whereas the decline in measured GFR (mGFR) was 0.1 mL/min/1.73 m^2. The mean eGFR and mGFR at baseline were 132 vs 101 mL/min/1.73 m^2 [50].

Tøndel et al, using both mGFRs and eGFRs, concluded that most 'hyperfiltration' eGFRs of young patients with FD could not be confirmed by mGFRs and were likely spurious [58]. Our exploratory analysis, which stratified patients based on a baseline eGFR below and above the 'hyperfiltration' threshold [40], included small numbers of LRI patients. The decline in eGFR among patients with a baseline eGFR >135 mL/min/1.73 m^2 was 2.95 (seven males) and 3.20 mL/min/1.73 m^2/year (six females) with wide 95% CIs. The patient demographics and clinical characteristics, compared with LRI patients with a baseline eGFR ≤135 mL/min/1.73 m^2, were similar for the males, whereas the females were significantly younger at diagnosis and at initiation of treatment. A more rapid 'decline' in patients with a high baseline eGFR (Supplementary Fig. 1) may represent regression toward the mean or other non-true GFR variables related to increases in muscle mass because of greater exercise capability consequent to agalsidase beta treatment and the effects of puberty, or related to the imprecision of eGFR vs mGFR methods at higher GFRs [58–60]. Although it has been proposed that hyperfiltration is a common early-stage sign indicating glomerular damage in FD patients [61], the concept of hyperfiltration in patients with this disorder should be used with caution until validated with mGFRs vs eGFRs [58].

Progressive GL-3 accumulation within the heart affects various cardiac cell types, including vascular endothelial and smooth muscle cells, cardiomyocytes, conduction system tissue, and valvular fibroblasts [62]. Specific trophic factors, cardiomyocyte injury, and microcirculatory ischemia are believed to contribute to tissue injury leading to inflammation and development of LVH and cardiac replacement fibrosis [5]. Evidence of LVH may be present among pediatric and adolescent patients [63–65]. A study in untreated male patients aged ≥18 years with a predicted classic phenotype reported an association between age and left ventricular mass (LVM). Moreover, a Fabry Registry study showed that LVM progressively increased among untreated male patients aged 18–29 and 30–39 years (not stratified by predicted phenotype) with slope estimates of 9.5 vs 8.4 g/year [66].

In the current analysis, we found overall stable *Z*-scores of IVST and LVPWT over time among younger and older males who were followed till the median ages of ~22 vs 31 years. Data for female patients were more limited. Younger females had stable *Z*-scores, whereas results for the older females were mixed (stable *Z*-scores of IVST, significant increase in *Z*-scores of LVPWT). However, the slopes did not statistically differ from slopes of younger females. The median ages at last follow-up were 18.8 vs ~30 years.

The aforementioned registry studies found that LVM decreased significantly among 31 males aged 18–29 years following agalsidase beta treatment [66], and LVM (indexed) did not significantly progress among 38 males aged 18–30 years at start of agalsidase alfa treatment who had a normal mean LVM (≤50 g/$m^{2.7}$) at baseline [57].

Abdominal pain and diarrhea are believed to result from GL-3-induced enteric small-fiber neuropathy and ganglionopathy, vasculopathy in structures of the gastrointestinal tract, and inflammatory processes [67,68]. GL-3 accumulation in dorsal root ganglia and endothelial cells of the vasa nervorum have been proposed as possible causes of the length-dependent small-fiber neuropathy, which may induce a variety of neurological symptoms, including chronic neuropathic pain and acute pain crises [69–71].

The frequencies of occurrence of abdominal pain and diarrhea among patients in this study substantially exceeded those reported for young untreated FD patients of both sexes [12,13]. Significant reductions in reports of abdominal pain and diarrhea by males were only found after longer follow-up. Among females, the reduction in reports of abdominal pain was only statistically significant after longer follow-up, whereas the change in reports of diarrhea, albeit significant in the first follow-up analysis (median 4.1 years follow-up), was not significant after longer follow-up. Most patients reporting absence of gastrointestinal symptoms at treatment baseline also reported their absence at last follow-up.

A few small studies evaluated gastrointestinal symptoms among FD patients starting agalsidase beta treatment at a young age. Among 16 pediatric patients (14 males) enrolled in a 48-week open-label study of agalsidase beta, patient reports showed significant reductions in post-prandial pain, nausea, and vomiting after 6 months of treatment initiated at a median age of 11.7 years [72]. In another pediatric study, 10 patients (six males) started agalsidase beta treatment at a mean age of 12.3 years. Five of the seven patients reporting abdominal pain at baseline had decreased pain (assessed using a Visual Analog Scale) during a maximum follow-up of 8 years [73].

