Long-term follow-up of renal function in patients treated with migalastat for Fabry disease

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ABSTRACT

The effect of migalastat on long-term renal outcomes in enzyme replacement therapy (ERT)–naive and ERT-experienced patients with Fabry disease is not well defined. An integrated posthoc analysis of the phase 3 clinical trials and open-label extension studies was conducted to evaluate long-term changes in renal function in patients with Fabry disease and *amenable GLA* variants who were treated with migalastat for ≥2 years during these studies. The analysis included ERT-naive ($n = 36$ [23 females]; mean age 45 years; mean baseline estimated glomerular filtration rate (eGFR), 91.4 mL/min/mL/1.73 m^2) and ERT-experienced ($n = 42$ [24 females]; mean age, 50 years; mean baseline eGFR, 89.2 mL/min/1.73m^2) patients with amenable variants who received migalastat 123 mg every other day for ≥2 years. The annualized rate of change from baseline to last observation in estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR$_{CKD-EPI}$) was calculated by both simple linear regression and a random coefficient model. In ERT-naive patients, mean annualized rates of change from baseline in eGFR$_{CKD-EPI}$ were -1.6 mL/min/1.73 m^2 overall and -1.8 mL/min/1.73 m^2 and -1.4 mL/min/1.73 m^2 in male and female patients, respectively, as estimated by simple linear regression. In ERT-experienced patients, mean annualized rates of change from baseline in eGFR$_{CKD-EPI}$ were -1.6 mL/min/1.73 m^2 overall and -2.6 mL/min/1.73 m^2 and -0.8 mL/min/1.73 m^2 in male and female patients, respectively. Mean annualized rate of change in eGFR$_{CKD-EPI}$ in ERT-naive patients with the classic phenotype (defined by white blood cell alpha galactosidase A [α-Gal A] activity of <3% of normal and multiorgan system involvement) was -1.7 mL/min/1.73 m^2. When calculated using the random coefficient model, which adjusted for sex, age, and baseline renal function, the annualized eGFR$_{CKD-EPI}$ change was minimal (mean: -0.1 and 0.1 mL/min/1.73 m^2 in ERT-naive and ERT-experienced patients, respectively). In conclusion, patients with Fabry disease and amenable *GLA* variants receiving long-term migalastat treatment (≤8.6 years) maintained renal function irrespective of treatment status, sex, or phenotype.

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1. Introduction

Fabry disease is a rare, multisystemic disorder caused by pathogenic *GLA* gene variants that result in functional deficiency of lysosomal enzyme α-galactosidase A (α-Gal A) and accumulation of globo-triaosylceramide (Gb$_3$) throughout the body [1,2].

In the kidney, glycosphingolipids accumulate in multiple kidney cell types, such as podocytes, endothelial cells, and tubular epithelial cells, causing proteinuria and a decline in glomerular filtration rate (GFR) [3]. Furthermore, the accumulation of Gb$_3$ activates inflammatory and profibrotic processes that subsequently lead to glomerular injury [4,5].

Fabry disease is X-linked, and hemizygous males typically experience the most severe manifestations; however, heterozygous females can develop complications in major organs [1]. Renal manifestations are a significant cause of mortality and morbidity in Fabry disease [6,7], with renal disease being reported as the third most common cause of death after cardiac and cerebrovascular disease based on registry data [7]. Furthermore, decreased renal function and kidney failure have been associated with cardiovascular events and stroke, suggesting that renal and cardiac manifestations may be interrelated in Fabry disease [8,9].
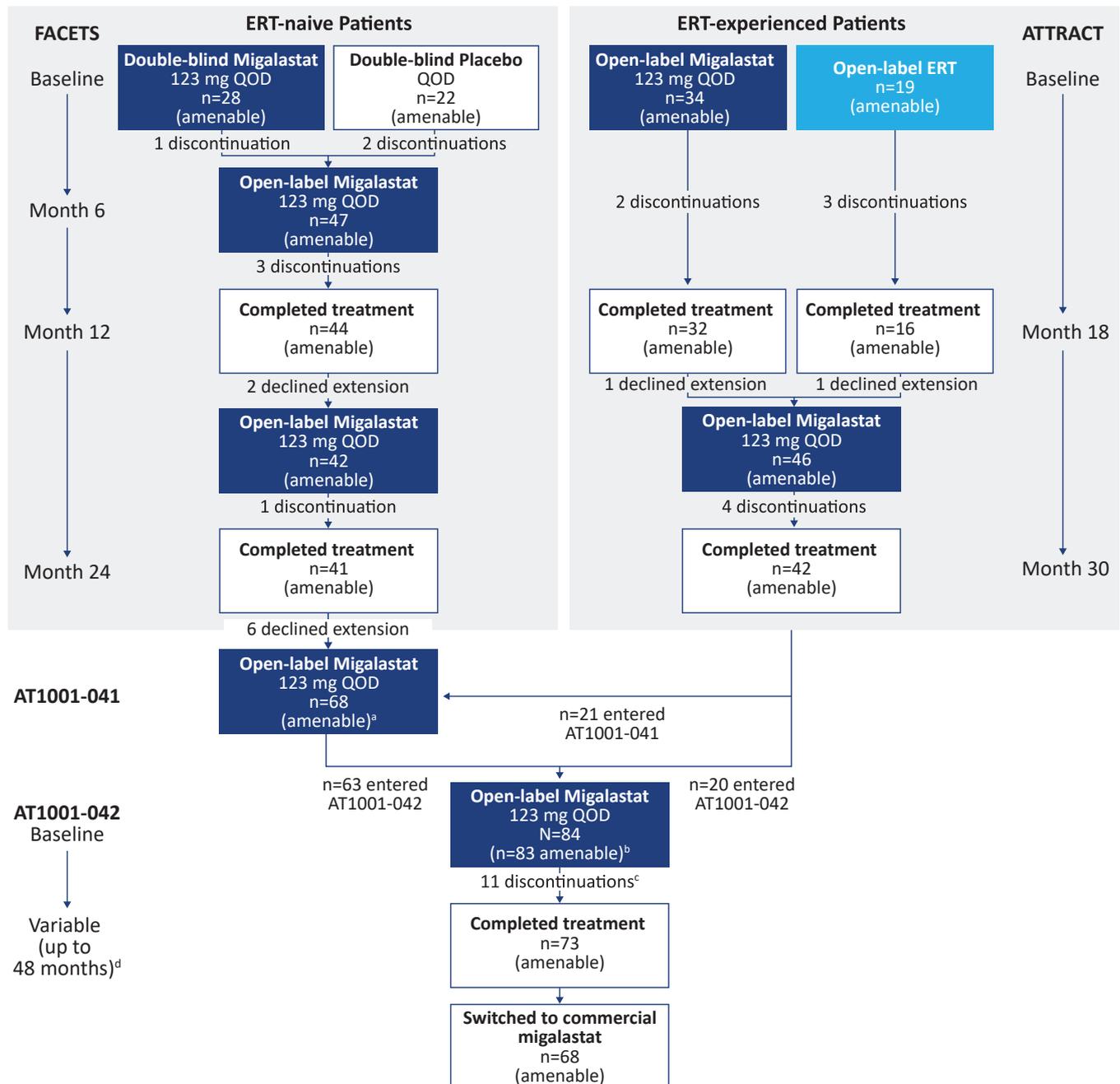
Fig. 1. Patient flow in phase 3 studies of migalastat.
[a]The AT1001–041 study also included 12 amenable patients from phase 2 studies.
[b]The AT1001–042 study also enrolled 1 patient from a phase 2 study, for a total of 84 patients, including 1 patient who had a nonamenable *GLA* variant.
[c]One patient discontinued due to an adverse event, 3 patients met protocol-defined stopping criteria (ie, estimated glomerular filtration rate < 30 mL/min/1.73 m^2), 1 patient was lost to follow-up, 4 patients discontinued per physician decision, and 2 patients chose to withdraw.
[d]Duration of the treatment varied among patients. Patients completed the study when they switched to commercial migalastat or had access to migalastat through an alternate source. ERT, enzyme replacement therapy; QOD, every other day.

