Antiproteinuric Therapy and Fabry Nephropathy: Sustained Reduction of Proteinuria in Patients Receiving Enzyme Replacement Therapy with Agalsidase-β

Hindia Tahir, Leslie L. Jackson, and David G. Warnock

Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama

ABSTRACT

This report describes an open-label, nonrandomized, prospective evaluation of the effects of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapy on patients who have Fabry disease and also received enzyme replacement therapy with agalsidase-β, given at 1 mg/kg body wt every 2 wk. Previous placebo-controlled phase III and phase IV trials with agalsidase-β demonstrated clearing of globotriaosylceramide from vascular endothelia but little effect on proteinuria or progressive loss of kidney function in patients with Fabry disease and severe chronic kidney disease marked by overt proteinuria and/or estimated GFR $<$60 ml/min per 1.73 m^2. Angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker therapy is the standard of care for patients with proteinuric kidney diseases, but their use is challenging in patients with Fabry disease and low or low-normal baseline systemic BP. A group of patients with Fabry disease were treated with antiproteinuric therapy, in conjunction with agalsidase-β; sustained reductions in proteinuria with stabilization of kidney function were achieved in a group of six patients who had severe Fabry nephropathy; the progression rate was -0.23 ± 1.12 ml/min per 1.73 m^2 per yr with 30 mo of follow-up.

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Fabry disease is an X-linked disorder caused by lysosomal α-galactosidase A deficiency, with resulting accumulation of glycosphingolipids, and progressive kidney, cardiac, and neurologic involvement that can cause death in the fifth decade.[1,2] Women can also have serious disease manifestations.[3] Enzyme replacement therapy (ERT) with agalsidase-β (recombinant human α-galactosidase A) clears globotriaosylceramide from vascular endothelial cells of patients with Fabry disease.[4,5] We use the term "Fabry nephropathy" for this spectrum of kidney involvement: Focal, segmental, and global sclerosis; mesangial widening; epithelial deposits; ischemic changes; tubulointerstitial fibrosis; and vascular changes including GL-3 deposits and hyalinosis.[6]

Studies have demonstrated clinical benefit of ERT in patients with mild Fabry disease[7,8] but relatively little impact on patients with initial estimated GFR (eGFR) $<$60 ml/min per 1.73 m^2 and baseline proteinuria $>$1 g/d. ERT had no evident impact on proteinuria in an open-label study[9]; placebo-controlled, double blind phase III[4,5] and phase IV studies[8]; and an open-label extension study of the original phase III cohort.[10] ERT may have dosage-related effects on eGFR progression[11,12] but, *per se*, does not reduce urinary protein excretion.[13]

The recommended BP target in chronic kidney disease (CKD) is $<$130/80 mmHg, with the use of angiotensin-converting enzyme inhibitor (ACEI) or an-

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Correspondence: Dr. David G. Warnock, Room 647 THT UAB Station, 1530 3rd Avenue South, Birmingham, AL 35294-0006. Phone: 205-934-3585; Fax: 205-934-1879; E-mail: dwarnock@uab.edu

giotensin receptor blocker (ARB) therapy as the treatment of choice for overt proteinuria, which is an important factor in the progression of CKD. Systolic BP <130 mmHg is recommended if the urine protein/creatinine ratio is >0.5 g/g in CKD[14] or the urine albumin/creatinine ratio is >500 mg/g in diabetic kidney disease.[15] These clinical practice recommendations are challenging in Fabry nephropathy, because many patients have relatively normal or low BP in the early stages of their disease.[1,16]

The objective of our study was to describe the effects of ACEI/ARB therapy on urinary protein excretion in patients who had Fabry disease and were treated with ERT. The hypothesis was that reduction of proteinuria with ACEI/ARB therapy in conjunction with ERT would be associated with slowing of the progressive decline of eGFR, especially in high-risk patients who had proteinuria and initial eGFR rates <60 ml/min per 1.73 m^2. Our patients tolerated ACEI/ARB therapy and had sustained reductions in BP and proteinuria and eGFR stabilization compared with previous experiences with similar patients who were treated with ERT alone.[7–10,12]

RESULTS

Patient Characteristics

The median age for the eight mens and three women was 37.1 yr (range 18.3 to 56.7) at the time ERT was begun. Nine families with seven distinct mutations were represented, and there were two relative pairs: Mother (patient 10) and son (patient 8), and brother (patient 6) and brother (patient 7; Table 1). The clinical manifestations were diverse, with multiple organ system involvement in addition to Fabry nephropathy. Some patients had hyperlipidemia, coronary artery disease, and hypertension, in addition their Fabry disease (Table 1).

Timing of ACEI/ARB and Agalsidase-β Therapy

Most patients were begun on ACEI/ARB therapy before starting ERT. The subsequent duration of ERT is shown in Table 1 (mean 30.3 ± 9.8 mo; median 30.1 mo; range 16 to 43; excludes patient 11). Some patients received both ACEI and ARB; the dosages were adjusted empirically, depending on the baseline proteinuria, the response to antiproteinuric therapy, and tolerance of the antihypertensive effects of ACEI/ARB therapy. Other agents that could affect kidney function and proteinuria are also listed in Table 1.