Chronic neuropathic pain (chronic peripheral pain) was the most frequently reported symptom by male and female patients included in our analyses, and reports of acute pain crises were the least frequent. We found significant reductions in reports of chronic peripheral pain and acute pain crises by males in both follow-up analyses, and in reports of acute pain crises by females in the first follow-up analysis but not after longer follow-up. Changes in reports of chronic peripheral pain by females were not significant.

The previously mentioned pediatric study by Borgwardt et al assessed pain outcomes after agalsidase beta initiation using a Visual Analog Scale, and found decreased neuropathic pain in eight of

10 pediatric patients [73]. Another study reported a reduction in the mean total symptom score for neuropathic pain among 22 classic male patients initiating agalsidase beta treatment at a mean age of 27.9 years [74].

The classic phenotype of FD is characterized by early and progressive disease manifestations, and the underlying pathogenic mechanisms are complex. Organ-specific goals of FD-specific treatment and appropriate non-specific adjunctive therapies have been developed by a European panel of experts in FD [30]. The goals particularly relevant to patients aged 5–30 years include stabilization of eGFR or reduction in the slope of eGFR decline, prevention of LVH, mitigation of gastrointestinal symptoms and, rather than eliminating pain, reduction in the intensity of chronic neuropathic pain to manageable levels and reduction in the intensity and frequency of pain crises. Our findings suggest an overall improvement of the analyzed variables after longer term treatment with agalsidase beta in patients in this age category. However, since longitudinal studies providing sufficient detail on the evolution and progression of kidney dysfunction, cardiomyopathy, and common early symptoms during childhood, adolescence, and early adulthood have not been reported, the present study is limited in drawing firm conclusions about the disease-moderating impact of agalsidase beta treatment in young patients with FD.

Strengths and limitations of the present study should be weighed carefully. Our analyses comprehensively investigated several important clinical outcomes among young FD patients receiving agalsidase beta treatment. To ensure reliable eGFR, IVST *Z*-score and LVPWT *Z*-score slope estimations based on sufficient numbers of male and female patients, we included patients with *GLA* variants predicted to be associated with classic FD or with unclassified variants in the analyses. For both males and females in these two variant groups, the demographics and clinical characteristics of patients were overall similar (Supplementary Table 2) and, therefore, the impact of phenotype heterogeneity on the analyses is expected to be minimal. However, patient-specific data on clinical presentation, residual α-Gal A activity, and biochemical parameters, required to confirm genotype-phenotype correlations in these patients, beyond the scope of this manuscript, were not analyzed. Moreover, we were unable to determine which patient-specific clinical considerations led to initiation of treatment in individual patients. Therefore, it cannot be concluded that all these patients consistently showed the features of the more severe, classic phenotype of FD expected to occur during childhood, adolescence, or early adulthood prior to initiation of agalsidase beta treatment. The interpretation of data is limited by the lack of an appropriately matched control group. The treated female patients included in the analyses may have more unfavorable patterns of skewing of X-chromosome inactivation, and may not be representative of the overall population of young female FD patients. For female patients, sufficient data for eGFR slope estimation were mostly available for patients with LRI, and estimations of slopes of echocardiographic variables were based on relatively small numbers of patients. In addition, *Z*-scores of IVST and LVPWT were computed based on values derived from a study population limited to individuals aged ≤18 years [41,42]. This may have introduced some measurement errors in patients aged >18 years that could have affected the precision of the slope, thus widening the 95% CIs of the estimated slopes. We lacked sufficient data on LVM, cardiovascular risk factors, and on biomarkers of FD (e.g., plasma or urinary GL-3, lyso-GL-3 [3,4]) for assessment of biochemical responses. Furthermore, interpretation of changes in FD symptoms is limited by using binary responses of 'yes' (present) and 'no' (absent) to describe self-reported outcomes, rather than validated symptom rating scales. These rigorous endpoints prevented any relative symptom improvements or deteriorations from being analyzed (data on changes in intensity and frequency of symptoms were insufficient). Moreover, the analyses did not assess non-FD-related causes of the symptoms. Data on the timing of ACEi/ARB initiation (if applicable) and the uniformity in their use, including dose and titration, were lacking. Because ACEi/ARBs are presumably prescribed as nephroprotective agents and could be seen as confounding by indication, these data were not included in our analyses. The use of gastrointestinal agents and pain control agents (which use for chronic pain may be restricted till the age of 14 years) may have influenced the results, but could not be analyzed due to limited data in the Fabry Registry. Finally, although regular monitoring of serum anti-α-galactosidase A IgG antibody levels is recommended as part of the routine care for patients with FD receiving agalsidase beta treatment, the study did not include this information due to limited antibody data availability for many patients that precluded meaningful analyses of IgG antibody titer changes as related to eGFR, IVST *Z*-score, or LVPWT *Z*-score changes over time.