Current treatments for Fabry disease include enzyme replacement therapy (ERT) with recombinant human α-Gal A and the oral pharmacological chaperone migalastat [10–12]. As a small molecule pharmacological chaperone, migalastat binds to and stabilizes *amenable* mutant forms of α-Gal A in the endoplasmic reticulum, facilitating trafficking of α-Gal A to lysosomes and restoring endogenous enzyme activity [13,14]. Migalastat 123 mg every other day is approved for the treatment of Fabry disease in adult patients in the United States and in patients aged ≥16 years in the European Union who have an amenable *GLA* variant.

In phase 3 clinical trials, migalastat demonstrated efficacy in reducing Gb_3 in diverse renal cell types and in stabilizing renal function [15–17]. ERT-naive patients demonstrated stable renal function for ≤2 years in the double-blind, placebo-controlled study FACETS, as calculated by simple linear regression [15]. In the open-label, active-controlled ATTRACT study, ERT-experienced patients who switched to migalastat experienced an annualized rate of change in GFR comparable to that of patients who continued ERT [16]. In ERT-naive patients, the mean annualized rate of change from baseline to month 24 was −0.3 mL/min/1.73 m^2 with migalastat [15]. In ERT-experienced patients, the mean annualized rate of change in estimated glomerular filtration rate (eGFR) from baseline to month 18 was −0.4 mL/min/1.73 m^2 after switching to migalastat and − 1.0 mL/min/1.73 m^2 in patients continuing ERT [16].

Studies are ongoing to evaluate long-term renal outcomes in ERT-naive and ERT-experienced patients treated with migalastat. Here, a post hoc analysis was conducted to evaluate long-term changes in renal function in 78 patients with Fabry disease and amenable *GLA* variants who were treated with migalastat for ≥2 years in the phase 3 FACETS and ATTRACT trials and long-term open-label extension (OLE) studies.

2. Materials and methods

2.1. Design

ERT-naive and ERT-experienced patients enrolled in the phase 3 FACETS (AT1001–011; NCT00925301) or ATTRACT (AT1001–012; NCT01218659) clinical trials received migalastat 123 mg every other day for ≥2 years; details of these studies have been described previously [15,16]. Patients completing FACETS or ATTRACT were also allowed to enter an additional OLE study of ≤5 years (AT1001–041 [NCT01458119] and/or AT1001–042 [NCT02194985]).

We performed a post hoc analysis in which data collected during FACETS, ATTRACT, and the subsequent 5-year OLE studies (AT1001–041 and/or AT1001–042) (Fig. 1) were integrated across studies. The data cutoff date for the ongoing AT1001–042 study was March 11, 2020.

2.2. Participants

Selection criteria for patients enrolled in the FACETS and ATTRACT studies have been previously published [15,16]. Briefly, patients were ERT-naive (FACETS; never received ERT or had not received ERT for ≥6 months) or ERT-experienced (ATTRACT; initiated ERT ≥ 12 months before study entry); aged 16–74 years; had genetically confirmed Fabry disease; and had *GLA* variants that met the amenability criteria. Patients had an eGFR of ≥30 mL/min/1.73 m^2 at enrollment, and those taking angiotensin-converting-enzyme inhibitors and/or angiotensin II receptor blockers had to be on a stable dose for ≥4 weeks before the screening visit [15,16]. This post hoc analysis included all patients who received migalastat for ≥2 years and had migalastat-amenable *GLA* variants based on results from the good laboratory practice-validated assay using human embryonic kidney 293 cells (GLP-HEK assay) [18].

2.3. Study endpoints and assessments

Serum creatinine values were used to calculate the estimated

glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR$_{CKD-EPI}$) [19]. eGFR$_{CKD-EPI}$ was determined at baseline and every 6 months through to the completion of each study, and annualized changes in eGFR$_{CKD-EPI}$ were calculated.

2.4. Statistical analyses

The annualized rate of change in eGFR$_{CKD-EPI}$ was calculated with two methods: by the slope of simple linear regression based on observed values and assessment times [15] and by a random coefficient model [20]. The simple linear regression was calculated individually for each patient using their longitudinal data. The random coefficient model comprised a mixed model that included eGFR as the dependent variable and study visit as a main effect, and the rate of eGFR decline was adjusted for the following baseline factors: sex, age, baseline eGFR$_{CKD-EPI}$, baseline proteinuria, and time from Fabry diagnosis. Random coefficients were used for the intercept and visit. The beginning of migalastat treatment was the baseline and corresponded to month 6 of FACETS for patients in the placebo arm and month 18 of ATTRACT for patients in the ERT arm. One model was fitted on all data which resulted in obtaining a slope for each patient adjusted for the covariates. Then the slopes were grouped by sex, baseline eGFR$_{CKD-EPI}$ (>30 to <60, 60–90, and > 90 mL/min/1.73 m^2), baseline urine protein (< 300, 300–1000, and > 1000 mg/24 h). For ERT-naive patients, the slope was also grouped by phenotype (male patients with the classic phenotype vs others). ERT-naive male patients were classified as having the classic phenotype if they had residual white blood cell α-Gal A activity of <3% of normal and multiorgan system involvement at baseline, defined as involvement of ≥2 of the following organ systems: renal, cardiac, central nervous system, peripheral nervous system, and gastrointestinal tract (Table A.1) [21]. The classification of "Other" included ERT-naive male patients who did not meet the above criteria and all ERT-naive female patients [21]. ERT-experienced male patients were not evaluated by phenotype because their baseline white blood cell α-Gal A activity may have been confounded by previous ERT. Instead, we analyzed a subset of ERT-experienced male patients who had multiorgan involvement at baseline.