Two of the patients participated in the previous phase IV study of agalsidase-β[8]; patient 9 was randomly assigned to the active treatment arm throughout the phase IV study, whereas patient 10 received placebo during the blinded phase and went on to open-label treatment with agalsidase-β after having sustained ventricular tachycardia. Three patients were previously

Table 1. Baseline characteristics, medications, and clinical events[a]

ID	Age at Start of ERT (Gender)	Family Group (Mutation)	Clinical Manifestations of Fabry Disease; Other Conditions	Months ACEI/ARB before ERT	ACEI/ARB and other Medications at Final Visit	ERT (Mo)	Events; Relative to ERT (Mo)
3	18.8 (F)	4 (Q221X)	Fabry pain crises, ACR, seizures	−7.0	Lisin (10); sodium valproate	25.2	None
8	33.8 (M)	1 (R227X)	ACR, ANG, deafness, Ledema, LVH	−2.7	Lisin 5, Losar (25), HCTZ (25)	35.2	KBx (11), LoBP (12), AF (40)
4	34.7 (F)	12 (Q283X)	ACR, CW, deafness, LVH	−5.7	Lisin (5)	25.1	MBx (0), Syncope (10), ICD (12)
5	47.8 (M)	9 (717delAA)	ACR, Afib, ANG, ANH, CVA, CW, deafness, LVH, CAD, HLipid	−4.1	Lisin (10); ASA, Atenol, Clopid, Isosor, Rosuv	27.5	Pacemaker (−120), CVA (−120), KBx (−4), LoBP (6), Cholecys (26), PTCA (38)
7	46.1 (M)	7 (R227X)	ACR, ANG, ANH, Brad, GI, HCM, VTach, HTN, Hlipid,	−0.3	Lisin (5), Losar (50); ASA, ESA	30.3	KBx (0), ICD (14)
9	35.5 (M)	10 (P409S)	ACR, CW, CAD HTN, HLipid,	−14.1	Lisin (10), Losar (25); ASA, Atrov, Aten,	42.2	CABG (−12), KBX (14), HiK (23)
6	37.9 (M)	7 (R227X)	ACR, ANG, ANH, Brad, LVH	−20.6	Enal (20), Losar (50); Coum, ESA	43.0	CVA (−216), KBx (0), LoBP (27)
10	58.3 (F)	1 (R227X)	ACR, HCM, Afib, CVA, MRegurg, VTach, HLipid, HTN	−14.8	Lisin (40), Losar (100); Amio, Aten, Atorv, ESA, Levo, ASA	37.1	ICD (0), KBx (−15)
12	33.2 (M)	8 (W236X)	ACR, ANG, Brad, GI, LVH; HLipid, HTN	−2.8	Enal (20), Irbes (150); ASA, ESA, Eze	10.8	KBx (−3), HiK (6), KBx (12), LURDKT (13)
13	55.7 (M)	13 (G147RR)	ACR, ANG, Afib, deafness, Ledema, CHB, HCM	−2.7	Lisin (5), Losar (50); ASA, Clopid, Fur, Metop, Rosuv	21.6	Pacemaker (−24), HiK (1), Cholecys (9), LoBP (13)
11	29.0 (M)	14 (Q221X)	ACR, ANG, CW, LVH	−5.0	Lisin (10), Losar (50); ESA	6.0	KBx (−5), SBE and AKI (−4), Chol, Pan (−3), Cholecys (−2) ESRD (6)

[a]ACEI, angiotensin-converting enzyme inhibitor; ACR, acroparesthesias; Afib; atrial fibrillation; AKI, acute kidney injury requiring dialysis; Amio, amiodarone; ANG, angiokeratomas; ARB, angiotensin receptor blocker; ASA, aspirin; Aten, atenolol; Atorv, atorvastatin; Brad, bradycardia; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHB, complete heart block; Chol, cholecystitis; Cholecys, cholecystectomy; Clopid, clopidogrel; Coum, Coumadin; CVA, cerebrovascular accident; CW, corneal whirls; Enal, enalapril; ERT, enzyme replacement therapy with agalsidase-β ; ESA, erythropoiesis stimulating agent; Eze, ezetimibe, Fur, furosemide; GI, gastrointestinal disturbance; HCM, hypertrophic cardiomyopathy; HCTZ, hydrochlorothiazide; HiK, hyperkalemia; HLipid, hyperlipidemia; HTN, hypertension; ICD, intracardiac defibrillator; Irbes, irbesartan; Isosob, isosorbide; KBx, kidney biopsy; Ledema, lymphedema; Levo, levothyroxine; Lisin, lisinopril; LoBP, hypotension; Losar, losartan; LURDKT, living unrelated donor, kidney transplant; LVH, left ventricular hypertrophy; MBx, myocardial biopsy; Metop, metoprolol; MRegurg, mitral regurgitation; Pan, pancreatitis; PTCA, percutaneous transluminal angioplasty; Rosuv, rosuvastatin; SBE, subacute bacterial endocarditis; VTach, ventricular tachycardia.

treated with agalsidase-α (Replagal; Shire, Cambridge, MA) at 0.2 mg/kg every 2 wk at the National Institutes of Health and switched to agalsidase-β at the University of Alabama at Birmingham (UAB). These patients received agalsidase-α for 60 mo (patient 7), 16 mo (patient 6), and 24 mo (patient 8) before switching to agalsidase-β therapy. Two patients (9 and 12) started ACEI/ARB therapy at outside clinics; their referring physicians provided their baseline information when these patients were transferred to UAB.

