Nephrol Dial Transplant (2008) 23: 1628–1635
doi: 10.1093/ndt/gfm813
Advanced Access publication 5 December 2007

Original Article

NDT
Nephrology Dialysis Transplantation

Agalsidase therapy in patients with Fabry disease on renal replacement therapy: a nationwide study in Italy

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Abstract

Background. In Fabry disease, end-stage renal disease (ESRD) and severe neurologic and cardiac complications represent the leading causes of late morbidity and mortality. A comprehensive Italian nationwide survey study was conducted to explore changes in cardiac status and renal allograft function in Fabry patients on renal replacement therapy (RRT) and enzyme replacement therapy (ERT).

Methods. This study was designed as a cross-sectional survey study with prospective follow-up. Of the 34 patients identified via searches in registries, 31 males and 2 females who received RRT and ERT (agalsidase beta in 30 patients, agalsidase alpha in 3) were included. Left ventricular mass index (LVMI), interventricular septal thickness at end diastole (IVSD), left ventricular posterior wall thickness (LVPWT) and renal allograft function were assessed at ERT baseline and subsequently at yearly intervals.

Results. The patients in the dialysis and transplant groups had been started on dialysis at age 42.0 and 37.1 years (mean), respectively, and patients in the transplant group received their renal allograft at age 39.8 years (mean). The mean age at the start of ERT was similar, 44.1 and 44.6 years, respectively. The mean RRT follow-up was 61.1 and 110.6 months for dialysis and transplant patients, respectively, whereas the ERT duration was 45.1 and 48.4 months, respectively. Cardiac parameters increased in dialysis patients. In transplant patients, mean LVMI seemed to plateau during agalsidase therapy at a lower level as compared to baseline. Decline in renal allograft function was relatively mild (−1.92 ml/min/year). Agalsidase therapy was well tolerated. Serious ERT-unrelated events occurred more often in the dialysis group.

Conclusions. Kidney transplantation should be the standard of care for Fabry patients progressing towards ESRD. Transplanted Fabry patients on ERT may do better than patients remaining on maintenance dialysis. Larger, controlled studies in Fabry patients with ESRD will have to demonstrate if ERT is able to change the trajectory of cardiac disease and can preserve graft renal function.

Keywords: agalsidase; dialysis; end-stage renal disease; enzyme replacement therapy; Fabry disease; transplantation

Introduction

Fabry disease is a rare X-linked recessive metabolic disorder resulting from deficient activity of the lysosomal enzyme α-galactosidase A (α-Gal A). The enzymatic defect leads to progressive accumulation of glycosphingolipids in a variety of cell types, including vascular endothelial cells, renal cells and cardiomyocytes. Proteinuria usually manifests before the fourth decade of life and chronic renal failure (CRF) rapidly progresses to end-stage renal disease (ESRD) requiring dialysis and kidney transplantation [1].

Patients on renal replacement therapy (RRT) are prone to suffer severe cardiomyopathy, premature stroke and transient ischaemic attacks causing morbidity and high mortality [2,3]. In patients with Fabry disease, these complications are due to progression of primary Fabry-related organ disease and, in addition, are driven by cardiovascular disease seen in most patients on dialysis [2]. Kidney transplantation

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has been reported to restore renal function, to ameliorate extrarenal clinical symptoms of Fabry disease, and in the long term, to improve graft and patient survival [4,5].

Two studies have provided some evidence that, in patients on RRT, enzyme replacement therapy (ERT) with agalsidase is safe and well tolerated and may be able to alter the trajectory of Fabry cardiomyopathy [6,7]. Both studies have analysed a small number of patients that received agalsidase therapy for a relatively short duration.

The current study provides a unique insight into the population of Italian Fabry patients on RRT and explores changes in cardiac status and renal allograft function after longer term agalsidase therapy.

