Agalsidase Alfa Slows the Decline in Renal Function in Patients with Fabry Disease

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Key Words

Agalsidase alfa • Enzyme replacement therapy •
Fabry disease • Glomerular filtration rate • Renal function

Abstract

The aim of this study was to determine the effects of enzyme replacement therapy with agalsidase α on renal function in patients with Fabry nephropathy. Serum creatinine data were collected from 165 adult patients during 3 years of treatment. Serum creatinine increased in all men whereas it was stable in women, except in stage II renal disease (Kidney Disease Outcomes Quality Initiative). The estimated glomerular filtration rate (eGFR) declined in males with stage I and II (from 115.0 ± 22.2 to 98.3 ± 27.3 and from 76.5 ± 8.1 to 66.3 ± 21.6 ml/min/1.73 m², respectively; both $p < 0.01$), whereas eGFR was stable in stage III. In females, eGFR was stable in stages I and III, and decreased in stage II (from 72.5 ± 8.3 to 67.3 ± 13.6 ml/min/1.73 m²; $p = 0.01$). The 24-hour proteinuria was <1 g in all patients, and most patients (96%) were treated with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors. Agalsidase α in combination with ACE inhibitors/ARB may be effective in slowing the deterioration in renal function in Fabry nephropathy.

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Introduction

Fabry disease is an X-linked lysosomal storage disorder caused by complete or partial deficiency in the enzyme α -galactosidase A, which results in accumulation of globotriaosylceramide (Gb₃) within lysosomes in the cells of many tissues, including the kidneys [1]. Renal manifestations (proteinuria and progressive renal impairment) occur relatively early in the course of Fabry disease and, in many patients, progress to renal failure [2].

The disease tends to be more severe and to progress more rapidly in males than in females, with renal failure occurring at approximately 40 years of age in men; however, significant numbers of heterozygous females also have a poor renal prognosis [3].

Enzyme replacement therapy (ERT) has been available since 2001. Studies with agalsidase α and β have shown that ERT may significantly slow the rate of renal dysfunction [4, 5]. ERT was associated with the clearance of microvascular endothelial deposits of Gb₃ from the kidneys, heart and skin of patients with Fabry disease and with an improvement in both histological lesions and renal function.

Interpretation of the available data, however, is limited due to the small number of patients, disease heterogene-

ity and the short duration of initial studies [6]. With regard to renal function, it is important to establish the effect of ERT in relation to the degree of existing renal impairment and the role of concomitant medication. There are also outstanding questions concerning the dosage of ERT and the time of treatment initiation, particularly in pediatric patients and in females with no, or only mild, features of Fabry disease [7].

To be able to study a larger number of patients clinically, the Fabry Outcome Survey (FOS) was initiated in 2001 to monitor the long-term effects and the safety of ERT with agalsidase α [8].

The aim of the present study was to determine the effect of 3 years of ERT with agalsidase α on renal function in a large cohort of patients enrolled in FOS.

Patients and Methods

FOS is a worldwide database of patients with Fabry disease who are receiving, or are candidates for, ERT with agalsidase α (Replagal[®]; Shire Human Genetic Therapies, Cambridge, Mass., USA). The database and criteria for inclusion have been described elsewhere [8].

Data from adult FOS patients (>18 years of age) with renal assessments (serum creatinine) at the start of ERT and throughout the 3-year treatment were analyzed. Patients with a renal transplant or on dialysis were excluded. Measurements of serum creatinine recorded in FOS were adjusted according to the Jaffe non-compensated detection method [9]. Creatinine values were used to estimate the glomerular filtration rate (GFR) according to the Modification of Diet in Renal Disease (MDRD) formula [10]. Measurements of serum creatinine and estimated GFR (eGFR) were reported at baseline and after 3 years of ERT for all patients. The increase in serum creatinine and the decrease in eGFR were calculated from the differences between the mean values at baseline and at the follow-up visit at ≥ 3 years of ERT. The rate of reduction of eGFR per year was also calculated.

In all patients, 24-hour urinary protein excretion was assessed at baseline and annually. Values >2 g/24 h were considered as missing values. In addition, all data regarding blood pressure and antihypertensive therapy during the study were collected. Blood pressure was recorded at each clinic visit every 6 months. Due to the global nature of FOS, arterial hypertension was defined by individual physicians according to national and local guidelines, generally a blood pressure $>130/90$ mm Hg.

At the time of data collection for this analysis, there were details on 1,356 patients in FOS: 848 were treated with agalsidase α , and 733 of them were adults at treatment initiation. Of these adults, 238 received ERT for at least 36 months. A further 29 patients were excluded as they had end-stage renal disease. The number of patients eligible for the study was 165 (115 men and 50 women). Each patient received 40-min infusions of agalsidase α at a dose of 0.2 mg/kg every 2 weeks.