Descriptive statistics including mean, standard deviation (SD), median, range, and percent of total were used for efficacy analyses.

2.5. Ethics

FACETS, ATTRACT, AT1001–041, and AT1001–042 were designed and monitored in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki. Clinical protocols for these studies were reviewed and approved by the appropriate Independent Ethics Committee/Institutional Review Board at each study site. All patients provided written informed consent prior to initiation of the study.

3. Results

3.1. Demographics and baseline characteristics of the integrated analysis population

Demographic characteristics of the 78 patients who had ≥2 years of migalastat treatment are shown in Table 1. Of these, 36 were ERT-naive (23 females), and 42 were ERT-experienced (24 females). The mean (SD) age of patients at treatment initiation was 45.1 (10.5) years in the ERT-naive group and 50.1 (13.8) years in the ERT-experienced group. The mean (SD) time since Fabry diagnosis was 7.4 (8.0) years in ERT-naive patients and 12.6 (12.4) years in ERT-experienced patients. Overall, 78% of patients had multiorgan involvement (81% of ERT-naive patients and 76% of ERT-experienced patients). In particular, male patients with the classic phenotype comprised 27.8% of the ERT-naive group and male patients with multiorgan involvement made up 35.7% of the ERT-

Table 1
Baseline characteristics.

Variable	Overall (N = 78)	ERT-naive patients			ERT-experienced patients (n = 42)	Males (n = 31)	Females (n = 47)
		All (n = 36)	Classic phenotype[a] (n = 10)	Other (n = 26)			
Age (years)							
Mean (SD)	47.8 (12.6)	45.1 (10.5)	45.6 (12.0)	44.9 (10.2)	50.1 (13.8)	48.7 (12.2)	47.2 (12.9)
Median (range)	48.0 (18–70)	45.5 (25–68)	45.0 (25–62)	46.0 (27–68)	53.5 (18–70)	48.0 (20–67)	48.0 (18–70)
Sex, n (%)							
Male	19 (24.4)	13 (36.1)	10 (100)	2 (11.5)	18 (42.9)	31 (100)	0
Female	59 (75.6)	23 (63.9)	0	23 (88.5)	24 (57.1)	0	47 (100%)
Race, n(%)							
White	70 (89.7)	34 (94.4)	9 (90.0)	25 (96.2)	36 (85.7)	27 (87.1)	43 (91.5)
Asian	5 (6.4)	0	0	0	5 (11.9)	3 (9.7)	2 (4.3)
Multiple	1 (1.3)	0	0	0	1 (2.4)	0	1 (2.1)
Other	2 (2.6)	2 (5.6)	1 (10.0)	1 (2.8)	0	1 (3.2)	1 (3.2)
eGFR$_{CKD-EPI}$ (mL/min/ 1.73 m^2)							
Mean (SD)	90.2 (21.0)	91.4 (22.4)	86.4 (27.5)	93.3 (20.4)	89.2 (19.9)	85.8 (22.1)	93.1 (19.9)
Median (range)	90.3 (41.4–131.3)	92.0 (41.4–125.6)	94.8 (41.4–119.0)	92.0 (44.6–125.6)	88.9 (51.4–131.3)	84.0 (41.4–131.3)	95.9 (44.6–125.6)
eGFR$_{CKD-EPI}$ category, n (%)							
>30–<60 mL/min/ 1.73 m^2	5 (6.4)	3 (8.3)	2 (20.0)	1 (3.8)	2 (4.8)	4 (12.9)	1 (2.1)
60–90 mL/min/1.73 m^2	33 (42.3)	14 (38.9)	3 (30.0)	11 (42.3)	19 (45.2)	15 (48.4)	18 (38.3)
>90 mL/min/1.73 m^2	40 (51.3)	19 (52.8)	5 (50.0)	14 (53.8)	21 (50.0)	12 (38.7)	28 (59.6)
Urinary protein, mg/24 h, n (%)							
<300 mg/24 h	54 (69.2)	22 (61.1)	4(40.0)	18 (69.2)	32 (76.2)	18 (58.1)	36 (76.6)
300–1000 mg/24 h	18 (23.1)	10 (27.8)	4 (40.0)	6 (23.1)	8 (19.0)	9 (29.0)	9 (19.1)
>1000 mg/24 h	6 (7.7)	4 (11.1)	2 (20.0)	2 (7.7)	2 (4.8)	4 (12.9)	2 (4.3)
Patients taking ACEI/ ARB/RI, n (%)	32 (41.0)	10 (27.8)	4 (40.0)	6 (23.1)	22 (52.4)	13 (41.9)	19 (40.4)
Time since diagnosis (years)							
Mean (SD)	10.2 (10.9)	7.4 (8.0)	6.5 (4.4)	7.8 (9.1)	12.6 (12.4)	7.9 (8.6)	11.8 (11.9)
Median (range)	5.5 (1.0, 44.0)	5.0 (1.0, 34.0)	6.0 (1–14)	5.0 (1–34)	6.0 (3.0, 44.0)	5.0 (1.0, 39.0)	6.0 (1.0, 44.0)
LVMi (g/m^2)							
Mean (SD)	95.7 (30.3)	99.2 (35.3)	120.5 (24.8)	89.9 (35.5)	92.9 (25.8)	116.4[b] (35.3)	82.4 (16.3)[b]
Median (range)	88.8 (47.7, 234.4)	88.8 (61.0, 234.4)	115.4 (89.6–176.2)	81.2 (61.0–234.4)	87.9 (47.7, 165.7)	109.4 (69.9, 234.4)	77.6 (47.7, 121.8)

α-Gal A, alpha galactosidase; ACEI, angiotension-converting enyzme inhibitor; ARB, angiotension II receptor blockers; eGFR$_{CKD-EPI}$, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT,enzyme replacement therapy; LVMi, left ventricular mass index; RI, renin inhibitor; SD, standard deviation.

[a] ERT-naive male patients who had residual white blood cell α-Gal A activity of <3% of normal and multiorgan system involvement, defined as involvement of ≥2 of the following organ systems: renal, cardiac, central nervous system, peripheral nerves, and gastrointestinal tract [21].