5. Conclusions

During sustained treatment with agalsidase beta in young FD patients with classic or unclassified *GLA* variants who had similar characteristics, the decline in eGFR was modest among male and female patients with LRI. Older, proteinuric (HRI) males had a greater decline in eGFR, which may suggest a benefit of earlier treatment. Overall, echocardiographic variables remained stable, particularly among males and younger females. Among older females, the results varied, but slopes of echocardiographic variables did not statistically differ from slopes of younger females. After longer follow-up, reports of all analyzed FD symptoms significantly reduced among males, whereas changes among females were less noticeable. These findings extend the current limited clinical data regarding therapeutic outcomes among young FD patients and suggest an overall improvement of the analyzed variables after sustained treatment in patients in this age category. The observed trends are informative for clinical care decisions for these young patients directed toward reducing the burden of FD and improving the overall clinical outcomes. However, the findings merit caution in their interpretations, given the study limitations, and warrant larger longitudinal studies.

Funding

This research was funded by Sanofi, the sponsor of the Fabry Registry. The funder had a role in Fabry Registry data collection and analysis. The authors received medical writing/editing support in the preparation of this manuscript from Tom Rouwette and Emma Butterworth of Excerpta Medica, funded by Sanofi, and Hans Ebels of Sanofi. The authors were responsible for all content and editorial decisions and received no honoraria related to the development of this publication. Ulla Feldt-Rasmussen's research salary is funded by The Kirsten and Freddy Johansen's Fund.

Data availability

Data are available on reasonable request (Sanofi's guidance on data sharing).

Declaration of Competing Interest

R.J.H. is a member of the Fabry Registry Advisory Board, consults with Amicus Therapeutics and Sanofi, and has been an investigator in clinical trials sponsored by Amicus Therapeutics, Idorsia Pharmaceuticals, Protalix Biotherapeutics, Sangamo Therapeutics, Sanofi, and Takeda. These activities have been monitored and found to be in compliance with the conflict-of-interest policies at Cincinnati Children's Hospital Medical Center.

G.H.C. has consulting arrangements with and received speaking fees from Sanofi, and has received travel support from Sanofi and Takeda.

J.L.J. has received Advisory Board honoraria from Sanofi.

M.Y. is a former employee of Sanofi. E.P. is a full-time employee of Sanofi. Both may hold/have held stock and/or stock options in that company.

E.B. has received Advisory Board honoraria from Amicus Therapeutics, Chiesi Pharmaceuticals, Greenovation Biotech, Sanofi, and Takeda, speaker honoraria and research grants from Amicus Therapeutics, Chiesi Pharmaceuticals, Sanofi, and Takeda, and travel support from Amicus Therapeutics.

U.F.R. has received Advisory Board honoraria from Amicus Therapeutics, Freeline Therapeutics, Sanofi, and Takeda, speaker honoraria from Amicus Therapeutics, Sanofi, and Takeda, grant support from Sanofi and Takeda, and is a member of the European Advisory Board of the Fabry Registry.

D.P.G. has received consulting honoraria from Idorsia Pharmaceuticals, Sanofi, and Takeda, and speaker honoraria and travel support from Amicus Therapeutics, Sanofi, and Takeda.

N.G. has received travel support from Sanofi and Takeda.

A.J. has received Advisory Board honoraria from Amicus Therapeutics, Sanofi, and Takeda, speaker honoraria from Amicus Therapeutics, BioMarin Pharmaceutical, and Sanofi, and travel support from Amicus Therapeutics and Sanofi.

I.K. has received speaker honoraria and travel support from Sanofi and Takeda.

A.K. has received research grants, reimbursement for travel, and consulting payments from Sanofi, Stealth BioTherapeutics, and Takeda, received research grants and reimbursement for travel from Protalix Biotherapeutics and Reata Pharmaceuticals, received research grants from Astellas Pharma, Cyclerion Therapeutics, Idorsia Pharmaceuticals, Mitobridge, and PTC Therapeutics, and received consulting payments from Akros Pharma, Alexion Pharmaceuticals, Astellas Pharma, Homology Medicines, Lumleian, Mitobridge, NeuroVive Pharmaceutical, Reneo Pharmaceuticals, and Zogenix.