Subjects and methods

Data collection

To identify patients diagnosed with Fabry disease among the Italian population of patients on RRT, we submitted specific queries to the managers of three registries, i.e. the Fabry Registry, the Fabry Outcome Survey and the Italian Registry of Dialysis and Transplant (RIDT, Registro Italiano Dialisi e Trapianto). A study questionnaire was sent to the centres providing care to the identified patients. The questionnaire collected anonymized data on demographics, clinical characteristics, diagnosis, molecular analyses and specifics of ERT. We extended the survey by including sites that had not been identified by the registry searches but where, based on the authors' personal knowledge, Fabry patients were on RRT. Eventually, we submitted the study questionnaire to a total of 21 out of the 267 nephrology centres in Italy. Once enrolled in this cross-sectional survey study, patients' data were prospectively reviewed at yearly intervals. The extraction of data was approved by the Hospital Ethics Board.

Clinical and biochemical evaluations

Data were collected at ERT baseline and every 12 months thereafter. At all laboratories, serum creatinine levels were analysed using the Hitachi 911 Autoanalyzer (Roche Diagnostics®). Creatinine clearance (Ccr) was determined using the Cockcroft–Gault formula. Proteinuria was measured using a nephelometer technique (Dade–Behring®) with a 20% trichloroacetic acid solution. Globotriaosylceramide (Gb3) analyses in plasma and urine samples were performed at the Mass Spectrometry Center of the University of Florence using a method described elsewhere [8].

A standard cardiologic evaluation, including electrocardiography and cardiac ultrasound (conventional 2D-guided M-mode echo-Doppler with a 4-chamber technique), had been performed prior to the start of ERT and was subsequently done at yearly intervals by the same consultant cardiologist at each patient's medical centre. Left ventricular mass (LVM) was calculated using the Devereux formula based on three to five averaged measurements of IVSD, LVPWT and left ventricular end diastolic diameter. LVM was indexed to body surface area to yield the LVM index (LVMI) [9].

Occurrences of acute cardiologic and neurologic ischaemic attacks were recorded during the control visits.

Enzyme replacement therapy

At the individual investigator's discretion, patients had been started on biweekly intravenous infusions of agalsidase alpha (Replagal®, Shire Corp.) at a dose of 0.2 mg/kg bodyweight infused over 40 min, or with agalsidase beta (Fabrazyme®, Genzyme Corp.) at biweekly doses of 1 mg/kg bodyweight. Agalsidase beta infusions were initially administered over 4 h, but after the first month of therapy the infusion duration could be safely decreased by 15 min per infusion. At 6 months, agalsidase beta infusions were administered over 2 h. As dialysis is not expected to interfere with agalsidase pharmacokinetics [10], agalsidase infusions were administered either during or after the dialysis session, or on the day after dialysis.

Statistical analysis

Results are expressed as mean, SD and range. Correlations were investigated by simple regression analysis (Pearson's correlation coefficient). The Chi-square test was used to evaluate the numbers of events. A P-value of <0.05 was used as the level of statistical significance.

Results

Out of the 21 Italian nephrology centres, 19 returned the study questionnaire and 34 patients (32 males/2 females) with Fabry disease on RRT (17 on dialysis, 17 with a functioning kidney transplant; Table 1) were identified. The data from an 80-year-old male dialysis patient who did not have evidence of classic multisystemic disease and had not been started on agalsidase therapy were not included in the analyses. Two sites did not return the questionnaire because their two patients did not sign the informed consent form. Table 2 presents details on timing of diagnosis, start of RRT and ERT, follow-up and disease outcomes. The diagnosis of Fabry disease had been established either via renal biopsy (18 patients) or via biochemical screening (16 patients) at the mean age of 39.3 and 36.8 years for the patients in the dialysis and transplant groups, respectively. The mean age at completion of the study questionnaire was similar, 48.2 and 49.1 years, respectively. Prior to the start of ERT, patients in the dialysis group had received 1.1 year (mean) of dialysis therapy. Patients in the transplant group had received 2.7 years (mean) of dialysis therapy prior to transplantation that was performed 4.8 years (mean) before the start of ERT. The mean total duration of RRT was 61.1 months for the dialysis patients and 110.6 months (excluding dialysis) for the transplant patients. Symptoms of Fabry disease reported at clinical onset are presented in Table 3. ERT was initiated in 33 out of the 34 patients at comparable mean ages, 44.1 and 44.6 years for dialysis and transplant patients, respectively. The vast majority of the patients ($N = 30$) received agalsidase beta therapy; three patients were treated with agalsidase alpha. The overall mean ERT follow–up was 45.1 and 48.4 months, respectively (Table 4).