[b] LVMi data were not available for 2 male patients and 2 female patients.

experienced group. The median (range) migalastat treatment duration was 7.0 (2.0–8.6) years and 5.1 (2.1–7.2) years for ERT-naive and ERT-experienced patients, respectively.

3.2. Effects on renal function

During long-term follow-up, renal function was generally stable in both ERT-naive and ERT-experienced patients and in both male and female patients (Table 2). Using simple linear regression, the mean (SD) annualized rates of change in eGFR$_{CKD-EPI}$ were − 1.6 (3.1) mL/min/ 1.73 m^2 and − 1.6 (3.6) mL/min/1.73 m^2 in ERT-naive and ERT-experienced patients, respectively. eGFR$_{CKD-EPI}$ over time and annualized rate of change in eGFR$_{CKD-EPI}$ in individual patients are shown in Fig. 2 and Fig. A.1A, respectively. Using the random coefficient model, which adjusted for age, sex, baseline renal function, and time since Fabry diagnosis, the mean (SD) annualized rates of change in eGFR$_{CKD-EPI}$ were − 0.1 (1.8) mL/min/1.73 m^2 and 0.1 (1.7) mL/min/1.73 m^2 in ERT-naive and ERT-experienced patients, respectively. When patients were analyzed by sex, the mean annualized rates of change in eGFR$_{CKD-EPI}$ were − 0.5 mL/min/1.73 m^2 in (ERT-naive) and − 0.4 mL/min/1.73 m^2 in (ERT-experienced) in males, and 0.1 mL/min/1.73 m^2 in (ERT-naive) and 0.5 mL/min/1.73 m^2 (ERT-experienced) in females (Table A.2).

Table 2
Annualized rate of change in eGFR$_{CKD-EPI}$ in ERT-naive and ERT-experienced patients treated with migalastat for ≥2 years using simple linear regression.

	ERT-naive patients			ERT-experienced patients		
	Overall (n = 36)	Male (n = 13)	Female (n = 23)	Overall (n = 42)	Male (n = 18)	Female (n = 24)
Mean (SD)	−1.6 (3.1)	−1.8 (2.7)	−1.4 (3.3)	−1.6 (3.6)	−2.6 (4.8)	−0.8 (2.1)
Median (Q1, Q3)	−1.1 (−2.4, −0.6)	−1.0 (−3.8, −0.8)	−1.1 (−1.7, −0.6)	−1.3 (−2.2, −0.5)	−1.4 (−2.6, −0.7)	−1.1 (−2.1, −0.4)

eGFR$_{CKD-EPI}$, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT, enzyme replacement therapy; SD, standard deviation; Q1, quartile 1; Q3, quartile 3.

eGFR$_{CKD-EPI}$, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT, enzyme replacement therapy.

Annualized rates of change from baseline in eGFR$_{CKD-EPI}$ by baseline renal function are provided in Table 3 (simple linear regression) and
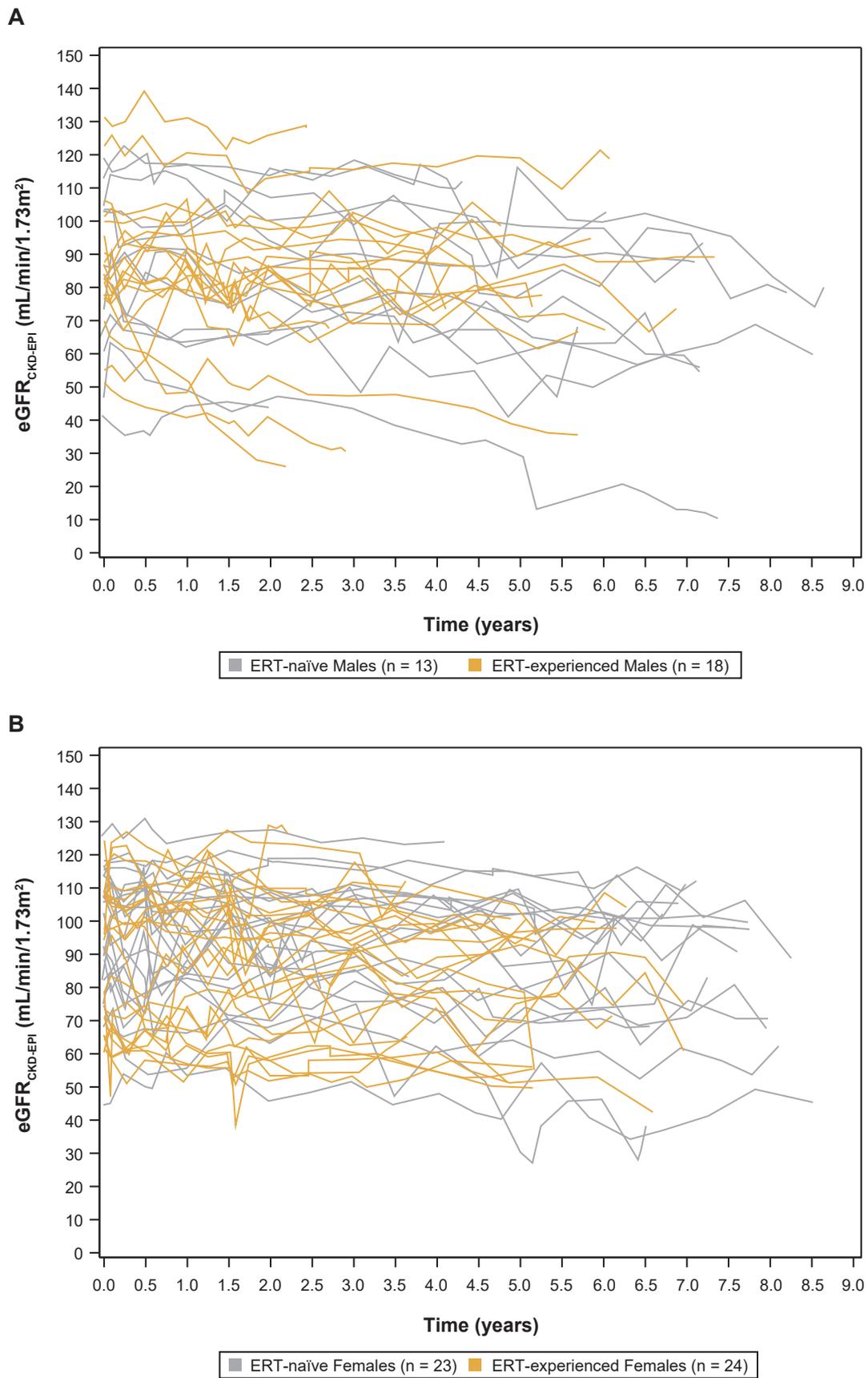
A

B

Fig. 2. Estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation over time in (A) male and (B) female patients receiving long-term migalastat treatment.