To analyze the effects of ERT, patients were subdivided according to sex and baseline renal function: stage I represents a

Table 1. Arterial hypertension in male and female patients with Fabry disease at varying stages of renal disease

Stage of renal disease	Patients n	Mean age at baseline, years	Patients with arterial hypertension, n
Men			
Stage I	66	30 $\pm$ 8	6
Stage II	32	40 $\pm$ 10	9
Stage III	17	42 $\pm$ 7	5
Total	115	37 $\pm$ 8	20
Women			
Stage I	6	43 $\pm$ 13	0
Stage II	34	46 $\pm$ 14	6
Stage III	10	60 $\pm$ 9	5
Total	50	50 $\pm$ 12	11

Stage I: eGFR ≥ 90 ml/min/1.73 m²; stage II: eGFR 60–89 ml/min/1.73 m²; stage III, eGFR ≤ 59 ml/min/1.73 m².

normal GFR (>90 ml/min/1.73 m²), stage II represents mild renal failure (GFR 60–89 ml/min/1.73 m²) and stage III represents moderate/severe renal failure (GFR ≤ 59 ml/min/1.73 m²).

All patients gave written informed consent for data collection and analysis. Ethical approval was obtained from each patient's local health institution.

Data are reported as means $\pm$ SD. Statistical analyses were carried out using the paired Student's *t* test or the Wilcoxon's signed rank test, as appropriate. A *p* value ≤ 0.05 was considered significant.

Results

Mean age at baseline was 37.3 years (range, 18.4–68.0 years) for men and 49.6 years (18.4–70.9 years) for women (table 1).

There was a small but statistically significant increase in serum creatinine in men at each stage of kidney disease, and for the male group as a whole (+0.23 mg/dl; *p* < 0.01; table 2a). In women, the increase in serum creatinine was significant only in those with stage II disease (+0.07 mg/dl; *p* = 0.02); however, the increase was significant for the female group as a whole (0.08 mg/dl; *p* < 0.01). Overall, 29 (17.6%) patients had a $\geq 33\%$ increase in serum creatinine. The increase in serum creatinine was significant in the subgroup of patients with hypertension at baseline and in those with no hypertension: patients with hypertension had slightly higher serum creatinine levels at baseline and after treatment than those with no hypertension. The increase in serum creatinine in hypertensive patients was greater in patients using angiotensin

Table 2. Change in serum creatinine at baseline and after 3 years of ERT with agalsidase α in patients with Fabry disease

a Listed by gender and presence/absence of hypertension

Stage of renal disease	Serum creatinine, mg/dl		Mean change in serum creatinine mg/dl	p value	Increase $\geq 33\%$, %	n
	baseline	after 3 years of ERT				
Men						
Stage I	0.86 $\pm$ 0.12	1.00 $\pm$ 0.27	+0.14	<0.01	15.2	
Stage II	1.15 $\pm$ 0.11	1.42 $\pm$ 0.60	+0.28	<0.01	25.0	
Stage III	1.67 $\pm$ 0.25	2.14 $\pm$ 0.99	+0.47	0.04	29.4	
Total	1.06 $\pm$ 0.32	1.28 $\pm$ 0.66	+0.23	<0.01	20.0	
Women						
Stage I	0.67 $\pm$ 0.05	0.72 $\pm$ 0.13	+0.04	0.50	16.7	
Stage II	0.91 $\pm$ 0.09	0.98 $\pm$ 0.19	+0.07	0.02	8.8	
Stage III	1.22 $\pm$ 0.24	1.35 $\pm$ 0.46	+0.13	0.16	20.0	
Total	0.94 $\pm$ 0.21	1.02 $\pm$ 0.31	+0.08	<0.01	12.0	
Hypertension at baseline (n = 31)						
Stage I	0.92 $\pm$ 0.12	1.40 $\pm$ 0.53	+0.48	0.08		6
Stage II	1.02 $\pm$ 0.17	1.24 $\pm$ 0.34	+0.22	<0.01		14
Stage III	1.40 $\pm$ 0.25	1.53 $\pm$ 0.41	+0.13	0.28		11
Total	1.13 $\pm$ 0.28	1.37 $\pm$ 0.42	+0.24	<0.01		
No hypertension at baseline (n = 134)						
Stage I	0.84 $\pm$ 0.13	0.93 $\pm$ 0.20	+0.10	<0.01		66
Stage II	1.03 $\pm$ 0.16	1.18 $\pm$ 0.53	+0.16	0.02		52
Stage III	1.58 $\pm$ 0.36	2.06 $\pm$ 1.10	+0.49	0.03		16
Total	1.00 $\pm$ 0.29	1.17 $\pm$ 0.62	+0.17	<0.01		