Table 1. Baseline laboratory findings (residual enzyme activity, GLA mutation)

Patient number	Gender	Leukocyte α-Gal A activity (nmol/h/mg protein)	*GLA* mutation
Dialysis group			
1	M	0.013	na
2	M	0	G260E (exon na)
3	M	1.80	A10646 (exon 6)
4	M	1.40	A10646 (exon 6)
5	M	na	na
6	M	0.20	A143T (exon na)
7	M	0.01	E59K (exon 1)
8	M	0.01	G360D (exon 7)
9	M	0.10	C1133G (exon 7)
10	M	0.20	T483C (exon 3)
11	M	0.04	G1085A (exon na)
12	F	4.50	G274S (exon 6)
13	M	na	na
14	M	na	na
15	M	0.90	R227Q (exon 4)
16	M	na	na
17	M	na	A143T (exon na)
Transplant group			
1	M	0.90	R227Q (exon 4)
2	M	0.10	I317T (exon 6)
3	M	0.80	I354K (exon 7)
4	M	0.20	512A (exon 3)
5	F	0.80	R220X (exon 5)
6	M	0.80	R112C (exon 2)
7	M	0.60	na
8	M	2.40	D313Y (exon 6)
9	M	0.16	R112C (exon 2)
10	M	0.01	R220X (exon 5)
11	M	0.10	V269M (exon 6)
12	M	0.60	1021insT (exon 5)
13	M	1.40	S78X (exon 2)
14	M	0.10	E59K (exon 1)
15	M	1.80	A10646 (exon 6)
16	M	na	na
17	M	na	na

M, male; F, female; na, not available.

Cardiac data collected at ERT baseline and at 1, 2, and 3 years of ERT are presented in Table 5. At 3 years of ERT, the mean LVMI had increased by 19% (from 210.9 to 251.0 g/m^2) in the seven dialysis patients with data [P = not significant (ns)], and decreased by 6% (from 234.6 to 220.8 g/m^2) in transplant patients (P = ns, Table 5, Figure 1). Both IVSD and LVPWT showed slight increases in the dialysis patients ($N = 7$, P = ns) and decreases in transplant patients ($N = 12$, P = ns). In transplant patients ($N = 8$), diastolic blood pressure dropped by 12% (from 82 to 72 mmHg) after 3 years of ERT, while changes in systolic blood pressure were minimal. Blood pressure data were available only for a small number of dialysis patients. In both groups, the analysis of comorbidity factors, including body weight and serum haemoglobin, did not reveal significant variations between baseline and the 36-month control visit (data not shown).

In transplant patients, mean serum creatinine increased from 1.78 at ERT baseline to 1.92 mg/dl (+8%) at 4 years of ERT ($N = 12$, P = ns), while mean Ccr decreased from 52.9 to 45.2 ml/min (−15%, P = ns, Figure 2). The rate of decline in renal function from baseline to the last control was only −1.92 ml/min/year. Mean (±SD) proteinuria was 92 ± 135 g/day at baseline ($N = 16$) and 66 ± 74, 75 ± 131, 180 ± 292 and 180 ± 307 g/day ($P = 0.23$) at 1 to 4 years of ERT follow-up.