Table 3
Annualized rates of change in eGFR$_{CKD-EPI}$ in ERT-naive and ERT-experienced patients treated with migalastat for ≥ 2 years by baseline renal function using simple linear regression.

	ERT-naive patients $n = 36$			ERT-experienced patients $n = 42$		
Baseline eGFR$_{CKD-EPI}$, mL/min/1.73 m^2	>90 ($n = 19$)	60–90 ($n = 14$)	>30–<60 ($n = 3$)	>90 ($n = 21$)	60–90 ($n = 19$)	>30–<60 ($n = 2$)
Mean (SD)	−2.2 (2.9)	−0.81 (2.9)	−1.2 (5.1)	−1.2 (1.5)	−1.6 (5.0)	−4.7 (2.1)
Median (Q1, Q3)	−1.0	−1.1	−1.2	−1.3	−0.9	−4.7
	(−2.3, −0.7)	(−2.6, 0.1)	(−6.3, 4.0)	(−2.0, −0.8)	(−2.2, −0.2)	(−6.2, −3.2)
Baseline urinary protein, mg/24 h	<300 ($n = 22$)	300–1000 ($n = 10$)	>1000 ($n = 4$)	<300 ($n = 32$)	300–1000 ($n = 8$)	>1000 ($n = 2$)
Mean (SD)	−2.0 (3.0)	−0.1 (3.1)	−2.9 (2.6)	−0.8 (1.9)	−1.9 (0.8)	−13.3 (10.1)
Median (Q1, Q3)	−1.1 (−2.3, −0.7)	−0.8 (−1.7, 0.0)	−2.3 (−5.0, −0.8)	−1.0 (−1.7, −0.3)	−1.7 (−2.6, −1.3)	−13.3 (−20.5, −6.2)

eGFR$_{CKD-EPI}$, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT, enzyme replacement therapy; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

Table 4
Annualized rates of change in eGFR$_{CKD-EPI}$ in ERT-naive and ERT-experienced patients treated with migalastat for ≥ 2 years by disease characteristics using simple linear regression.

	ERT-naive		ERT-experienced	
	Classic phenotype[a]	Others	Multiorgan involvement[b]	Others
	($n = 10$)	($n = 26$)	($n = 15$)	($n = 27$)
Mean (SD)	−1.7 (3.0)	−1.5 (3.2)	−2.5 (5.1)	−1.1 (2.3)
Median (Q1, Q3)	−0.9 (−4.0, 0.1)	−1.1 (−2.3, −0.7)	−1.3 (−2.6, −0.4)	−1.3 (−2.2, −0.5)

α-Gal A, alpha galactosidase; eGFR$_{CKD-EPI}$, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT, enzyme replacement therapy; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

[a] ERT-naive male patients with the classic phenotype had residual white blood cell α-Gal A activity of <3% of normal and multiorgan involvement, defined as involvement of ≥ 2 of the following organ systems: renal, cardiac, central nervous system, peripheral nerves, and gastrointestinal tract [21].

[b] Baseline white blood cell α-Gal A activity in ERT-experienced patients was confounded by ERT and the same classic phenotype definition could not be applied. Instead, male patients with multiorgan involvement were compared with males without multiorgan involvement and females (specified above as "others").

Table A.3 (random coefficient model); Fig. A.1B shows individual patient data. We analyzed the influence of each covariate included in the analysis and found that baseline eGFR was significant in predicting further decline in renal function ($p < 0.0001$), followed by age ($p = 0.046$). Baseline urine protein was approaching statistical significance ($p = 0.059$). Other covariates were not significant.

Annualized change in eGFR$_{CKD-EPI}$ up to 24 months has been reported for 16 male patients with the classic phenotype in FACETS [21]. Among them, 10 patients had received migalastat for ≥ 2 years and were included in the current post hoc analysis. The mean (SD) annualized rates of change in eGFR$_{CKD-EPI}$ were − 1.7 (3.0) mL/min/1.73 m^2 in this subset of male patients with the classic phenotype and − 1.5 (3.2) mL/min/1.73 m^2 in other patients in FACETS (simple regression) during long-term follow-up (Table 4). Using the random coefficient model, the mean (SD) annualized rates of change in eGFR$_{CKD-EPI}$ were − 0.5 (2.1) mL/min/1.73 m^2 in ERT-naive males with the classic phenotype and 0.0 (1.7) mL/min/1.73 m^2 in other patients in FACETS, respectively (Table A.4). Annualized rate of change in eGFR$_{CKD-EPI}$ in male patients with multiorgan involvement versus others have been similarly analyzed for ERT-experienced patients (Table A4 and Table A.4) The genotype, phenotype, and annualized rate of change in eGFR$_{CKD-EPI}$ of individual patients are presented in Table A.5. Multiorgan involvement for patients is listed in Table A.6. Individual eGFR$_{CKD-EPI}$ slopes are plotted against patient age in Fig. A.2.

4. Discussion

This post hoc analysis assessed long-term renal measures associated with migalastat therapy in ERT-naive and ERT-experienced patients with Fabry disease and amenable *GLA* variants. With either the random coefficient model or simple linear regression, ERT-naive and ERT-experienced patients who received migalastat treatment for ≥ 2 and $\leq$ 8.6 years in the current study had a rate of eGFR decline that was slower than that in untreated historical cohorts [22,23] and similar to the normal rate of decline with age [24]. Renal function was also generally stable in patients receiving long-term migalastat treatment irrespective of treatment status, sex, or phenotype.

Although linear regression models have often been used to estimate rates of change in eGFR over time, this statistical method fails to consider the correlation among repeated measurements in the same patient. A subject-specfic mixed model with random intercepts and slopes for each patient may be more suitable to the heterogeneous nature of Fabry disease and has been used to describe the natural history of Fabry nephropathy [22], which showed that untreated males and females (mean age 41 years at baseline) with a baseline eGFR$_{MDRD}$ of ≥ 60 mL/min/1.73 m^2 experienced an annual loss in eGFR of −3.0 mL/min/ 1.73 m^2 and − 0.9 mL/min/1.73 m^2, respectively; males and females with chronic kidney disease at baseline experienced an annual loss in eGFR of −6.8 mL/min/1.73 m^2 and − 2.1 mL/min/1.73 m^2, respectively [22]. Using a similar model, we found that eGFR$_{CKD-EPI}$ remained stable during median follow-ups of 7 years and 5 years in ERT-naive and ERT-experienced patients, respectively (mean annualized rate of change was −0.1 mL/min/1.73 m^2 and 0.1 mL/min/1.73 m^2, respectively).