b Listed by use or non-use of ACE inhibitors or ARBs

Stage of renal disease	Serum creatinine, mg/dl		Mean change in serum creatinine mg/dl	n
	baseline	after 3 years of ERT		
Patients not using ARBs or ACE inhibitors (n = 6)				
Stage I	1.01 ± 0.05	1.02 ± 0.19	+0.01	2
Stage II	0.86	0.99	+0.13	1
Stage III	1.41 ± 0.29	1.39 ± 0.71	−0.02	3
Total	1.18 ± 0.31	1.20 ± 0.50	+0.02	
Patients using ARBs or ACE inhibitors (n = 25)				
Stage I	0.88 ± 0.13	1.59 ± 0.56	+0.72	4
Stage II	1.03 ± 0.17	1.26 ± 0.35	+0.23	13
Stage III	1.39 ± 0.26	1.58 ± 0.30	+0.19	8
Total	1.12 ± 0.27	1.41 ± 0.39	+0.29	

Stage I: eGFR ≥ 90 ml/min/1.73 m²; stage II: eGFR 60–89 ml/min/1.73 m²; stage III: eGFR ≤ 59 ml/min/1.73 m².

receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors (+0.29 mg/dl) than in those not using ARBs or ACE inhibitors (+0.02 mg/dl; table 2b), but the small number of patients involved renders statistical analysis unrealistic.

The eGFR remained stable in men with stage III disease (table 3a). In those with stage I or II renal disease, there was a small but significant decrease in eGFR ($p < 0.01$). The mean decrease in eGFR in all male patients was 2.66 ± 5.07 ml/min/1.73 m²/year, with a mean change of

Table 3. eGFR (means $\pm$ SD) in patients with Fabry disease at baseline and after 3 years of ERT with agalsidase α
a Listed by gender and presence/absence of hypertension

Stage of renal disease	eGFR, ml/min/1.73 m ²		Mean change in eGFR ml/min/1.73 m ²	p value	Slope change ml/min/1.73 m ² per year
	baseline	after 3 years of ERT			
Men					
Stage I	115.0 ± 22.2	98.3 ± 27.3	-16.3	<0.01	-3.19 ± 5.51
Stage II	76.5 ± 8.1	66.3 ± 21.6	-10.1	<0.01	-2.30 ± 3.86
Stage III	49.1 ± 6.6	42.8 ± 19.9	-6.3	0.18	-1.29 ± 5.25
Total	94.5 ± 30.8	81.2 ± 32.5	-13.3	<0.01	-2.66 ± 5.07
Women					
Stage I	103.2 ± 10.4	96.4 ± 17.8	-6.8	0.46	-1.48 ± 5.58
Stage II	72.5 ± 8.3	67.3 ± 13.6	-5.2	0.01	-1.29 ± 3.07
Stage III	49.5 ± 8.3	46.3 ± 13.8	-3.2	0.28	-0.74 ± 2.56
Total	71.6 ± 17.1	66.6 ± 19.6	-5.0	<0.01	-1.20 ± 3.28
Hypertension at baseline (n = 31)					
Stage I (90+)	102.8 ± 17.8	69.3 ± 28.5	-33.6	0.04	-5.86 ± 5.34
Stage II (60-90)	76.1 ± 8.4	62.5 ± 16.2	-13.5	<0.01	-3.38 ± 2.84
Stage III (0-60)	50.9 ± 4.3	48.4 ± 18.8	-2.5	0.68	-0.41 ± 5.98
Total	72.3 ± 21.2	58.8 ± 20.8	-13.5	<0.01	-2.81 ± 4.93
No hypertension at baseline (n = 135)					
Stage I (90+)	115.0 ± 21.8	100.8 ± 24.9	-14.2	<0.01	-2.79 ± 5.48
Stage II (60-90)	74.0 ± 8.4	68.0 ± 18.1	-6.1	<0.01	-1.35 ± 3.54
Stage III (0-60)	48.2 ± 8.6	41.2 ± 16.8	-7.0	0.05	-1.54 ± 3.01
Total	91.1 ± 29.8	81.0 ± 30.2	-10.2	<0.01	-2.08 ± 4.58