Clinical Events during the Observation Period

The clinical manifestations are listed in Table 1. Eight patients had kidney biopsies, and all had Fabry nephropathy.[6] Transient ischemic attacks and strokes did not occur during the observation period despite fairly aggressive lowering of systolic BP with ACEI/ARB therapy. Two patients received pacemakers before the start of ERT, and one patient (8) developed atrial fibrillation 5 mo after the completion of the observation period. Two female and 1 male patient developed ventricular ectopy after starting ERT and now have intracardiac defibrillator devices. Four patients developed hyperkalemia with serum $K^+ > 6.0$, but these episodes were minor and managed with reductions in dietary K^+ intake.

One male patient (11) with severe Fabry nephropathy (initial eGFR 25.3 ml/min per 1.73 m^2 and urine protein/creatinine ratio 3.54 g/g) developed acute pancreatitis as a result of pancreas divisum, acute cholecystitis with cholecystectomy, and subacute bacterial endocarditis and required acute dialysis soon after the start of ERT. His kidney function slightly improved, but his urine protein excretion remained elevated and chronic dialysis was needed within 6 mo of starting ERT. His data are presented in the figures but are not included in the summary statistics for evaluation of the effects of ACEI/ARB therapy on urine protein/creatinine ratio or the eGFR progression rate. Two other male patients also had laparoscopic cholecystectomy during the observation period, but these events were deemed to be coincidental and not related to ERT.

Systemic BP, Urine Protein/Creatinine Ratios, and eGFR

The four patients with stages 1 and 2 CKD were younger (mean 33.8 $\pm$ 11.8 yr) than the seven patients with stages 3 and 4 CKD (mean 42.2 $\pm$ 11.4 yr; Table 1). As shown in Table 2, the baseline BP were higher for the patients with stages 3 and 4 CKD than for the patients with stages 1 and 2 CKD (135/82 and 98/63 mmHg, respectively). ERT was started 7.3 $\pm$ 6.4 mo (median 4.9; range 0.3 to 20.6) after initiation of ACEI/ARB

Table 2. BP, urine P/C ratio, and GFR[a]

ID	No. of Visits (Months of Follow-Up)	At Start of ACEI or ARB			At Start of ERT				At Final Visit			
		BP (mmHg)	P/C Ratio	GFR	BP (mmHg)	P/C Ratio	GFR	ACEI ARB Dosage	BP (mmHg)	P/C Ratio	GFR	ACEI ARB Dosage
Initial GFR >90 ml/min per 1.73 m^2 at start of ERT												
3	3 (24.9)	104/66	0.17	115	88/68	0.07	115	Lisin 10	100/62	0.01	116	Lisin 10
8	9 (34.8)	90/60	0.30	104	90/60	0.19	75	Losar 50 HCTZ 12.5	104/70	0.20	88	Lisin 5 Losar 25
4	7 (24.7)	92/60	0.46	102	100/64	0.26	102	Lisin 2.5	107/66	0.21	86	Lisin 5
5	8 (34.9)	120/80	0.41	96	120/80	0.37	96	Lisin 10 Losar 50 HCTZ 12.5	106/67	0.58	109	Lisin 10
median		98/63	0.36	103	95/66	0.23	99		105/67	0.21	99	
Initial GFR <60 ml/min per 1.73 m^2 at start of ERT												
7	9 (31.4)	160/84	0.33	54	114/62	0.11	54	Lisin 10 Losar 25 HCTZ 6.2	123/74	0.14	63	Lisin 5 Losar 25
9	14 (41.7)	130/80	0.58	67	120/70	0.15	42	Lisin 20	136/80	0.18	47	Lisin 10 Losar 50
6	29 (42.1)	130/84	1.91	73	96/68	0.24	51	Enal 10 Losar 50 HCTZ 12.5	98/60	0.45	41	Enal 10 Losar 50
10	21 (40.8)	154/72	6.29	50	108/72	1.60	35	Losar 50 HCTZ 12.5	135/75	1.00	24	Lisin 40 Losar 100
12	13 (15.6)	140/90	2.14	30	106/80	0.51	26	Irbes 150	110/70	0.51	24	Irbes 150
13	7 (21.6)	104/68	0.23	38	120/70	0.23	37	Lisin 10 Losar 50	120/63	0.46	39	Losar 50
11	5 (9.0)	104/70	3.54	26	116/78	4.74	21	Lisin 10 Losar 25	120/78	3.91	9.7	Lisin 10 Losar 25
median[b]		135/82	1.24	52	110/70	0.21	40		122/72	0.46	40	

[a]P/C ratio, urine protein/creatinine ratio.
[b]Excludes patient 11.

therapy. At that point, the BP were decreased by ACEI/ARB therapy, especially for patients with stages 3 and 4 CKD, and these effects were sustained throughout the period of follow-up (Table 2). The average BP measurements relative to the start of ERT are shown in Figure 1. Despite more aggressive ACEI/ARB therapy, the BP in the patients with stages 3 and 4 remained higher than the BP in patients with stages 1 and 2 CKD.