A.M.M. has received Advisory Board honoraria from BioMarin Pharmaceutical and Sanofi, and speaker honoraria and travel support from Alexion Pharmaceuticals, BioMarin Pharmaceutical, and Sanofi.

C.T. is a member of the European Fabry Registry Board of Advisors, has received consultancy honoraria from Acelink Therapeutics, Amicus Therapeutics, Chiesi Pharmaceuticals, Freeline Therapeutics, and Sanofi, and is investigator in studies supported by Freeline Therapeutics, Idorsia Pharmaceuticals, Protalix Biotherapeutics, Sanofi, and Takeda.

W.R.W. consults for Amicus Therapeutics, Sanofi, and Takeda, and is an investigator in clinical studies for Fabry disease sponsored by Amicus Therapeutics, Freeline Therapeutics, Idorsia Pharmaceuticals, 4D Molecular Therapeutics, Protalix Biotherapeutics, Sangamo Therapeutics, and Sanofi. These activities are monitored and are in compliance with the conflict-of-interest policies at Emory University School of Medicine.

H.W.Y. has received honoraria from Sanofi.

A.P.B. has received speaker honoraria and travel support from Amicus Therapeutics, Freeline Therapeutics, Sanofi, and Takeda, and is a member of the European Advisory Board of the Fabry Registry.

M.M. is a member of the Fabry Registry Board, has an investigator-initiated research grant from Sanofi, performs laboratory work and is a consultant to Sanofi for clinical trial design, received speaker fees and travel support from Sanofi for non-promotional presentations (these interests have been reviewed and managed by the University of Minnesota in accordance with its conflict-of-interest policies), is a consultant and performs laboratory work for Amicus Therapeutics, and is a consultant to Acelink Therapeutics, Avrobio, Freeline Therapeutics, and Sangamo Therapeutics.

Acknowledgements

The authors would like to thank the patients who have agreed to participate in the Fabry Registry, the physicians and research coordinators who entered clinical data on these patients, and Badari Gudivada (Sanofi) for statistical programming support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2022.106967.