A range of mean eGFR declines has been reported for ERT using different statistical methods [25–28]. In a 5-year follow-up of adult patients treated with agalsidase alfa or agalsidase beta, the mean annualized rates of change in eGFR were approximately −3 mL/min/ 1.73 m^2 in males (mean age 38.9 years, mean baseline eGFR 88.5 mL/ min/1.73 m^2) and approximately −0.9 mL/min/1.73 m^2 in females (mean age 46.8 years, mean eGFR 86.6 mL/min/1.73 m^2) using a random coefficient model [25]. In another long-term study of patients (median age 33 years) receiving agalsidase alfa or agalsidase beta for a median of 7 years, the mean annualized rates of change in eGFR were − 1.8 mL/min/1.73 m^2 and − 0.01 mL/min/1.73 m^2 in males (mean baseline eGFR 121 mL/min/1.73 m^2) and females (mean baseline eGFR 98 mL/min/1.73 m^2), respectively, using a linear mixed model [29]. These rates of eGFR decline during ERT are generally similar to or greater than those reported here for migalastat.

It is known that baseline clinical status plays a critical role in renal outcomes with treatment [25–27]. In long-term studies, ERT did not stabilize renal function in patients with severe renal involvement (ie, proteinuria >1 g/24 h or eGFR <60 mL/min/1.73 m^2, or urinary protein:creatinine ratio ≥ 1 g/g) [30–32]. In our study, renal outcomes were similar across baseline renal function groups in ERT-naive patients with the random coefficient model that adjusted for baseline factors. Unsurprisingly, with the simple linear regression method, larger annualized rates of change in eGFR were observed in ERT-experienced patients with low eGFR (> 30 to <60 mL/min/1.73 m^2) or high urine protein (> 1000 mg/24 h) at baseline in the current study compared with other analyzed subgroups. However, our results are severely limited by the small sample sizes of these 2 patient subgroups ($n = 2$ each). Results were also distorted by one patient with an eGFR decline of >20 mL/min/1.73 m^2; however, it is likely that this patient had irreversible nephropathy prior to migalastat initiation. as evidenced by the large decline in renal function that also occurred during ERT treatment.

Long-term data are especially important when assessing annualized change in eGFR. A recent Delphi consensus has recommended at least 2 years of data for reliable eGFR analyses [33], and the current analysis provides data on patients who were treated with migalastat for at least 2 years (median exposure 5.9 years). Published real-world evidence can also be helpful in guiding treatment decisions. A recent 24-month real-world cohort publication from Lenders et al. in Germany provided further evidence of LVMi reduction in migalastat-treated patients with Fabry disease (primary outcome), especially in those with left ventricualr hypertrophy at baseline [34]. That publication also examined annualized eGFR slopes over 24 months and found antihypertensive medication use was associated with greater annualized eGFR decline over time, and the authors posited that either this may have been causative of the larger decline in eGFR, or that these patients were more severely affected at baseline. When excluding the patients on inhibitors of angiotensin-converting enzyme, angiotensin II receptor 1, or aldosterone, eGFR was found to be stable over 24 months in migalastat-treated patients (mean change over 24 months: -3.0 ± 10.9 mL/min/1.73 m^2; $p = 0.4346$). These findings support the thinking that patient management decisions should be made holistically, and that treatment before irreversible damage has occurred may be beneficial.

The current study also extends findings from a previous analysis of male patients with the classic phenotype in the FACETS study [21], which reported a mean annualized rate of change in eGFR$_{CKD-EPI}$ of -0.3 mL/min/1.73 m^2 over 2 years. The current study shows that renal function remained stable in ERT-naive male patients with the classic phenotype for ≤8.6 years (median exposure: 6.6 years), supporting long-term efficacy in this patient population. In comparison, male patients with the classic phenotype (mean age 31 years, median baseline eGFR ~120 mL/min/1.73 m^2) who received agalsidase beta for 54 months had an eGFR decline of -2.2 mL/min/1.73 m^2, as estimated by a random coefficient model [21,30]. The current study also included male patients with the classic phenotype who had relatively high eGFR values at baseline (mean [SD]: 88.5 [22.5] mL/min/1.73 m^2). Interestingly, one patient with the classic phenotype in our study had a *GLA* variant associated with the late-onset phenotype (p.I253T) according to the International Fabry Disease Genotype-Phenotype Database, which consolidates data in the literature as well as available biochemical data to set a reasonable expectation of phenotypic severity [35], This supports the thinking that that genotype-phenotype correlation is complex and that environmental factors and genetic modifiers may be at work. This observation highlights the importance of evaluating each patient holistically, and of making individualized treatment decisions that account for the multiple organ systems affected by Fabry disease. It also highlights the fact that the GLP-HEK amenability assay should be used only to determine a patient's eligibility for treatment with migalastat and that the assay is not prognostic of clinical outcomes or disease course. Finally, some patients with the same variant had different severity of disease at study baseline, possibly related to entering the study at different stages during the progressive disease course [1], which highlights the importance of multisystemic monitoring and early treatment initiation when managing this disease.

There is a growing consensus that treatment should be initiated early to limit or prevent irreversible organ damage and improve treatment outcomes in patients with Fabry disease [31,37,38]. In this study, we defined the classic phenotype as multiorgan system involvement at baseline, and < 3% enzyme activity for male patients (ERT-naive only). We used this phenotypic definition in accordance with the definition used in the FACETS trial [15,21] in order to analyze patients with clinically advanced Fabry disease at study start. Fabry disease phenotypes and rates of disease progression are highly variable, even within families with the same variant [39]. A binary definition of "classic" versus "other" does not capture the true complexity of Fabry disease. We posit that Fabry disease is a continuum, dependent upon many factors, including genetic, epigenetic, environmental, and lifestyle, and that such binary classifications should be considered as only one factor in terms of guiding treatment decisions. Biopsy studies suggest that podocyte injury occurs in early childhood, progresses with increasing age, and may act as an early marker for renal damage in Fabry disease [40–42]. Therefore, treatment before substantial renal damage occurs is imperative because renal function may not be restored when podocyte loss and damage to glomeruli have occurred [43,44]. There is also evidence of a strong correlation between proteinuria and renal disease progression in patients with Fabry disease [45]. Therefore, stabilizing or slowing the decline in renal function requires strategies that control proteinuria (ie, angiotensin-converting-enzyme inhibitors and/or angiotensin II receptor blockers) [46].Furthermore, inflammatory processes in podocytes have been linked to Fabry nephropathy, suggesting inflammatory pathways could potentially be therapeutic targets in Fabry disease [4]. Further studies are needed to investigate the impact of current therapies, including migalastat, on these pathophysiological processes in renal tissues and optimal time for treatment initiation.