The urinary protein/creatinine ratios are shown in Table 2; three of the patients with stages 1 and 2 CKD had overt proteinuria (≥0.3 g/g) at baseline. The median urinary protein/creatinine ratio was 0.36 (range 0.17 to 0.46) for the patients with stages 1 and 2 CKD and 1.24 (range 0.23 to 6.3) for patients with stages 3 and 4 CKD, excluding patient 11. ACEI/ARB treatment reduced the median urinary protein/creatinine ratio for patients with stages 3 and 4 CKD to 0.21 (range 0.1 to 1.6) and for patients with stages 1 and 2 CKD to 0.22 (range 0.07 to 0.37; Table 2). The individual urinary protein/creatinine ratios at baseline, at initiation of ERT, and throughout the observation period are shown in Figure 2. Higher baseline urine protein/creatinine ratios and sustained reductions were more evident in patients with stages 3 and 4 CKD (Figure 2B) than in patients with stages 1 and 2 CKD (Figure 2A). Two of these patients (5 and 8 in Figure 2A) had initial decreases in their urine protein/creatinine ratios that were not sustained

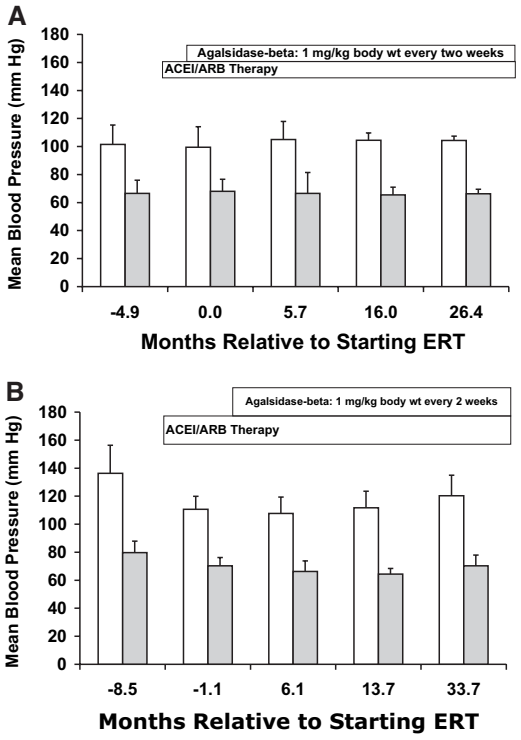

Figure 1. Summary of mean BP measurements (±SD). (A) Patients with initial GFR >60 ml/min per 1.73 m^2. (B) Patients with initial GFR ≤60 ml/min per 1.73 m^2. The zero time was set at which agalsidase-β therapy was initiated. □, Systolic BP; ▨, diastolic BP. ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ERT, enzyme replacement therapy.

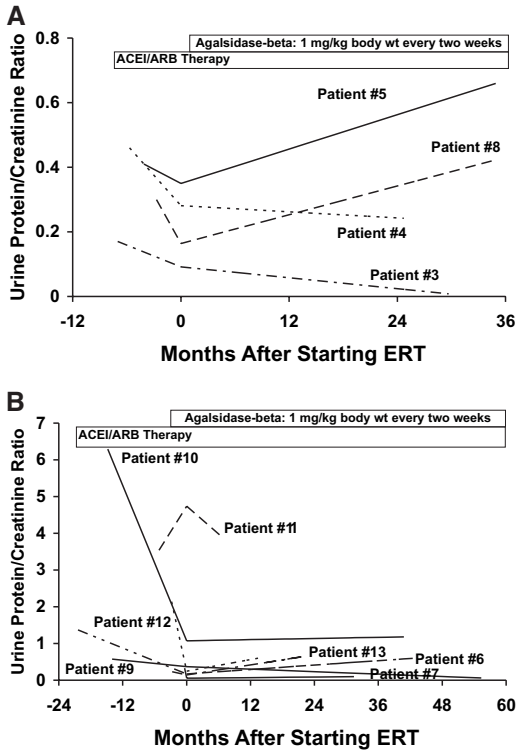

Figure 2. Urinary protein/creatinine ratio for individual patients. (A) Patients with initial GFR >60 ml/min per 1.73 m^2. (B) Patients with initial GFR ≤60 ml/min per 1.73 m^2. Each patient is shown as an individual regression line, starting with the zero time at which agalsidase-β therapy was initiated. Note the 10-fold difference in the *y* axis scale between A and B.

because they chose to stop or reduce their ACEI/ARB therapy during the observation period.

The regressions of urine protein/creatinine ratios over time are presented in Table 3. The second column represents the baseline ratio for each patient obtained at the time that ACEI/ARB therapy was started. The third column represents the intercept value, corresponding to the point at which ERT was started in each patient. The duration of follow-up on ERT and the number of complete evaluations for each patient are also presented in Table 3.