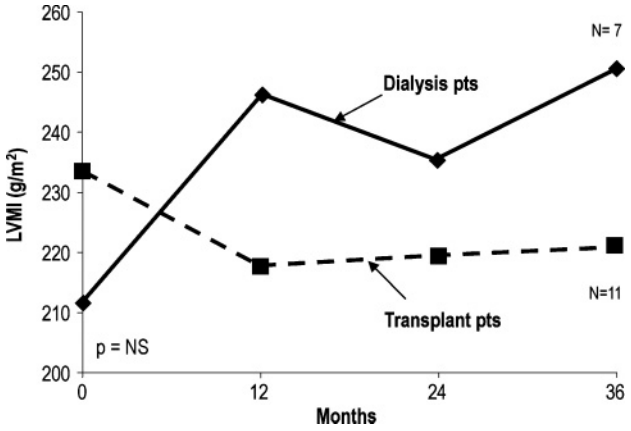

Fig. 1. Left ventricular mass index (LVMI) in dialysis and transplant patients with 36 months of follow-up.

In a small group of four transplant patients, mean (±SD) serum Gb3 concentration reduced from 6.76 ± 2.66 at baseline to 4.0 ± 1.63 at 12-month control ($P < 0.05$).

Table 2. Ages at the start of RRT and ERT and outcomes in Fabry patients

Dialysis group Patient number	Age at diagnosis	Age at start of dialysis and type	Age at start of ERT	Age at survey	Dialysis follow-up (months)	ERT follow-up (months)	6-year outcome
1	40	43 HD	40	46	24	72	Tx
2	19	27 HD	26	32	61	63	Tx
3	46	46 HD	46	52	37	22	Died
4	47	50 PD	50	52	39	22	Died
5	50	51 PD	50	55	59	72	
6	55	52 HD	55	58	81	55	Died
7	49	50 HD	48	52	21	38	Tx
8	25	22 HD	25	27	63	31	
9	22	32 PD	31	36	44	51	Tx
10	33	33 HD	45	50	190	52	Tx
11	52	52 HD	52	54	61	59	Died
12[a]	61	58 HD	60	66	91	66	
13	54	47 HD	55	61	–	69	Died
14	32	31 HD	33	37	–	14	Tx
15	15	40 HD	42	45	59	37	Died
16	30	39 HD	39	41	19	19	
17[b]	*77*	*70 HD*	*NA*	*NA*	*136*	*NA*	*Died*
Mean ± SD (range)	39.3 ± 14.9 (15–61)	42.0 ± 10.8 (22–58)	44.1 ± 10.5 (25–60)	48.2 ± 11.5 (27–66)	61.1 ± 43.0 (19–190)	45.1 ± 19.8 (14–72)	

Transplant group Patient number	Age at diagnosis	Age at Start of dialysis	Age at Transplant	Age at start of ERT	Age at survey	Transplant follow-up (months)	ERT follow-up (months)	6-year outcome
1	30	30	33	35	41	75	48	HD
2	31	55	56	58	63	83	65	
3	37	40	41	49	54	163	62	
4	21	21	22	29	34	141	61	
5[a]	40	28	35	40	45	122	55	
6	35	39	40	45	49	107	54	
7	38	39	40	54	58	226	53	
8	27	24	27	28	31	55	13	ERT stop
9	47	47	49	57	62	153	52	
10	45	39	40	45	49	116	51	
11	40	28	31	40	44	156	49	
12	36	32	33	36	40	79	45	
13	21	30	33	39	44	136	36	
14	58	49	52	58	61	103	39	
15	46	46	49	49	52	34	34	HD
16	33	33	42	49	50	14	14	
17	40	43	45	45	46	19	19	
Mean ± SD (range)	36.8 ± 9.5 (21–58)	37.1 ± 9.4 (21–55)	39.8 ± 8.9 (22–56)	44.6 ± 10.0 (28–58)	49.1 ± 9.3 (31–63)	110.6 ± 48.6 (14–226)	48.4 ± 13.2 (13–65)	

RRT, renal replacement therapy; ERT, enzyme replacement therapy; SD, standard deviation; [a]female; [b]elderly patient who was not started on ERT (excluded from analyses); HD, haemodialysis; PD, peritoneal dialysis; –, not available; NA, not applicable; Tx, transplant.
All ages in years. For clarity, years and months are presented without decimals. Means are calculated using one decimal value.