References

[1] D.P. Germain, Fabry disease, Orphanet J. Rare Dis. 5 (2010) 30, https://doi.org/10.1186/1750-1172-5-30.
[2] A. Ortiz, D.P. Germain, R.J. Desnick, et al., Fabry disease revisited: management and treatment recommendations for adult patients, Mol. Genet. Metab. 123 (4) (2018) 416–427, https://doi.org/10.1016/j.ymgme.2018.02.014.
[3] C. Auray-Blais, C.M. Blais, U. Ramaswami, et al., Urinary biomarker investigation in children with Fabry disease using tandem mass spectrometry, Clin. Chim. Acta 438 (2015) 195–204, https://doi.org/10.1016/j.cca.2014.08.002.
[4] J. Krämer, F. Weidemann, Biomarkers for diagnosing and staging of Fabry disease, Curr. Med. Chem. 25 (13) (2018) 1530–1537, https://doi.org/10.2174/0929867324666170616102112.
[5] F. Weidemann, M.D. Sanchez-Nino, J. Politei, et al., Fibrosis: a key feature of Fabry disease with potential therapeutic implications, Orphanet J. Rare Dis. 8 (2013) 116, https://doi.org/10.1186/1750-1172-8-116.
[6] B.L. Thurberg, J.M. Politei, Histologic abnormalities of placental tissues in Fabry disease: a case report and review of the literature, Hum. Pathol. 43 (4) (2012) 610–614, https://doi.org/10.1016/j.humpath.2011.07.020.
[7] O. Tsutsumi, M. Sato, K. Sato, K. Sato, M. Mizuno, S. Sakamoto, Early prenatal diagnosis of inborn error of metabolism: a case report of a fetus affected with Fabry's disease, Asia Oceania J. Obstet. Gynaecol. 11 (1) (1985) 39–45, https://doi.org/10.1111/j.1447-0756.1985.tb00045.x.
[8] C. Tøndel, T. Kanai, K.K. Larsen, et al., Foot process effacement is an early marker of nephropathy in young classic Fabry patients without albuminuria, Nephron 129 (1) (2015) 16–21, https://doi.org/10.1159/000369309.
[9] D.A. Laney, D.S. Peck, A.M. Atherton, et al., Fabry disease in infancy and early childhood: a systematic literature review, Genet. Med. 17 (5) (2015) 323–330, https://doi.org/10.1038/gim.2014.120.
[10] D.P. Germain, P. Avan, A. Chassaing, P. Bonfils, Patients affected with Fabry disease have an increased incidence of progressive hearing loss and sudden deafness: an investigation of twenty-two hemizygous male patients, BMC Med. Genet. 3 (2002) 10, https://doi.org/10.1186/1471-2350-3-10.
[11] B. Hoffmann, M. Beck, G. Sunder-Plassmann, et al., Nature and prevalence of pain in Fabry disease and its response to enzyme replacement therapy–a retrospective analysis from the Fabry Outcome Survey, Clin. J. Pain 23 (6) (2007) 535–542, https://doi.org/10.1097/ajp.0b013e318074c986.
[12] B. Hoffmann, M. Schwarz, A. Mehta, S. Keshav, Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy, Clin. Gastroenterol. Hepatol. 5 (12) (2007) 1447–1453, https://doi.org/10.1016/j.cgh.2007.08.012.
[13] R.J. Hopkin, J. Bissler, M. Banikazemi, et al., Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry, Pediatr. Res. 64 (5) (2008) 550–555, https://doi.org/10.1203/pdr.0b013e318183f132.
[14] U. Ramaswami, R. Parini, G. Pintos-Morell, et al., Fabry disease in children and response to enzyme replacement therapy: results from the Fabry Outcome Survey, Clin. Genet. 81 (5) (2012) 485–490, https://doi.org/10.1111/j.1399-0004.2011.01671.x.
[15] M. Arends, C. Wanner, D. Hughes, et al., Characterization of classical and nonclassical Fabry disease: a multicenter study, J. Am. Soc. Nephrol. 28 (5) (2017) 1631–1641, https://doi.org/10.1681/asn.2016090964.
[16] A. Mehta, J.T. Clarke, R. Giugliani, et al., Natural course of Fabry disease: changing pattern of causes of death in FOS - Fabry Outcome Survey, J. Med. Genet. 46 (8) (2009) 548–552, https://doi.org/10.1136/jmg.2008.065904.
[17] S. Waldek, M.R. Patel, M. Banikazemi, R. Lemay, P. Lee, Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry, Genet. Med. 11 (11) (2009) 790–796, https://doi.org/10.1097/gim.0b013e3181bb05bb.
[18] L. Echevarria, K. Benistan, A. Toussaint, et al., X-chromosome inactivation in female patients with Fabry disease, Clin. Genet. 89 (1) (2016) 44–54, https://doi.org/10.1111/cge.12613.
[19] W.R. Wilcox, J.P. Oliveira, R.J. Hopkin, et al., Females with Fabry disease frequently have major organ involvement: lessons from the Fabry registry, Mol. Genet. Metab. 93 (2) (2008) 112–128, https://doi.org/10.1016/j.ymgme.2007.09.013.
[20] D.P. Germain, T. Levade, E. Hachulla, et al., Challenging the traditional approach for interpreting genetic variants: lessons from Fabry disease, Clin. Genet. 101 (4) (2022) 390–402, https://doi.org/10.1111/cge.14102.
[21] Fabrazyme [Prescribing Information]. Sanofi, Cambridge, Massachusetts, U.S.A., 2021, Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103979s5135lbl.pdf Accessed 22 July 2022.
[22] Fabrazyme [Summary of Product Characteristics]. Genzyme Europe B.V., Amsterdam, The Netherlands, 2021, Available at: https://www.ema.europa.eu/en/documents/product-information/fabrazyme-epar-product-information_en.pdf Accessed 22 July 2022.
[23] Replagal [Summary of Product Characteristics]. Shire Human Genetic Therapies A.B., Stockholm, Sweden, 2021, Available at: https://www.ema.europa.eu/en/documents/product-information/replagal-epar-product-information_en-0.pdf Accessed 22 July 2022.