The baseline urine protein/creatinine ratio was 0.34 ± 0.13 (median 0.36) for patients with stages 1 and 2 CKD, and this ratio was significantly different from the regression intercept (0.22 ± 0.12; median 0.22). The baseline urine protein/creatinine ratio was 1.91 ± 2.29 (median 1.24) for patients with stages 3 and 4 CKD, and this ratio was also significantly different from the regression intercept (0.30 ± 0.38; median 0.15), which reflects the antiproteinuric effects of ACEI/ARB therapy. The regression slopes for both groups were not significantly different from zero, indicating that the reductions in urine protein/creatinine ratio were maintained throughout the observation period. Urine protein and urine albumin measurements are shown in Table 4. Albumin excretion accounted for approximately half of the total urinary protein excretion

Table 3. Individual patient regression analysis of P/C ratios over time[a]

Patient	Initial P/C Ratios[b]	Intercept of P/C Ratio Regression[c]	Slope of P/C Ratios Regression	Follow-Up: Months on Agalsidase-β	No. of Complete Evaluations
CKD stages 1 and 2					
3	0.17	0.09	−0.003	24.9	3
8	0.30	0.16	0.089	34.8	9
4	0.46	0.28	−0.019	24.7	7
5	0.41	0.35	0.106	34.9	8
mean ± SD (median)	0.34 ± 0.13 (0.36)	0.22 ± 0.12 (0.22)[d]	0.043 ± 0.063 (0.043)	29.8 ± 5.8 (29.8)	6.8 ± 2.6 (7.5)
CKD stages 3 and 4					
7	0.33	0.06	0.016	30.3	9
9	0.58	0.13	0.005	42.2	14
6	1.91	0.16	0.126	43.0	29
10	6.29	1.06	0.038	37.1	21
12	2.14	0.24	0.319	10.8	13
13	0.23	0.14	0.275	21.6	7
mean ± SD (median)	1.91 ± 2.29 (1.24)	0.30 ± 0.38 (0.15)[e]	0.130 ± 0.137 (0.082)	28.1 ± 14.7 (29.4)	15.5 ± 8.2 (13.5)

[a]CKD, chronic kidney disease.
[b]Value obtained before ACEI/ARB therapy was initiated.
[c]Zero time assigned to the point at which ERT was initiated.
[d]$P = 0.0161$, two-tailed t test, comparing fourth-root transformation of regression intercept to initial P/C ratio.
[e]$P = 0.0054$, two-tailed t test, comparing fourth-root transformation of regression intercept to initial P/C ratio.

and was reduced in parallel with total protein by ACEI/ARB therapy.

The individual regressions of eGFR for each patient are presented in Figure 3, and the results are presented in Table 5. The second column presents the baseline eGFR obtained when ACEI/ARB therapy was started, and the third column presents the intercept, corresponding to the point at which ERT was started in each patient. The initial eGFR was 108 ± 10.8 ml/min per 1.73 m^2 for patients with stages 1 and 2 CKD and was reduced to 96.9 ± 17.2 ml/min per 1.73 m^2 by ACEI/ARB therapy (Table 2). The initial eGFR was 52.0 ± 16.5 ml/min per 1.73 m^2 for patients with stages 3 and 4 CKD and was significantly reduced to 39.4 ± 10.9 ml/min per 1.73 m^2 by ACEI/ARB therapy (Table 2). As was seen in other forms of proteinuric kidney disease,[17] eGFR was initially reduced by ACEI/ARB therapy as BP was lowered.

Excluding the initial change in eGFR before ERT was begun, the average progression rate for patients with stages 1 and 2 CKD was 1.18 ± 2.78 ml/min per 1.73 m^2 per yr and −0.23 ± 1.12 ml/min per 1.73 m^2 per yr for patients with stages 3 and 4 CKD. The individual regressions are presented in Table 5, and the averaged values for both groups are presented in Figure 4. The slopes for both groups were not significantly different

Table 4. Urine P/C and A/C ratios and 24-hour urine protein and albumin excretion[a]

ID	At Start of ACEI or ARB				At Start of ERT				At Final Visit			
	P/C Ratio	A/C Ratio	Protein (mg/d)	Albumin (mg/d)	P/C Ratio	A/C Ratio	Protein (mg/d)	Albumin (mg/d)	P/C Ratio	A/C Ratio	Protein (mg/d)	Albumin (mg/d)
Initial eGFR >60 ml/min per 1.73 m^2												
3	0.17	19.9	144	16.7	0.07	0.11	60	8.8	0.09	45.0	91.0	45.0
8	0.30	101.2	560	188.2	0.19	0.15	338	106.9	0.20	84.9	385.0	160.0
4	0.46	307.0	412	276.0	0.26	0.24	324	165.4	0.21	105.3	288.0	142.2
5	0.41	157.8	574	219.7	0.37	1.60	405	137.3	0.58	291.9	680.0	344.7
median	0.36	129.5	486	204.0	0.23	124.4	331.0	122.1	0.21	95.1	336.5	151.1
Initial eGFR <60 ml/min per 1.73 m^2												
7	0.33	156.0	413	195.4	0.11	34.0	189	56.0	0.14	35.8	186.0	48.3
9	0.58	459.3	720	575.0	0.15	88.7	221	126.7	0.18	118.7	324.0	211.6
6	1.91	1333	2684	852.8	0.24	127.5	352	188.0	0.45	284.7	657.0	413.9
10	6.29	3942	2797	1754.0	1.60	999	1616	1009	1.00	634.8	794.0	504.0
12	2.14	1290	3312	1550.0	0.51	391.5	864	664.0	0.51	291.4	759.0	436.8
13	0.23	117.2	462	239.3	0.23	109.6	409	194.4	0.46	266.5	871.0	503.1
11	3.54	1906	6178	3329	4.74	2521	3440	1830	3.91	1897	3741	1815
median[b]	1.24	875	1702	713.9	0.23	118.6	380.5	191.2	0.46	121.5	708.0	425.3

[a]A/C ratio, urine albumin/creatinine ratio.
[b]Excludes patient 11.