Table 3. Symptoms reported at clinical onset of Fabry disease

Fabry symptom	Number of patients with symptom (%)
Pain/acroparaestesias	13 (38)
Fever	2 (6)
Angiokeratomas	11 (32)
Cornea verticillata	19 (56)
Hypohidrosis	2 (6)
Hearing loss	3 (9)
Abdominal pain	4 (12)
Proteinuria	23 (68)
Cardiac involvement	7 (20)
Chronic renal failure	12 (35)
Transient ischaemic attack/stroke	1 (3)

Table 4. Specifics of ERT in patients with Fabry disease on RRT

	Dialysis patients	Transplant patients
Patients on ERT	16/17	17/17
Mean age of start of ERT (years ± SD)	44.1 ± 10.5	44.6 ± 10.0
Mean ERT duration (months ± SD)	45.1 ± 19.8	48.4 ± 13.2
Patients on Fabrazyme® 1 mg/kg	14/16	16/17
Mean infusion time (min)	113	128
Patients on Replagal® 0.2 mg/kg	2/16	1/17
Mean infusion time (min)	40	40

ERT, enzyme replacement therapy; RRT, renal replacement therapy; SD, standard deviation.

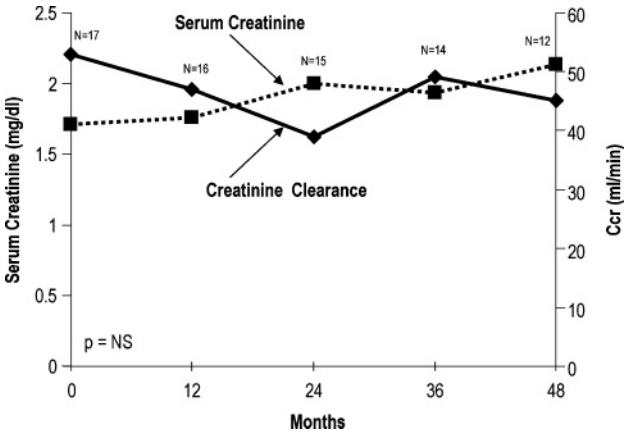

Fig. 2. Renal function expressed as mean serum creatinine and mean creatinine clearance (Ccr) in all transplant patients on enzyme replacement therapy.

Urinary Gb3 was not detectable at baseline and at 1-year follow-up.

During ERT, nine acute cardiac and cerebrovascular events occurred in the dialysis group and three in the group of allograft recipients ($P < 0.05$). All were considered to be unrelated to agalsidase therapy. Six years after the survey, 6 of the 16 dialysis patients who started on ERT had deceased, 6 were successfully transplanted and only 4 continued to receive dialysis plus ERT. By contrast, of the 17 transplant patients, 14 patients still have a functioning kidney and continue to receive ERT, while 2 patients suffered graft failure and returned to dialysis treatment. Agalsidase therapy was discontinued in one patient who was found to have the chromosomal polymorphism D313Y that causes α-Gal A pseudodeficiency in plasma [11].