[24] E.R. Benjamin, M.C. Della Valle, X. Wu, et al., The validation of pharmacogenetics for the identification of Fabry patients to be treated with migalastat, Genet. Med. 19 (4) (2017) 430–438, https://doi.org/10.1038/gim.2016.122.
[25] Galafold [Prescribing Information]. Amicus Therapeutics Inc., Cranbury, New Jersey, U.S.A., 2020, Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208623s003lbl.pdf Accessed 22 July 2022.
[26] Galafold [Summary of Product Characteristics]. Amicus Therapeutics Europe Limited, Dublin, Ireland, 2021, Available at: https://www.ema.europa.eu/en/documents/product-information/galafold-epar-product-information_en.pdf Accessed 22 July 2022.
[27] M. Arends, F.A. Wijburg, C. Wanner, et al., Favourable effect of early versus late start of enzyme replacement therapy on plasma globotriaosylsphingosine levels in men with classical Fabry disease, Mol. Genet. Metab. 121 (2) (2017) 157–161, https://doi.org/10.1016/j.ymgme.2017.05.001.
[28] D.P. Germain, A. Fouilhoux, S. Decramer, et al., Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients, Clin. Genet. 96 (2) (2019) 107–117, https://doi.org/10.1111/cge.13546.
[29] R.J. Hopkin, J.L. Jefferies, D.A. Laney, et al., The management and treatment of children with Fabry disease: a United States-based perspective, Mol. Genet. Metab. 117 (2) (2016) 104–113, https://doi.org/10.1016/j.ymgme.2015.10.007.
[30] C. Wanner, M. Arad, R. Baron, et al., European expert consensus statement on therapeutic goals in Fabry disease, Mol. Genet. Metab. 124 (3) (2018) 189–203, https://doi.org/10.1016/j.ymgme.2018.06.004.
[31] M. Spada, R. Baron, P.M. Elliott, et al., The effect of enzyme replacement therapy on clinical outcomes in paediatric patients with Fabry disease - a systematic literature review by a European panel of experts, Mol. Genet. Metab. 126 (3) (2019) 212–223, https://doi.org/10.1016/j.ymgme.2018.04.007.
[32] D.P. Germain, M. Arad, A. Burlina, et al., The effect of enzyme replacement therapy on clinical outcomes in female patients with Fabry disease - a systematic literature review by a European panel of experts, Mol. Genet. Metab. 126 (3) (2019) 224–235, https://doi.org/10.1016/j.ymgme.2018.09.007.
[33] D.P. Germain, P.M. Elliott, B. Falissard, et al., The effect of enzyme replacement therapy on clinical outcomes in male patients with Fabry disease: a systematic literature review by a European panel of experts, Mol. Genet. Metab. Rep. 19 (2019) 100454, https://doi.org/10.1016/j.ymgmr.2019.100454.
[34] L. Selistre, M. Rabilloud, P. Cochat, et al., Comparison of the Schwartz and CKD-EPI equations for estimating glomerular filtration rate in children, adolescents, and adults: a retrospective cross-sectional study, PLoS Med. 13 (3) (2016), e100197https://doi.org/10.1371/journal.pmed.1001979.
[35] L. Selistre, V. De Souza, P. Cochat, et al., GFR estimation in adolescents and young adults, J. Am. Soc. Nephrol. 23 (6) (2012) 989–996, https://doi.org/10.1681/asn.2011070705.
[36] G.J. Schwartz, A. Munoz, M.F. Schneider, et al., New equations to estimate GFR in children with CKD, J. Am. Soc. Nephrol. 20 (3) (2009) 629–637, https://doi.org/10.1681/ASN.2008030287.
[37] G.M. Fitzmaurice, N.M. Laird, J.H. Ware, Applied Longitudinal Analysis, second ed. John Wiley & Sons, New York, 2011.
[38] KDIGO, 2012 clinical practice guideline for the management of blood pressure in chronic kidney disease, Kidney Int. (Suppl. 2) (2012) 337–405.
[39] D.M. Kent, T.H. Jafar, R.A. Hayward, et al., Progression risk, urinary protein excretion, and treatment effects of angiotensin-converting enzyme inhibitors in nondiabetic kidney disease, J. Am. Soc. Nephrol. 18 (6) (2007) 1959–1965, https://doi.org/10.1681/asn.2006101081.
[40] F. Cachat, C. Combescure, M. Cauderay, E. Girardin, H. Chehade, A systematic review of glomerular hyperfiltration assessment and definition in the medical literature, Clin. J. Am. Soc. Nephrol. 10 (3) (2015) 382–389, https://doi.org/10.2215/cjn.03080314.