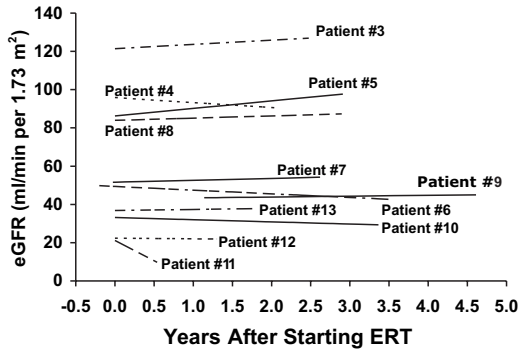

Figure 3. Estimated Modification of Diet in Renal Disease (MDRD) GFR during the observational study. Regression lines are shown for each patient and correspond to their individual progression rates (ml/min per 1.73 m^2 per yr). The zero point for each patient was set at the start of agalsidase-β therapy.

from zero, indicating that eGFR was stabilized in Fabry nephropathy that was treated with ACEI/ARB therapy and ERT during the 30-mo observation period.

DISCUSSION

Our results demonstrate the feasibility of using ACEI/ARB therapy in patients with Fabry nephropathy, most of whom are not overtly hypertensive. The patients tolerated ACEI/ARB therapy and had sustained reductions of urinary protein excretion (Table 1, Figure 2). The progression rate for patients with stages 3 and 4 CKD (0.22 ± 1.47 ml/min per 1.73 m^2 per yr) is better than previously described in patients who had moderately severe Fabry nephropathy and who were treated ERT but did not receive antiproteinuric therapy.[7–10,12] Agalsidase-β given at 1 mg/kg had no evident effect on urinary protein excretion in patients with Fabry disease in an open-label study,[9] in placebo-controlled double blind phase III[4,5] and phase IV trials,[8] and in an open-label extension of the phase III trial.[10] Agalsidase-α, at the usual dosage of 0.2 mg/kg, did not reduce proteinuria.[7,12] Although weekly infusions may have slowed progression compared with infusions every 2 wk, agalsidase-α still did not affect proteinuria.[12]

Relatively low systemic BP was described early as a feature of Fabry disease.[16] Nevertheless, the use of antiproteinuric therapy has been recommended for treatment of Fabry disease with kidney involvement.[18,19] ACEI/ARB therapy reduced systemic BP in our patients with Fabry nephropathy, but our approach is consistent with the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for proteinuric kidney disease,[14,15] in which the goal of reducing urine protein excretion to <500 mg/d is recommended even if systolic BP falls below 130 mmHg. BP reductions in patients with stages 3 and 4 CKD did limit the total dosing of ACEI/ARB therapy but was generally well tolerated. No serious adverse events were observed during this study other than occasional hypotensive symptoms that quickly responded to reductions in the dosage of the ACEI/ARB therapy and mild episodes of hyperkalemia. Whereas the reduction in BP in patients with stages 3 and 4 CKD was evident, the systolic pressures were not reduced below that observed in patients with stages 1 and 2 CKD before ACEI/ARB therapy was started (Table 2, Figure 1).

Previous reports documented the progressive course of Fabry nephropathy. Branton *et al.*[1] reported that 14 male patients developed "chronic renal insufficiency" with a progression rate of −12.2 ± 9.1 ml/min per yr. Breunig *et al.*[9] described 26 patients who were treated with agalsidase-β. Eight patients with stage 2 or 3 CKD (baseline GFR 71 ± 17 ml/min per 1.73 m^2) showed progressive deterioration of their GFR to 60 ± 23 ml/min per 1.73 m^2 during a 26.4-mo follow-up period, with an apparent progression rate of −4.7 ± 5.4 ml/min per 1.73 m^2 per yr. Fourteen patients received ACEI/ARB therapy, but there were no effects on BP or proteinuria with the dosages that were used.