Discussion

ESRD due to rapidly progressive CRF is a common complication in male patients with Fabry disease and may manifest in female patients, although generally later in life [2,12]. Large registries have reported a frequency of occurrence of Fabry disease in ESRD patient populations of up to 0.017% [2,3] but the true prevalence may be almost 10 times as high [13]. Only 10% of the Fabry patients in RRT registries were females. As part of our survey study, three different registries were searched for patients on RRT in Italy. We found 34 patients with a confirmed diagnosis of Fabry disease in an estimated population of 43 986 patients on dialysis and 15 198 patients with a functioning renal allograft (as per most recent update from 31 December 2004) [14]. This results in a theoretical prevalence of Fabry disease amongst the Italian population of RRT patients of 0.057%. This may be an underestimation due to the voluntary nature of participation in the registries that have been searched, due to misdiagnosis of unidentified Fabry patients in the RIDT, or due to unavailability of data on diagnosis of patients enrolled in the aforementioned registry. Indeed, there may have been some individuals with Fabry disease amongst the 2% of the total number of patients enrolled in the RIDT with missing data on diagnosis [14].

Three-year survival rates among the Fabry patients on dialysis in the American USRDS registry (63%) [2] and the European EDTA-ERA registry (60%) [3] were comparable, but significantly lower as compared to non-Fabry, non-diabetic controls. At present, the experiences with ERT in Fabry patients with ESRD on RRT are limited to a few studies that enrolled only a small number of patients. A study of six Fabry patients receiving dialysis plus agalsidase beta therapy at 1 mg/kg for 2 years revealed improvement in extrarenal symptoms (e.g. acroparaesthesias, pain crises) and quality of life, as well as slowing of the progression of cardiomyopathy [7]. In our pilot study, we have demonstrated the safety and efficacy of an 18-month course of agalsidase beta therapy in three Fabry patients with a renal transplant who had severe cardiac involvement [5]. Renal function, as restored by kidney transplantation, was preserved and no adjustments of the immunosuppressive regimens were required. Cardiac responses were not uniform but echocardiography demonstrated an appreciable reduction in LVM in two of the three patients. Plasma Gb3 levels reduced in all patients by ∼30 to 50%.

We have explored the changes in cardiac parameters and renal allograft function abnormalities in the largest cohort of Fabry patients on RRT and ERT reported to date. The mean ERT follow-up of the 33 individuals was longer as compared to previous studies [5,7], i.e. 4 years for transplant patients and 3.8 years for dialysis patients. Although the number of patients with 3-year cardiac data was modest, we made some interesting observations. The mean LVMI, IVSD and LVPWT values at pre-ERT baseline were higher in transplant patients as compared to dialysis patients. An increase in mean LVMI was seen in dialysis patients, particularly during the first year of ERT. Mean IVSD and LVPWT levels slightly increased mainly during the third year of ERT. Such a persistence of progressive extrarenal signs and symptoms is a phenomenon that is generally observed in patients with other underlying diseases who undergo maintenance dialysis therapy. Of the 16 patients on dialysis and ERT treatment, 8 were on the waiting list for renal transplantation at baseline (before ERT). Six years after the survey, 6 of these 8 patients had been transplanted, one deceased while on the waiting list and one is still on this list. By contrast, five of eight dialysis patients not eligible for renal

Table 5. Cardiac parameters at baseline and at yearly ERT follow-up in Fabry patients on ERT and RRT

ERT treatment duration		Baseline	*N*	1 year	*N*	2 year	*N*	3 year	*N*	Change
LVMI (g/m^2)	D	210.9	*7*	247.5	*7*	235.5	*7*	251.0	*7*	+19%
	Tx	234.6	*11*	218.7	*11*	219.3	*11*	220.8	*11*	−6%
IVSD (cm)	D	1.55	*15*	1.56	*15*	1.50	*12*	1.68	*7*	+8%
	Tx	1.63	*15*	1.65	*14*	1.69	*13*	1.49	*12*	−9%
LVPWT (cm)	D	1.39	*15*	1.41	*15*	1.37	*12*	1.46	*7*	+5%
	Tx	1.56	*15*	1.56	*14*	1.51	*13*	1.50	*12*	−4%
sBP (mmHg)	D	150	*6*	155	*4*	139	*4*	142	*2*	NA
	Tx	127	*11*	112	*10*	112	*10*	124	*8*	−2%
dBP (mmHg)	D	92	*6*	89	*4*	81	*4*	82	*2*	NA
	Tx	82	*11*	74	*10*	74	*10*	72	*8*	−12%