Limitations of this study that should be considered when interpreting the results include its post hoc design, small sample sizes in some subgroups, and the lack of statistical comparisons with untreated or ERT-treated historical cohorts. Assessment of renal function using eGFR may also be a limitation, given that eGFR has been associated with pseudo-hyperfiltration in some patients with Fabry disease [36]. In addition, the heterogeneity of statistical methods used to estimate eGFR slopes in the literature limited direct comparisons.

In summary, the results of this post hoc analysis suggest that patients with Fabry disease and amenable *GLA* variants had stable renal function during long-term migalastat treatment (≤8.6 years) irrespective of treatment status, sex or phenotype. Early treatment should be encouraged to stabilize or slow the decline in renal function in patients with Fabry disease.

Data availability statement

All relevant data, including deidentified participant data, are contained in this manuscript and its supplemental materials.

Author contributions

D.G.B., R.T., D.H., R.G., N.S., U.F.R. and K.N. contributed to conceptualization; D.H., N.S., U.F.R. and K.N., participated in data curation; R.T., D.H., R.G., N.S., U.F.R. and K.N. participated in investigation; R.T., R.G., N.S., E.K., U.F.R. and K.N. contributed to methodology; D.G.B. and D.H. participated in supervision; R.T. and D.H. contributed to validation; R.T. and E.W. contributed to visualization; N.S. and E.K. analyzed and interpreted the data; R.T. participated in writing the original draft; D.G.B., R.T., E.W., D.H., R.G., N.S., E.K., U.F.R., R.S. and K.N. participated in reviewing and editing the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2021.100786.

References

[1] D.P. Germain, Fabry disease, Orphanet J. Rare Dis. 5 (2010) 30.

[2] R.J. Desnick, Y. Ioannou, C.M. Eng, a-Galactosidase a deficiency: Fabry disease, in: D. Valle (Ed.), The Online Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill Companies, Inc., 2016.

[3] J. Alroy, S. Sabnis, J.B. Kopp, Renal pathology in Fabry disease, J. Am. Soc. Nephrol. 13 (Suppl. 2) (2002) S134–S138.

[4] M.D. Sanchez-Nino, A.B. Sanz, S. Carrasco, M.A. Saleem, P.W. Mathieson, J. M. Valdivielso, et al., Globotriaosylsphingosine actions on human glomerular podocytes: implications for Fabry nephropathy, Nephrol. Dial. Transplant. 26 (2011) 1797–1802.

[5] P.A. Rozenfeld, M. de Los Angeles Bolla, P. Quieto, A. Pisani, S. Feriozzi, P. Neuman, et al., Pathogenesis of Fabry nephropathy: the pathways leading to fibrosis, Mol. Genet. Metab. 129 (2020) 132–141.

[6] A. Mehta, J.T. Clarke, R. Giugliani, P. Elliott, A. Linhart, M. Beck, et al., Natural course of Fabry disease: changing pattern of causes of death in FOS - Fabry Outcome Survey, J. Med. Genet. 46 (2009) 548–552.

[7] 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 (2009) 790–796.

[8] A. Ortiz, B. Cianciaruso, M. Cizmarik, D.P. Germain, R. Mignani, J.P. Oliveira, et al., End-stage renal disease in patients with Fabry disease: natural history data from the Fabry registry, Nephrol. Dial. Transplant. 25 (2010) 769–775.

[9] A.S. Go, G.M. Chertow, D. Fan, C.E. McCulloch, C.Y. Hsu, Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization, N. Engl. J. Med. 351 (2004) 1296–1305.

[10] Fabrazyme (Agalsidese Beta) Injection, Powder, lyophilized for Solution for Intravenous Use. Prescribing Information, Genzyme Corporation, 2010.

[11] Replagal 1 mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics, Shire Pharmaceuticals Limited, 2016.

[12] Galafold (migalastat) capsules, for oral use. Prescribing information, Amicus Therapeutics Inc., 2019.

[13] G.H. Yam, C. Zuber, J. Roth, A synthetic chaperone corrects the trafficking defect and disease phenotype in a protein misfolding disorder, FASEB J. 19 (2005) 12–18.

[14] S. Ishii, H.H. Chang, K. Kawasaki, K. Yasuda, H.L. Wu, S.C. Garman, et al., Mutant alpha-galactosidase a enzymes identified in Fabry disease patients with residual enzyme activity: biochemical characterization and restoration of normal intracellular processing by 1-deoxygalactonojirimycin, Biochem. J. 406 (2007) 285–295.

[15] D.P. Germain, D.A. Hughes, K. Nicholls, D.G. Bichet, R. Giugliani, W.R. Wilcox, et al., Treatment of Fabry's disease with the pharmacologic chaperone migalastat, N. Engl. J. Med. 375 (2016) 545–555.

[16] D.A. Hughes, K. Nicholls, S.P. Shankar, G. Sunder-Plassmann, D. Koeller, K. Nedd, et al., Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study, J. Med. Genet. 54 (2017) 288–296.

[17] M. Mauer, A. Sokolovskiy, J.A. Barth, J.P. Castelli, H.N. Williams, E.R. Benjamin, et al., Reduction of podocyte globotriaosylceramide content in adult male patients with Fabry disease with amenable GLA mutations following 6 months of migalastat treatment, J. Med. Genet. 54 (2017) 781–786.

[18] E.R. Benjamin, M.C. Della Valle, X. Wu, E. Katz, F. Pruthi, S. Bond, et al., The validation of pharmacogenetics for the identification of Fabry patients to be treated with migalastat, Genet. Med. 19 (2017) 430–438.

[19] A.S. Levey, L.A. Stevens, C.H. Schmid, Y.L. Zhang, A.F. Castro III, H.I. Feldman, et al., A new equation to estimate glomerular filtration rate, Ann. Intern. Med. 150 (2009) 604–612.

[20] L.M. Sullivan, K.A. Dukes, E. Losina, Tutorial in biostatistics. An introduction to hierarchical linear modelling, Stat. Med. 18 (1999) 855–888.

[21] D.P. Germain, K. Nicholls, R. Giugliani, D.G. Bichet, D.A. Hughes, L.M. Barisoni, et al., Efficacy of the pharmacologic chaperone migalastat in a subset of male patients with the classic phenotype of Fabry disease and migalastat-amenable variants: data from the phase 3 randomized, multicenter, double-blind clinical trial and extension study, Genet. Med. 21 (2019) 1987–1997.