Banikazemi *et al.*[8] reported a prospective, placebo-controlled trial of agalsidase-β in patients with Fabry disease and mild to moderate kidney disease. The baseline eGFR in the treatment group was 53 ± 18 ml/min per 1.73 m^2, and BP was 126 ± 16 mmHg (systolic) and 77 ± 10 mmHg (diastolic). The baseline urine protein/creatinine ratios were 1.5 ± 1.0, similar to what we observed for patients with Fabry

Table 5. Individual patient regression analysis of eGFR over time

Patient	Initial eGFR (ml/min per 1.73 m^2)[a]	Intercept of eGFR Regression (ml/min per 1.73 m^2 per yr)[b]	Slope of eGFR Regression (ml/min per 1.73 m^2 per yr)
CKD stages 1 and 2			
3	115	121.4	2.229
8	104	83.9	1.164
4	102	95.8	−2.617
5	96	86.2	3.947
mean ± SD (median)	104 ± 7.9 (103)	96.9 ± 17.2 (91.0)	1.18 ± 2.78 (1.70)
CKD stages 3 and 4			
7	54	51.6	0.9890
9	67	43.0	0.444
6	73	49.4	−1.918
10	50	33.2	−1.135
12	30	22.3	−0.322
13	38	36.8	0.580
mean ± SD (median)	52.0 ± 16.5 (52.0)	39.4 ± 10.9 (39.9)[c]	−0.23 ± 1.12 (0.06)

[a]Value before ACEI/ARB therapy was initiated.
[b]Zero time assigned to the point at which ERT was initiated.
[c]$P = 0.0298$, two-tailed t test, comparing the regression intercept to initial eGFR when ACEI/ABR therapy was started.

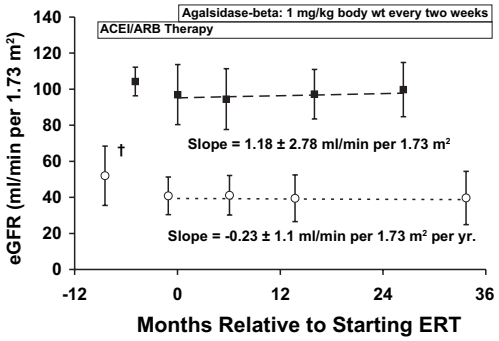

Figure 4. Estimated MDRD GFR and progression rates during the observational study. ■, Mean (±SD) values for the four patients with less severe Fabry nephropathy; ○, mean values (±SD) for the six patients with more advanced Fabry nephropathy. The mean progression slopes (±SD) are shown for both groups and are not significantly different from zero. $^{\dagger}P = 0.0298$, two-tailed *t* test, comparing the average regression intercept with average initial eGFR when ACEI/ABR therapy was started.

disease and stages 3 and 4 CKD, before the institution of ACEI/ARB therapy (Table 2). Some of the patients did received ACEI/ARB therapy, but there was no systematic effort to reduce urinary protein excretion. The final BP were 121 ± 15 mmHg (systolic) and 72 ± 10 mmHg (diastolic), and the final urine protein/creatinine ratios were 1.4 ± 1.6,[8] values that are much higher than we report for our patients with stages 3 and 4 CKD and Fabry disease at the end of the 30-mo follow-up period (Table 2).

A phase III extension study with agalsidase-β has been reported[10]; minimal rates of progression during a 5-yr follow-up period were seen patients who did not initially have overt proteinuria. Of note, a subset of patients who had normal initial eGFR but had glomerulosclerosis in 50% of their glomeruli and/or proteinuria >1 g/d had rapid decline of their eGFR.[10]

Schiffmann *et al.*[12] described 14 patients with overt baseline proteinuria; 11 were switched from bimonthly to weekly infusions of agalsidase-α and followed for 24 mo. At the switch, mean eGFR was 53.7 ± 20.9 ml/min per 1.73 m^2, and mean rate of progression was −8.0 ± 2.7 ml/min per 1.73 m^2 per yr. With weekly dosing of agalsidase-α, the progression rate was −3.3 ± 4.6 ml/min per 1.73 m^2/yr, but urinary protein excretion remained the same. The improved progression rate suggests an effect of increasing the dosage of ERT, as has previously been noted,[11,13] but these progression rates are greater than reported herein with agalsidase-β and ACEI/ARB therapy.

The importance of BP control[17,20,21] and the renal protective effects of antiproteinuric therapy have received well-deserved attention.[22–26] The primary effect is undoubtedly due to reductions in BP, but other, nonhemodynamic effects may account for improved outcomes with ACEI/ARB compared other antihypertensive agents.

We have applied this approach for reducing proteinuria to patients who had Fabry nephropathy and were also being treated with agalsidase-β. Our earlier experience suggested that the beneficial effects of ACEI/ARB therapy on eGFR progression requires optimal dosing of ERT; we would not expect ACEI/ARB therapy to slow eGFR progression in the absence or with suboptimal dosages of ERT.[11] Schiffmann *et al.*[12] recently confirmed this conclusion that 0.2 mg/kg body wt agalsidase-α given every 2 wk is not an effective dosage of ERT for treating moderately severe Fabry nephropathy.

Although ACEI/ARB therapy reduced systemic BP, the urinary protein/creatinine ratios were reduced to ≤0.5 g/g. The achieved systemic BP levels were similar in our patients with stages 3 and 4 CKD to patients with stages 1 and 2 CKD before or after institution of ACEI/ARB therapy and were reasonably well tolerated without any serious adverse events. This approach is similar to that recently proposed for treating diabetic nephropathy,[26] with the goal of reducing urinary protein excretion to ≤0.5 g/d, rather than simply lowering systemic BP to a preset target level.