ERT, enzyme replacement therapy; RRT, renal replacement therapy; LVMI, left ventricular mass index; IVSD, interventricular septal thickness at end diastole; LVPWT, left ventricular posterior wall thickness; sBP, systolic blood pressure; dBP, diastolic blood pressure; D, dialysis; Tx, transplant.

transplant had died by the end of the survey study. Mortality is high in these patients due to gradually developing life-threatening cardiologic and neurologic complications [15]. Fabry patients on dialysis suffer from both primary Fabry-related cardiac disease and cardiovascular disease driven by dialysis therapy. Larger scale, controlled clinical studies will be required to determine if sustained ERT has any impact on the trajectory of cardiac deterioration in Fabry patients on dialysis.

In transplant patients, the mean LVMI value seemed to plateau at a level lower than the baseline level and the mean IVSD and LVPWT levels did not increase during agalsidase therapy either. There are literature reports describing amelioration of extrarenal Fabry symptoms correlated to the autonomic dysfunction (e.g. neuropathic pain, hypohidrosis, acroparaesthesias) within a few months after renal transplantation [4,16]. The mechanisms underlying such improvements are largely unknown. Some authors have attributed them to increased levels of circulating α-Gal A [17]. However, others believe that the natural α-Gal A level in renal allograft tissue may be insufficient to normalize the serum enzyme level or to modify systemic substrate deposition or progression of systemic Fabry complications, including cardiac disease [18]. Transplanted Fabry patients are at increased risk of developing potentially fatal complications involving vital organs [19]; however, results from the aforementioned registries suggest that survival in these patients may be similar to survival in allograft recipients with other primary renal diseases.

With the current state of knowledge, it is not possible to ascribe any of the findings in transplanted patients in our study to ERT, although positive effects of ERT on cardiac status in non-RRT Fabry patients have been reported. Improvements or stabilization of LV hypertrophy (LVH) has been noted after 2 years of agalsidase beta therapy in Fabry patients with a normal or marginally impaired renal function [20]. Clearance of the Gb3 substrate from cardiomyocytes, reduction in LVM and improvement of cardiac performance have been described after 23 months of agalsidase beta therapy [21]. It should be noted that it is unlikely that reduction in LVH is caused mainly by substrate clearance as the amount of Gb3 supposedly represents only 1% of increased LVM [22] and that myocardial fibrosis [23] in advanced Fabry disease may preclude improvement in functionality of the heart. As for Fabry patients on dialysis, further controlled studies in larger groups of patients, ifethically feasible, will have to elucidate if ERT can have any positive effect on the decline of cardiac hypertrophy in transplanted Fabry patients.

Hypertension is uncommon in Fabry disease patients and, therefore, may not be a determinant of hypertrophic Fabry cardiomyopathy [24,25]. Blood pressure data from dialysis patients were insufficient and no information was available on antihypertensive treatment. Therefore, it remains unsure what caused the decrease in mean diastolic blood pressure during the first year of ERT in transplanted Fabry patients. Changes in mean systolic blood pressure in this group were minimal.

Exploration of changes in renal allograft function showed that serum creatinine and Ccr remained relatively stable after 3 years of ERT. During 6 years of survey, two patients suffered graft failure and returned to dialysis treatment. At 4 years of ERT, the rate of decline in Ccr was lower than the reported natural loss of Ccr in non-transplanted, non-ERT-treated Fabry patients, i.e. −1.92 versus ∼−12 ml/min/year [26]. This seems to mirror the observed preservation of renal function in long-term ERT-treated patients without a renal transplant [27,28]. Out of 17 patients in our series, 10 currently have a graft survival of almost 10 years and 1 patient received his transplant more than 20 years ago. The positive outcome in transplant patients was also reflected by the low proteinuria levels (<200 mg/day) up to 4 years of ERT follow-up.