[22] R. Schiffmann, D.G. Warnock, M. Banikazemi, J. Bultas, G.E. Linthorst, S. Packman, et al., Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy, Nephrol. Dial. Transplant. 24 (2009) 2102–2111.

[23] M. Branton, R. Schiffmann, J.B. Kopp, Natural history and treatment of renal involvement in Fabry disease, J. Am. Soc. Nephrol. 13 (Suppl. 2) (2002) S139–S143.

[24] M. Baba, T. Shimbo, M. Horio, M. Ando, Y. Yasuda, Y. Komatsu, et al., Longitudinal study of the decline in renal function in healthy subjects, PLoS One 10 (2015), e0129036.

[25] S.M. Rombach, B.E. Smid, M.G. Bouwman, G.E. Linthorst, M.G. Dijkgraaf, C. E. Hollak, Long term enzyme replacement therapy for Fabry disease: effectiveness on kidney, heart and brain, Orphanet J. Rare Dis. 8 (2013) 47.

[26] A. Mehta, M. Beck, P. Elliott, R. Giugliani, A. Linhart, G. Sunder-Plassmann, et al., Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data, Lancet. 374 (2009) 1986–1996.

[27] M. Beck, D. Hughes, C. Kampmann, S. Larroque, A. Mehta, G. Pintos-Morell, et al., Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: a Fabry outcome survey analysis, Mol. Genet. Metab. Rep. 3 (2015) 21–27.

[28] D.P. Germain, J. Charrow, R.J. Desnick, N. Guffon, J. Kempf, R.H. Lachmann, et al., Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease, J. Med. Genet. 52 (2015) 353–358.

[29] C.V. Madsen, H. Granqvist, J.H. Petersen, A.K. Rasmussen, A.M. Lund, P. Oturai, et al., Age-related renal function decline in Fabry disease patients on enzyme replacement therapy: a longitudinal cohort study, Nephrol. Dial. Transplant. 34 (2018) 1525–1533.

[30] D.P. Germain, S. Waldek, M. Banikazemi, D.A. Bushinsky, J. Charrow, R.J. Desnick, et al., Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease, J. Am. Soc. Nephrol. 18 (2007) 1547–1557.

[31] D.G. Warnock, A. Ortiz, M. Mauer, G.E. Linthorst, J.P. Oliveira, A.L. Serra, et al., Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation, Nephrol. Dial. Transplant. 27 (2012) 1042–1049.

[32] M. Banikazemi, J. Bultas, S. Waldek, W.R. Wilcox, C.B. Whitley, M. McDonald, et al., Agalsidase-beta therapy for advanced Fabry disease: a randomized trial, Ann. Intern. Med. 146 (2007) 77–86.

[33] D. Moreno-Martinez, P. Aguiar, C. Auray-Blais, M. Beck, D.G. Bichet, A. Burlina, et al., Standardising clinical outcomes measures for adult clinical trials in Fabry disease: a global Delphi consensus, Mol. Genet. Metab. 132 (2021) 234–243.

[34] M. Lenders, P. Nordbeck, C. Kurschat, M. Eveslage, N. Karabul, J. Kaufeld, et al., Treatment of Fabry disease with migalastat-outcome from a prospective 24 months observational multicenter study (FAMOUS), Eur. Heart J. Cardiovasc. Pharmacother (2021), https://doi.org/10.1093/ehjcvp/pvab025.

[35] I.S.o.M.a.M. Sinai, International Fabry Disease Genotype-Phenotype Database (dbFGP), Icahn School of Medicine at Mount Sinai, New York, NY, 2016. Updated 2016, http://dbfgp.org/dbFgp/fabry/Mutation.html.

[36] E. Riccio, M. Sabbatini, D. Bruzzese, L. Annicchiarico Petruzzelli, A. Pellegrino, L. Spinelli, et al., Glomerular hyperfiltration: an early marker of nephropathy in Fabry disease, Nephron. 141 (2019) 10–17.

[37] R.J. Hopkin, J.L. Jefferies, D.A. Laney, V.H. Lawson, M. Mauer, M.R. Taylor, et al., The management and treatment of children with Fabry disease: a United States-based perspective, Mol. Genet. Metab. 117 (2016) 104–113.

[38] M. Biegstraaten, R. Arngrimsson, F. Barbey, L. Boks, F. Cecchi, P.B. Deegan, et al., Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry working group consensus document, Orphanet J. Rare Dis. 10 (2015) 36.

[39] M. Rigoldi, D. Concolino, A. Morrone, F. Pieruzzi, R. Ravaglia, F. Furlan, et al., Intrafamilial phenotypic variability in four families with Anderson-Fabry disease, Clin. Genet. 86 (2014) 258–263.

[40] M. Liern, A. Collazo, M. Valencia, A. Fainboin, L. Isse, C. Costales-Collaguazo, et al., Podocyturia in paediatric patients with Fabry disease, Nefrologia. 39 (2019) 177–183.

[41] C. Tondel, T. Kanai, K.K. Larsen, S. Ito, J.M. Politei, D.G. Warnock, et al., Foot process effacement is an early marker of nephropathy in young classic Fabry patients without albuminuria, Nephron. 129 (2015) 16–21.

[42] B. Najafian, E. Svarstad, L. Bostad, M.C. Gubler, C. Tondel, C. Whitley, et al., Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease, Kidney Int. 79 (2011) 663–670.

[43] W.R. Wilcox, M. Banikazemi, N. Guffon, S. Waldek, P. Lee, G.E. Linthorst, et al., Long-term safety and efficacy of enzyme replacement therapy for Fabry disease, Am. J. Hum. Genet. 75 (2004) 65–74.

[44] B. Najafian, C. Tøndel, E. Svarstad, M.C. Gubler, J.P. Oliveira, M. Mauer, Accumulation of Globotriaosylceramide in podocytes in Fabry nephropathy is associated with progressive podocyte loss, J. Am. Soc. Nephrol. 31 (2020) 865–875.

[45] C. Wanner, J.P. Oliveira, A. Ortiz, M. Mauer, D.P. Germain, G.E. Linthorst, 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 (2010) 2220–2228.

[46] A. Ortiz, J.P. Oliveira, C. Wanner, B.M. Brenner, S. Waldek, D.G. Warnock, Recommendations and guidelines for the diagnosis and treatment of Fabry nephropathy in adults, Nat. Clin. Pract. Nephrol. 4 (2008) 327–336.