b Listed by use or non-use of ACE inhibitors or ARBs

Stage of renal disease	eGFR, ml/min/1.73 m ²		Mean change in eGFR ml/min/1.73 m ²	Slope change ml/min/1.73 m ² per year	n
	baseline	after 3 years of ERT			
Patients not using ARBs or ACE inhibitors (n = 6)					
Stage I	91.5 ± 1.4	90.5 ± 24.4	−1.02	−1.06 ± 6.07	2
Stage II	81.1	67.1	−14.0		1
Stage III	53.4 ± 4.9	63.2 ± 34.0	+9.82	3.35 ± 11.84	3
Total	70.7 ± 19.6	73.0 ± 27.7	+2.23	0.77 ± 8.50	
Patients using ARBs or ACE inhibitors (n = 25)					
Stage I	108.4 ± 20.0	58.6 ± 26.5	−49.8	−8.26 ± 3.50	4
Stage II	75.7 ± 8.6	62.2 ± 16.8	−13.5	−3.38 ± 2.96	13
Stage III	49.9 ± 3.9	42.8 ± 6.4	−7.2	−1.83 ± 1.64	8
Total	72.7 ± 22.0	55.4 ± 17.9	−17.3	−3.66 ± 3.37	

-13.3 ml/min/1.73 m² (p < 0.01) over 3 years. The eGFR in women with stage I or stage III renal disease remained stable. The group with mild renal failure (stage II) had a small but significant change in mean eGFR of -5.2 ml/min/1.73 m² (p = 0.01). The mean rate of eGFR decline in all women was 1.20 $\pm$ 3.28 ml/min/1.73 m²/year, with a mean reduction in eGFR over 3 years of 5.0 ml/min/1.73

m² (p < 0.01). For all patients, the rate of decline in eGFR was 2.22 $\pm$ 4.64 ml/min/1.73 m²/year. The decrease in eGFR was significant in the subgroup of patients with hypertension at baseline and in those with no hypertension, and the mean eGFR decline was similar in the two subgroups of patients (-2.81 $\pm$ 4.93 and -2.08 $\pm$ 4.58 ml/min/1.73 m²/year, respectively). Patients not using

Table 3 (continued)**c** Listed by baseline proteinuria

Stage of renal disease	eGFR, ml/min/1.73 m ²		Mean change in eGFR ml/ min/1.73 m ²	Slope change ml/min/1.73 m ² per year	n
	baseline	after 3 years of ERT			
Protein >500 mg/24 h at baseline (n = 14)					
Stage I	112.42 ± 14.60	85.10 ± 20.83	-27.32	-7.08 ± 6.32	8
Stage II	69.97 ± 5.00	57.37 ± 8.67	-12.59	-3.08 ± 2.65	5
Stage III	49.25	100.79			1
Total	92.75 ± 26.57	76.32 ± 22.10	-16.43	-3.98 ± 7.86	
Protein <500 mg/24 h at baseline (n = 40)					
Stage I	109.58 ± 21.74	97.17 ± 22.00	-2.10	-2.98 ± 4.86	16
Stage II	76.35 ± 9.87	72.14 ± 12.42	-4.21	-0.97 ± 2.20	17
Stage III	51.94 ± 3.52	49.84 ± 8.16	-2.10	-0.44 ± 1.99	7
Total	85.37 ± 26.46	78.25 ± 23.82	-7.12	-1.68 ± 3.59	
Stage I: eGFR ≥90 ml/min/1.73 m ² ; stage II: eGFR 60–89 ml/min/1.73 m ² ; stage III: eGFR ≤59 ml/min/1.73 m ²					

ARBs or ACE inhibitors had a small increase in eGFR ($+0.77 \pm 8.50$ ml/min/1.73 m²/year; table 3b), but with only 6 patients not taking ARBs or ACE inhibitors, the significance of this result compared with declines in eGFR in other patients is not clear. The decline in eGFR was numerically larger in patients with urine protein levels >500 mg/24 h (-3.98 ± 7.86 ml/min/1.73 m²/year) than in patients with urine protein levels <500 mg/24 h (-1.68 ± 3.59 ml/min/1.73 m²/year; table 3c).

Hypertension was reported in 31 of the 165 patients at baseline and was present in all groups of patients except women with normal renal function (table 1). At baseline, the prevalence of hypertension was 22% in women (11/50) and 17% in men (20/115). Mean diastolic blood pressure was <90 mm Hg in all groups at all times. After 3 years of ERT, male patients with stage II and III renal disease and female patients with stage III renal disease showed a non-significant reduction in diastolic blood pressure. Mean systolic blood pressure was >130 mm Hg in males (stages II and III) at baseline and was reduced to normal by the 3rd year of ERT. This reduction was statistically significant in patients with stage II renal disease ($p < 0.01$). In women, only patients with stage III renal disease had a mean systolic blood pressure >130 mm Hg at baseline. In this group, there was an improvement in blood pressure control after 3 years of ERT, but the mean remained above normal. Patients in stages I and II had normal systolic blood pressure values throughout the study.