The number of patients who dropped out of the study was higher in the dialysis group than in the transplant group because 6 of the 16 ERT-treated patients died during the survey follow-up and 6 were transplanted. In our survey, only one patient who was on the waiting list for renal transplant died while the remaining five patients who deceased during the follow-up were not eligible for transplantation at baseline in all cases due to the severity of the cardiomyopathy.

Based on the authors' collective experience with maintenance dialysis and renal transplantation in patients with Fabry disease, and as previously proposed [16], transplantation should be the standard of care for Fabry disease patients with ESRD. These patients should be encouraged to participate in an early 'allograft replacement therapy' programme. Profound renal damage and CRF in Fabry patients

can probably be prevented in the future by early initiation of agalsidase ERT [28]. The results of the Phase IV agalsidase beta (1 mg/kg) clinical trial in patients with mild CRF have demonstrated the beneficial effects of agalsidase beta as it may slow the progression of CRF, particularly if therapy is started when eGFR is still above 55 ml/min [27]. The Phase III agalsidase beta extension study (4.5 years of therapy at 1 mg/kg) [28] has provided further proof that renal function may be preserved and CRF can be prevented if ERT is introduced early, perhaps even as early as in childhood [29]. If started too late, ERT cannot be expected to reverse glomerulosclerosis and renal fibrosis, and progression to ESRD may be inevitable [27,28]. For these patients, a kidney transplantation would be advantageous if performed before the start of dialysis treatment when CRF is still moderate and before the patient endures the negative effects of severe uraemia and dialysis on cardiomyopathy. Moreover, it is most likely that the cardiac damage due to Fabry disease at this stage has not yet advanced to a state that would prohibit the patient's entry onto the waiting list for renal transplantation.

Limitations of our study include the small sample size that was due to the rarity of Fabry disease and the resultant low number of available Fabry patients on RRT in Italy. The low prevalence of Fabry disease, in combination with ethical concerns, precluded the inclusion of control groups in the current study. Italian nephrology centres treating Fabry patients on dialysis or transplanted Fabry patients were identified by searching existing registries. Although we estimate that, based on the authors' personal knowledge and results of registry searches, our cohort represents practically all Fabry patients currently on RRT in Italy, theoretically we may have missed patients given the voluntary registry participation, incorrect diagnosis or lack of information on diagnosis. For example, we included two sites that had not been identified by the registry searches. Furthermore, the interpretation of the observations, including changes in slopes of disease progression, was limited by the unavailability of pre-ERT data collected throughout the course of the disease, particularly around the start of RRT, and during the first years of RRT.

In summary, in this nationwide cross-sectional survey study with prospective follow-up, we studied 33 Italian Fabry patients with ESRD. The patients had either undergone kidney transplantation or were on maintenance dialysis therapy and received agalsidase ERT. The cohort reported herein is the largest of its kind and follow-up is longer than in previous studies. Changes in cardiac parameters and renal allograft function abnormalities were explored in patients who received ERT for a minimum of 3 years. Although no conclusions can be drawn given the small sample sizes, we observed signs of progression of cardiomyopathy in Fabry patients on dialysis, while Fabry patients with a renal allograft generally did better. It is not certain if, in any way, ERT has positively influenced Fabry-induced cardiomyopathy and how renal transplantation may change the trajectory of cardiac disease in Fabry patients with ESRD. The rate of decline in allograft renal function after 4 years of ERT was well below levels reported for untreated non-ESRD Fabry patients.

It remains to be elucidated in larger, controlled studies if agalsidase therapy is able to impact on the rate of cardiac disease progression and can preserve graft renal function in Fabry patients, both in the short and long term.

Acknowledgements. We would like to thank Professor David G. Warnock for his kind review of the manuscript.

Conflict of interest statement. None declared.

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Received for publication: 21.5.07
Accepted in revised form: 17.10.07