Confirmation of our single-center experience with a larger group of patients in a multicenter study is under way, using combined agalsidase-β and ACEI/ARB therapy in which the primary treatment effect will be sustained reduction in urinary protein/creatinine ratio ≤0.5 g/g, with the primary outcome measure being the rate of progression of eGFR.[13,27]

CONCISE METHODS

Patient Selection and Treatment

We describe the first group of patients who had Fabry disease and were treated at UAB with agalsidase-β (Fabrazyme; Genzyme Corp., Cambridge MA), given intravenously at 1 mg/kg body wt every 2 wk. Four male patients who had kidney transplants before starting ERT and were not expected to have any effect of ERT on their kidney function are excluded from this report.[28] The 30-mo observation period was *a priori* chosen to extend 12 mo beyond the median follow-up period of the phase IV study of agalsidase-β therapy.[8]

The patients were seen on a regular basis in our outpatient clinic and received standard clinical care for patients with CKD.[14,29] After initial evaluation, the patients were started on ACEI/ARB therapy for proteinuria. After confirmation of their eligibility, ERT treatment was begun with agalsidase-β. Various infusion centers were used, all of which were separate from the UAB Fabry Clinic. Proteinuria, albuminuria, and urine creatinine were measured in 24-h urine collections at the initial evaluation and at nearly all subsequent visits. All patients signed consents approved by the UAB institutional review board (X050202007) and were enrolled in the Fabry registry (https://www.lsdregistry.net/fabryregistry/). This open-label observational study was registered at http://ClinicalTrials.gov (NCT00343577).

Data Presentation and Analyses

The primary goal was to determine the tolerability of ACEI/ARB therapy in dosages that would minimize the urinary protein/creatinine ratio in Fabry nephropathy. The eGFR rate of decline was the out-

come measure. The Modification of Diet in Renal Disease (MDRD) eGFR equation used serum creatinine, gender, and age (all participants were white).[30] Nearly all of the laboratory tests were performed at the UAB Clinical Laboratory; the creatinine method has been "calibrated."[30]

The progression rate (ml/min per 1.73 m^2 per yr) was calculated as the regression slope of the eGFR obtained at each patient's follow-up visit. The tables present data obtained before initiation of ACEI/ARB therapy, at the clinic visit closest to the start of agalsidase-β therapy, at the clinic visits closest to 6 and, 18 mo, and at the last available clinic visit for each patient. The figures present individual patient regressions for urine protein/creatinine ratio and eGFR.

The first patient was seen on August 27, 2001, and the last patient entered the study on October 24, 2004. The final visits occurred on December 11, 2006. The patients were treated with ACEI/ARB therapy for 7.3 $\pm$ 6.4 mo (median 5.2 mo; range -20.6 to 0) before starting ERT. The average duration of follow-up was 30.3 $\pm$ 9.8 mo (median 30.1 mo; range 16 to 43) after starting ERT for the 10 patients who could be fully analyzed. To facilitate comparison with the phase IV trial,[8] we divided the patients into two groups on the basis of the initial eGFR: Four patients with eGFR >60 ml/min per 1.73 m^2 (stages 1 and 2 CKD) and seven patients with eGFR ≤ 60 ml/min per 1.73 m^2 (stages 3 and 4 CKD).

Standard methods were used for descriptive statistics, comparison of means, and regression analyses (Microsoft Excel, Office 2004 for Macintosh; Microsoft, Redmond, WA). Normal distributions were assumed for BP and eGFR, and these were compared with two-tailed paired *t* test. Urine protein excretion is not normally distributed in Fabry nephropathy,[8] so these comparisons were carried out with transformed urinary protein/creatinine ratios. The fourth-root transformation of proteinuria was used in the phase IV study[8]; we used the same transformation because we had too few patients to assess the distribution normality independently. Linear regression analysis was performed for individual patients as well as grouped means. The intercepts of these analyses were compared with the last available determinations of urine protein/creatinine ratio and eGFR obtained before ACEI/ARB therapy was started. The regression slopes were used to evaluate the stability of urine protein/creatinine ratio and eGFR over time after ERT was begun. Significance was assumed when the calculated *P* values were <0.05. Descriptive data are presented as means $\pm$ SD and medians (range).

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Preliminary results from this study were presented at the annual meetings of the American Society of Nephrology; November 8 through 13, 2006; Philadelphia, PA; and November 14 through 19, 2996; San Diego, CA; and published in abstract form (*J Am Soc Nephrol* 16: 142, 2005; and *J Am Soc Nephrol* 17: 625, 2006).

DISCLOSURES

D.G.W. serves as a consultant for Genzyme Corp. and participates on Registry Advisory Panels and the Speakers Bureau on Fabry disease. He has received research support from Genzyme Corp. and participated in the phase IV agalsidase-β trial. L.L.J. has been supported by research grants from Genzyme Corp. The patients described in this study all have been registered in the Fabry Registry at https://www.lsdregistry.net/fabryregistry/. Data collection, analysis of the results, and preparation of the manuscript were carried out entirely independent of Genzyme Corp., including any and all medical writers and data analysts. H.T. has no relevant conflict of interest.

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See the related editorial, "Fabry Nephropathy and the Case for Adjunctive Renal Therapy," on pages 2426–2428.