Except for women with stage I or III renal disease, all groups had mild proteinuria (between 300 and 1,000 mg/24 h; table 4a). The values for proteinuria were characterized by a wide standard deviation in all patients. There was no significant change in proteinuria after 3 years of ERT. Similarly, when data were analyzed for patients with and without hypertension at baseline, there was no obvious difference in proteinuria between subgroups and no significant change after 3 years of ERT. The use or non-use of ARBs or ACE inhibitors had no obvious effect on changes in proteinuria after 3 years of ERT, but data were available for only a small number of patients (table 4b).

Discussion

Fabry nephropathy is progressive and eventually leads to end-stage renal disease in all male patients and in a smaller number of female patients. Although the short-term results of ERT are promising, data on long-term effects are scarce.

The results of our study suggest that ERT with agalsidase α slows the decline in renal function in patients with Fabry disease, and that this occurs in both males and females, even in those with advanced renal failure (eGFR ≤ 59 ml/min/1.73 m²).

Several studies have investigated the potential benefit of ERT in patients with Fabry disease. Different param-

Table 4. Proteinuria at baseline and after 3 years of ERT with agalsidase α in patients with Fabry disease**a** Listed by gender and presence/absence of hypertension

Stage of renal disease	Proteinuria, mg/24 h		Mean change in proteinuria, mg/24 h	p value	n
	baseline	after 3 years of ERT			
Men					
Stage I	398.8 ± 435.9	471.4 ± 347.0	+72.6 ± 373	0.35	24
Stage II	442.8 ± 440.5	445.0 ± 584.2	+2.2 ± 689	0.99	8
Stage III	476.0 ± 286.9	654.0 ± 99.1	+178.0 ± 335	0.45	3
Total	415.4 ± 417.1	481.0 ± 394.1	65 ± 448	0.39	
Women					
Stage I	195.0 ± 49.5	145.0 ± 63.6	-50.0 ± 113	0.64	2
Stage II	346.6 ± 383.9	307.5 ± 296.7	-39.1 ± 361	0.68	15
Stage III	246.4 ± 86.9	336.6 ± 225.1	+90.2 ± 223	0.42	5
Total	310.0 ± 320.9	299.3 ± 266.8	-10.7 ± 317	0.88	
Hypertension at baseline (n = 12)					
Stage I	890.0	690.0			1
Stage II	410.3 ± 250.1	475.9 ± 618.7	65.6 ± 649.4	0.80	7
Stage III	335.5 ± 297.9	397.0 ± 216.6	61.5 ± 194.1	0.57	4
Total	425.3 ± 284.6	467.4 ± 477.5	42.1 ± 496.1	0.78	
No hypertension at baseline (n = 45)					
Stage I	362.8 ± 417.4	436.6 ± 348.1	73.8 ± 363.2	0.32	25
Stage II	366.8 ± 453.5	302.6 ± 291.7	-64.2 ± 412.5	0.54	16
Stage III	329.5 ± 95.5	514.3 ± 284.6	184.8 ± 313.2	0.32	4
Total	361.3 ± 407.3	395.8 ± 325.6	34.6 ± 378.3	0.54	

b Listed by use or non-use of ACE inhibitors or ARBs

Stage of renal disease	Proteinuria, mg/24 h		Mean change in proteinuria, mg/24 h	n
	baseline	after 3 years of ERT		
Patients not using ARBs or ACE inhibitors (n = 4)				
Stage I	890.0	690.0		1
Stage II	180.0	211.0		1
Stage III	470.0 ± 438.4	573.0 ± 123.0	103.0 ± 315.4	2
Total	502.5 ± 386.6	511.8 ± 219.7	9.3 ± 231.9	
Patients using ARBs or ACE inhibitors (n = 8)				
Stage I				6
Stage II	448.7 ± 250.3	520.0 ± 665.6	71.3 ± 711.2	2
Stage III	201.0 ± 41.0	221.0 ± 41.0	20.0 ± 82.0	
Total	386.8 ± 241.1	445.3 ± 579.5	58.5 ± 602.3	
Stage I: eGFR ≥90 ml/min/1.73 m ² ; stage II: eGFR 60–89 ml/min/1.73 m ² ; stage III: eGFR ≤59 ml/min/1.73 m ²				

eters have been analyzed, including the reduction in Gb₃ deposits in the kidneys, heart and skin, the reduction in urinary excretion of Gb₃ and changes in renal function from baseline [4, 5, 11, 12]. These studies, however, involved small groups of patients for short periods of time. Other studies have employed a different approach.