[41] L. Lopez, S. Colan, M. Stylianou, et al., Relationship of echocardiographic Z scores adjusted for body surface area to age, sex, race, and ethnicity: the Pediatric Heart Network normal echocardiogram database, Circ. Cardiovasc. Imaging 10 (11) (2017), e006979https://doi.org/10.1161/circimaging.117.006979.
[42] M.D. Pettersen, W. Du, M.E. Skeens, R.A. Humes, Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study, J. Am. Soc. Echocardiogr. 21 (8) (2008) 922–934, https://doi.org/10.1016/j.echo.2008.02.006.
[43] U. Ramaswami, D.G. Bichet, L.A. Clarke, et al., Low-dose agalsidase beta treatment in male pediatric patients with Fabry disease: a 5-year randomized controlled trial, Mol. Genet. Metab. 127 (1) (2019) 86–94, https://doi.org/10.1016/j.ymgme.2019.03.010.
[44] S.J. van der Veen, S. Korver, A. Hirsch, et al., Early start of enzyme replacement therapy in pediatric male patients with classical Fabry disease is associated with attenuated disease progression, Mol. Genet. Metab. 135 (2) (2022) 163–169, https://doi.org/10.1016/j.ymgme.2021.12.004r.
[45] R. Schiffmann, D.G. Warnock, M. Banikazemi, et al., Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy, Nephrol. Dial. Transplant. 24 (7) (2009) 2102–2111, https://doi.org/10.1093/ndt/gfp031.
[46] B. Najafian, E. Svarstad, L. Bostad, et al., Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease, Kidney Int. 79 (6) (2011) 663–670, https://doi.org/10.1038/ki.2010.484.
[47] J. Politei, V. Alberton, O. Amoreo, et al., Clinical parameters, lysoGb3, podocyturia, and kidney biopsy in children with Fabry disease: is a correlation possible? Pediatr. Nephrol. 33 (11) (2018) 2095–2101, https://doi.org/10.1007/s00467-018-4006-3.
[48] U. Ramaswami, B. Najafian, A. Schieppati, M. Mauer, D.G. Bichet, Assessment of renal pathology and dysfunction in children with Fabry disease, Clin. J. Am. Soc. Nephrol. 5 (2) (2010) 365–370, https://doi.org/10.2215/cjn.08091109.
[49] C. Tøndel, L. Bostad, A. Hirth, E. Svarstad, Renal biopsy findings in children and adolescents with Fabry disease and minimal albuminuria, Am. J. Kidney Dis. 51 (5) (2008) 767–776, https://doi.org/10.1053/j.ajkd.2007.12.032.
[50] C.V. Madsen, H. Granqvist, J.H. Petersen, et al., Age-related renal function decline in Fabry disease patients on enzyme replacement therapy: a longitudinal cohort study, Nephrol. Dial. Transplant. 34 (9) (2019) 1525–1533, https://doi.org/10.1093/ndt/gfy357.
[51] C. Wanner, J.P. Oliveira, A. Ortiz, et al., Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry Registry, Clin. J. Am. Soc. Nephrol. 5 (12) (2010) 2220–2228, https://doi.org/10.2215/cjn.04340510.
[52] D.G. Warnock, A. Ortiz, M. Mauer, et al., Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation, Nephrol. Dial. Transplant. 27 (3) (2012) 1042–1049, https://doi.org/10.1093/ndt/gfr420.
[53] D.G. Warnock, C.P. Thomas, B. Vujkovac, et al., Antiproteinuric therapy and Fabry nephropathy: factors associated with preserved kidney function during agalsidase-beta therapy, J. Med. Genet. 52 (12) (2015) 860–866, https://doi.org/10.1136/jmedgenet-2015-103471.
[54] B. Najafian, C. Tøndel, E. Svarstad, et al., Accumulation of globotriaosylceramide in podocytes in Fabry nephropathy is associated with progressive podocyte loss, J. Am. Soc. Nephrol. 31 (4) (2020) 865–875, https://doi.org/10.1681/asn.2019050497.
[55] D.P. Germain, J. Charrow, R.J. Desnick, et al., Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease, J. Med. Genet. 52 (5) (2015) 353–358, https://doi.org/10.1136/jmedgenet-2014–102797.
[56] D.P. Germain, S. Waldek, M. Banikazemi, et al., Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease, J. Am. Soc. Nephrol. 18 (5) (2007) 1547–1557, https://doi.org/10.1681/asn.2006080816.