Schwarting et al. [13], for example, described a negative association of agalsidase α ERT with serum creatinine and duration of ERT in a multivariate analysis; moreover, ERT was able to prevent the progression of renal dysfunction. Banikazemi et al. [14] performed a prospective randomized placebo-controlled study of agalsidase β with

Table 5. Rate of change in GFR in patients with Fabry disease

Study and type of ERT used	Patients n	Patient groups studied	GFR, ml/min/1.73 m ²		ERT duration years	Rate of change in GFR ml/min/1.73 m ² per year
			before ERT	after ERT		
Branton et al. [2]	14	no ERT			0	–12.2 r
De Schoenmakere et al. [15] (Agalsidase β)	1	case report			0	–6.4 r
					1.5	–2.2 r
Germain et al. [16] (Agalsidase β)	52	all patients	NR	NR	4.5	–0.4 r
	10	Prot >1 g/24 h	NR	NR	4.5	–7.4 r
	42	Prot <1 g/24 h	NR	NR	4.5	–1 r
	8	GS >50%	NR	NR	4.5	–8.9 r
	32	GS <50%	NR	NR	4.5	–1.4 r
Schiffmann et al. [17] (Agalsidase α)	24	all patients	88.4 ± 26	71.5 ± 32.7	4	–3.3 e
	12	stage I	108.7 ± 14.1	101.5 ± 12.4	4	–1.8 e
	8	stage II	78.6 ± 8.2	67.1 ± 17	4	–2.8 e
	4	stage III	47.1 ± 9.4	25.1 ± 16.4	4	–5.5 e
Breunig et al. [7] (Agalsidase β)	9	GFR >90	115 ± 18	102 ± 14	2	–6.5 e
	16	GFR <90	71 ± 17	60 ± 23	2	–5.5 e
	6	females	108 ± 30	94 ± 30	2	–7 e
Schiffmann et al. [18] (Agalsidase α)	11	ERT/2 weeks	77.8 ± 30	53.7 ± 21	3.4	–8 r
	11	ERT/weekly	51.3 ± 22.7	44.7 ± 24.3	2	–3.3 r
Tahir et al. [27] (Agalsidase β)	4	GFR >60	96.9 ± 17.2	ND	4	–1.1 r
	6	GFR <60	39.4 ± 10.9	ND	2.2	–0.23 r

e = Mean value of the slope calculated from reported data in the paper; GS = glomerulosclerosis; ND = not done; NR = not reported; Prot = 24-hour urinary protein excretion; r = mean value of the slope reported in the paper.

heart disease, renal failure and stroke as clinical end-points. They found a benefit of ERT only in patients with GFR >55 ml/min and mild proteinuria.

Changes in renal function over time can best be described by the estimated or measured rate of reduction in GFR per year. In 2002, Branton et al. [2] reported a reduction of 12.2 ml/min/year in a small group of males with Fabry disease who were not receiving treatment. Since the advent of ERT, the rate of deterioration of GFR per year has been studied either explicitly or data have been provided from which calculations could be made (table 5). In 2003, De Schoenmakere et al. [15] reported a change in GFR in a young female from –6.4 ml/min/year without therapy to –2.2 ml/min/year with agalsidase β and irbesartan. Germain et al. [16] reported a mean change in GFR of –0.4 ml/min/year in 52 patients, excluding those with severe progression of renal disease. In addition, when they subdivided patients according to the degree of proteinuria and the percentage of sclerotic glomeruli on renal biopsy, the decreases in GFR were –7.4 ml/min/year (proteinuria >1 g/24 h) and –1.0 ml/min/year (proteinuria <1 g/24 h), and –1.4 ml/min/year (<50%

sclerotic glomeruli) and –8.9 ml/min/year (>50% sclerotic glomeruli). It is therefore possible to calculate the mean eGFR reduction in these groups as –2.2 and –2.9 ml/min/year according to the degree of proteinuria and sclerotic glomeruli, respectively. In 25 adults treated for 54 months with agalsidase α, Schiffmann et al. [17] revealed a reduction in proteinuria of 1.8 ml/min/year in stage I, 2.8 ml/min/year in stage II and 5.5 ml/min/year in stage III renal disease. Recently, they [18] reported that ERT infused every week rather than every 2 weeks can slow the decline in renal function (to –3.3 ml/min/year) in patients with a severe decrease in GFR (–8 ml/min/year). In a study cohort of 26 patients treated for 24 months with agalsidase β, Breunig et al. [7] found GFR reductions of 6.5 (GFR >90 ml/min at baseline) and 5.5 ml/min/year (GFR <90 ml/min at baseline). However, they excluded 3 patients with severe and progressive nephropathy necessitating dialysis. In the same study, there was a reduction in GFR of approximately 7.0 ml/min/year in female patients. Taken together, these studies show considerable variability in the reduction of GFR in patients receiving ERT with either agalsidase α or β. How-

ever, the studies were carried out in small groups of patients and for a limited time period.

In contrast, the present analysis was conducted on data from a large number of patients ($n = 165$) receiving ERT for 3 years. The mean increase in serum creatinine and the mean reduction in eGFR in these patients were satisfactory compared with other reports. In men, there was a mean decrease of 2.66 ml/min/1.73 m²/year and in women of 1.20 ml/min/1.73 m²/year; in the total population, the mean decrease was 2.22 ml/min/1.73 m²/year. When patients were subdivided according to disease stage, reductions in eGFR were mostly similar to or lower than those reported in the literature (table 5). Thus, we have demonstrated substantial stabilization of renal function in all groups of patients with Fabry disease. Importantly, renal function remained stable throughout the 3 years of ERT in patients with severe renal failure (stage III).

Factors other than ERT cannot be ruled out when explaining the reduction in deterioration of renal function in treated patients with Fabry disease. ACE inhibitors and ARBs are used extensively in patients with Fabry disease and are effective in controlling blood pressure and providing renoprotection due to their well-known actions on glomerular hemodynamics and their interactions with cytokines [19–21].

The degree of proteinuria also critically affects the progression of Fabry nephropathy. Proteinuria >1 g/24 h is associated with a reduced response to ERT and a more rapid decline in renal function [22–24]. The patients analyzed in FOS had mild proteinuria (mean <1 g/24 h) at baseline, which did not change during follow-up. Previously published data have also shown that ERT with either agalsidase α or β does not alter urinary protein excretion [25, 26]. Moreover, a sustained reduction in proteinuria associated with stabilization of renal function

has been described in a small group of Fabry patients receiving ACE inhibitors and/or ARBs, with no significant change after addition of agalsidase β therapy [27]. The use of ACE inhibitors and/or ARBs is therefore advisable to help prevent the deterioration in renal function and to reduce proteinuria in patients with Fabry disease, as it is for other proteinuric nephropathies [28, 29].

The present study has some limitations common to large multicenter, multinational studies: incomplete data reporting, differences in laboratory methods and the fact that there was no placebo group. In addition, the analysis focused only on patients with stage I–III renal disease and excluded patients with end-stage renal disease and renal transplant recipients. At present, controversy exists regarding the MDRD formula as a gold standard for estimating GFR, and therefore other formulae have been proposed [30]. The MDRD formula, however, remains a useful tool for investigating changes in renal function over time [31]. Despite the limitations common to outcome surveys, FOS provides consistent data indicating trends in renal function in patients with Fabry nephropathy on ERT.

Although we should be cautious about drawing definitive conclusions, the FOS data – obtained in normal clinical practice from a wide range of patients from many different countries – suggest that agalsidase α plays a significant role in slowing the progression of renal dysfunction in patients with Fabry nephropathy.

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References

- 1 Brady RO, Gal AE, Bradley RM, Martenson E, Warshaw AL, Laster L: Enzymatic defect in Fabry's disease. Ceramide trihexosidase deficiency. *N Engl J Med* 1967;276:1163–1167.
- 2 Branton MH, Schiffmann R, Sabnis SG, Murray GJ, Quirk JM, Altarescu G, Goldfarb L, Brady RO, Balow JE, Austin HA III, Kopp JB: Natural history of Fabry renal disease: influence of alfa-galactosidase A activity and genetic mutations on clinical course. *Medicine (Baltimore)* 2002;81:122–138.
- 3 MacDermot KD, Holmes A, Miners AH: Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Gen* 2001;38:769–775.
- 4 Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, Caplan L, Linthorst GE, Desnick RJ: Safety and efficacy of recombinant human alfa-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med* 2001;345:9–16.
- 5 Schiffmann R, Kopp JB, Austin HA III, Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO: Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA* 2001;285:2743–2749.
- 6 Lidove O, Joly D, Barbey F, Bekri S, Alexandra JF, Peigne V, Jaussaud R, Papo T: Clinical results of enzyme replacement therapy in Fabry disease: a comprehensive review of literature. *Int J Clin Pract* 2007;2:293–302.