[57] R. Parini, G. Pintos-Morell, J.B. Hennermann, et al., Analysis of renal and cardiac outcomes in male participants in the Fabry Outcome Survey starting agalsidase alfa enzyme replacement therapy before and after 18 years of age, Drug Des. Devel. Ther. 14 (2020) 2149–2158, https://doi.org/10.2147/dddt.s249433.
[58] C. Tøndel, U. Ramaswami, K.M. Aakre, F. Wijburg, M. Bouwman, E. Svarstad, Monitoring renal function in children with Fabry disease: comparisons of measured and creatinine-based estimated glomerular filtration rate, Nephrol. Dial. Transplant. 25 (5) (2010) 1507–1513, https://doi.org/10.1093/ndt/gfp658.
[59] M. Kanbay, L.A. Ertuglu, B. Afsar, et al., Renal hyperfiltration defined by high estimated glomerular filtration rate: a risk factor for cardiovascular disease and mortality, Diabetes Obes. Metab. 21 (11) (2019) 2368–2383, https://doi.org/10.1111/dom.13831.
[60] L.A. Stevens, J. Coresh, T. Greene, A.S. Levey, Assessing kidney function–measured and estimated glomerular filtration rate, N. Engl. J. Med. 354 (23) (2006) 2473–2483, https://doi.org/10.1056/nejmra054415.
[61] E. Riccio, M. Sabbatini, D. Bruzzese, et al., Glomerular hyperfiltration: an early marker of nephropathy in Fabry disease, Nephron 141 (1) (2019) 10–17, https://doi.org/10.1159/000493469.
[62] A. Linhart, D.P. Germain, I. Olivotto, et al., An expert consensus document on the management of cardiovascular manifestations of Fabry disease, Eur. J. Heart Fail. 22 (7) (2020) 1076–1096, https://doi.org/10.1002/ejhf.1960.
[63] S. Havranek, A. Linhart, Z. Urbanova, U. Ramaswami, Early cardiac changes in children with Anderson-Fabry disease, JIMD Rep. 11 (2013) 53–64, https://doi.org/10.1007/8904_2013_222.
[64] C. Kampmann, C.M. Wiethoff, C. Whybra, F.A. Baehner, E. Mengel, M. Beck, Cardiac manifestations of Anderson-Fabry disease in children and adolescents, Acta Paediatr. 97 (4) (2008) 463–469, https://doi.org/10.1111/j.1651-2227.2008.00700.x.
[65] H.C. Wilson, R.J. Hopkin, P.C. Madueme, et al., Arrhythmia and clinical cardiac findings in children with Anderson-Fabry disease, Am. J. Cardiol. 120 (2) (2017) 251–255, https://doi.org/10.1016/j.amjcard.2017.04.016.
[66] D.P. Germain, F. Weidemann, A. Abiose, et al., Analysis of left ventricular mass in untreated men and in men treated with agalsidase-beta: data from the Fabry Registry, Genet. Med. 15 (12) (2013) 958–965, https://doi.org/10.1038/gim.2013.53.
[67] M. Lenders, E. Brand, Fabry disease - a multisystemic disease with gastrointestinal manifestations, Gut Microbes 14 (1) (2022) 2027852, https://doi.org/10.1080/19490976.2022.2027852.
[68] C. Zar-Kessler, A. Karaa, K.B. Sims, V. Clarke, B. Kuo, Understanding the gastrointestinal manifestations of Fabry disease: promoting prompt diagnosis, Ther. Adv. Gastroenterol. 9 (4) (2016) 626–634, https://doi.org/10.1177/1756283X16642936.
[69] R. Baron, Mechanisms of disease: neuropathic pain–a clinical perspective, Nat. Clin. Pract. Neurol. 2 (2) (2006) 95–106, https://doi.org/10.1038/ncpneuro0113.
[70] M. Low, K. Nicholls, N. Tubridy, et al., Neurology of Fabry disease, Intern. Med. J. 37 (7) (2007) 436–447, https://doi.org/10.1111/j.1445–5994.2007.01366.x.
[71] J.M. Politei, D. Bouhassira, D.P. Germain, et al., Pain in Fabry disease: practical recommendations for diagnosis and treatment, CNS Neurosci. Ther. 22 (7) (2016) 568–576, https://doi.org/10.1111/cns.12542.
[72] J.E. Wraith, A. Tylki-Szymanska, N. Guffon, et al., Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease, J. Pediatr. 152 (4) (2008) 563–570, https://doi.org/10.1016/j.jpeds.2007.09.007 70 e1.
[73] L. Borgwardt, U. Feldt-Rasmussen, A.K. Rasmussen, M. Ballegaard, A. Meldgaard Lund, Fabry disease in children: agalsidase-beta enzyme replacement therapy, Clin. Genet. 83 (5) (2013) 432–438, https://doi.org/10.1111/j.1399-0004.2012.01947.x.
[74] M.J. Hilz, M. Brys, H. Marthol, B. Stemper, M. Dutsch, Enzyme replacement therapy improves function of C-, Adelta-, and Abeta-nerve fibers in Fabry neuropathy, Neurology 62 (7) (2004) 1066–1072, https://doi.org/10.1212/01.wnl.0000118207.84514.40.