- 7 Breunig F, Weidemann F, Strotmann J, Knoll A, Wanner C: Clinical benefit of enzyme replacement therapy in Fabry disease. *Kidney Int* 2006;69:1216–1221.
- 8 Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, Linhart A, Sunder-Plassmann G, Ries R, Beck M: Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur J Clin Invest* 2004;34:236–242.
- 9 Peake M, Whiting M: Measurement of serum creatinine – current status and future goals. *Clin Biochem Rev* 2006;27:173–184.
- 10 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461–470.
- 11 Thurberg BL, Rennke H, Colvin RB, Dikman S, Gordon RE, Collins AB, Desnick RJ, O'Callaghan M: Globotriaosylceramide accumulation in Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. *Kidney Int* 2002;62:1933–1946.
- 12 Sakuraba H, Murata-Ohsawa M, Kawashima I, Tajima Y, Kotani M, Ohshima T, Chiba Y, Takashiba M, Jigami Y, Fukushige T, Kanzaki T, Itoh K: Comparison of the effects of agalsidase alfa and agalsidase beta on cultured human Fabry fibroblasts and Fabry mice. *J Hum Genet* 2006;51:180–188.
- 13 Schwarting A, Dehout F, Feriozzi S, Beck M, Metha A: Enzyme replacement therapy and renal function in 201 patients with Fabry disease. *Clin Nephrol* 2006;2:77–84.
- 14 Banikazemi M, Bultas J, Waldek S, Wilcox WR, Whitley CB, McDonald M, Finkel R, Packman S, Bichet DG, Warnock DG, Desnick RJ: Agalsidase beta therapy for advanced Fabry disease. *Ann Intern Med* 2007;146:77–86.
- 15 De Schoenmakere G, Chauveau FD, Grunfeld JP: Enzyme replacement therapy in Anderson-Fabry's disease: beneficial effect on vital organ function. *Nephrol Dial Transplant* 2003;18:33–35.
- 16 Germain DP, Waldek S, Banikazemi M, Bushinsky D, Charrow J, Desnick RJ, Lee P, Loew T, Vedder AC, Abichandani R, Wilcox W, Guffon N: Sustained, long-term renal stabilization after 54 months of agalsidase β therapy in patients with Fabry disease. *J Am Soc Nephrol* 2007;18:1547–1557.
- 17 Schiffmann R, Ries M, Timmons M, Flaherty JT, Brady RO: Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting. *Nephrol Dial Transplant* 2006;21:345–354.
- 18 Schiffmann R, Askari H, Timmons M, Robinson C, Benko W, Brady RO, Ries M: Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing. *J Am Soc Nephrol* 2007;18:1576–1583.
- 19 Wright JT, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Herbert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG; African American Study of Kidney Disease and Hypertension Study Group: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK Trial. *JAMA* 2002;288:2421–2431.
- 20 Remuzzi G, Ruggenenti P, Perico N: Chronic renal diseases: renoprotective benefits of renin-angiotensin system inhibition. *Ann Intern Med* 2002;136:604.
- 21 Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG: Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med* 2004;12:929–937.
- 22 Wilcox WR, Banikazemi M, Guffon N, Waldek S, Lee P, Linthorst GE, Desnick RJ, Germain GP: Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. *Am J Hum Genet* 2004;75:65–74.
- 23 Warnock DG: Fabry disease: diagnosis and management, with emphasis on the renal manifestations. *Curr Opin Nephrol Hypertens* 2005;14:87–95.
- 24 Breunig F, Wanner C: Update on Fabry disease: kidney involvement, renal progression and enzyme replacement therapy. *J Nephrol* 2008;21:32–37.
- 25 Warnock D: Enzyme replacement therapy and Fabry disease: quo vadis? *J Am Soc Nephrol* 2007;18:1368–1370.
- 26 Wanner C, Breunig F: Fabry nephropathy and the case for adjunctive renal therapy. *J Am Soc Nephrol* 2007;18:2426–2428.
- 27 Tahir H, Jackson LL, Warnock DG: Antiproteinuric therapy and Fabry nephropathy: sustained reduction of proteinuria in patients receiving enzyme replacement therapy with agalsidase-beta. *J Am Soc Nephrol* 2007;18:2609–2617.
- 28 Ruggenenti P, Perna A, Gherardi G, Benini R, Remuzzi G: Chronic proteinuric nephropathies: outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury. *Am J Kidney Dis* 2000;35:1155–1165.
- 29 Sarafidis PA, Khosla N, Bakris GL: Antihypertensive therapy in the presence of proteinuria. *Am J Kidney Dis* 2007;49:12–26.
- 30 Stevens LA, Coresh J, Greene T, Levey AS: Assessing kidney function – measured and estimated glomerular filtration rate. *N Engl J Med* 2006;8:2473–2483.
- 31 Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, Levey AS: The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the Modification of Diet in Renal Disease Study. *Ann Intern Med* 2005;142:342–351.

Erratum

In the above article by S. Feriozzi et al. entitled 'Agalsidase alfa slows the decline in renal function in patients with Fabry disease' [*Am J Nephrol* 2009;29:353–361], in table 3c in the group of patients with protein <500 mg/24 h (stage I), the value of mean change in eGFR of –2.10 is not correct and should read –12.42.