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ORIGINAL ARTICLE

Kidney transplantation in patients with Fabry disease

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Summary

Little is known about the effects of enzyme replacement therapy (ERT) in kidney transplant recipients with Fabry disease. Clinical characteristics of transplant recipients in the Fabry Outcome Survey (FOS) were therefore examined in patients with Fabry disease with or without ERT. Of the 837 European patients in FOS (March 2006), 34 male patients and two female patients had received kidney transplants. Mean age at transplantation was 37.6 ± 10.9 years, mean time since transplantation was 7.7 ± 6.4 years, median estimated glomerular filtration rate (eGFR) was 44.4 ml/min/1.73 m^2, and median proteinuria was 296 mg/24 h. Of 27 patients with baseline data, 59% had hypertension, 74% had left ventricular hypertrophy, 22% had cardiac valve disease, 30% had arrhythmia, and 22% had transient ischaemic attacks and 15% stroke. Twenty patients (74%; two female patients, 18 male patients) were receiving ERT with agalsidase alfa. At enrolment or at the start of ERT, median eGFRs were 59 and 35 ml/min/1.73 m^2 ($P = 0.05$) and median proteinuria levels were 240 and 420 mg/24 h (not significant) in treated and untreated patients respectively. Renal function remained stable in patients receiving ERT. In conclusion, agalsidase alfa is well tolerated in patients with Fabry disease who have undergone renal transplantation.

Introduction

Fabry disease is a rare X-linked glycosphingolipid storage disorder that is caused by a deficiency of the lysosomal enzyme α-galactosidase A. This leads to progressive abnormal accumulation of neutral glycosphingolipids, primarily globotriaosylceramide (Gb_3), in lysosomes of various cells and tissues. Excessive deposition of Gb_3 particularly affects renal epithelial cells, myocardial cells, dorsal root ganglia, and cells of the autonomic nervous system and vascular endothelial cells.

The clinical features of Fabry disease include acroparaesthesia, angiokeratomas, hypohidrosis, corneal and lenticular opacities, and major end-organ disease (with involvement of the kidneys, heart and brain) [1]. Most affected male patients have proteinuria and ultimately develop renal failure [2]. The clinical course often also involves cardiac and cerebrovascular disease, which, combined with renal failure, leads to early death [1]. The clinical course in heterozygous female patients involves a delayed onset of symptoms and milder progression, although some female patients present with symptoms similar to those seen in classically affected male patients. The median lifespan is 50 years for affected male patients and 70 years for female patients [3,4].

Since Fabry disease was first described in 1898 [5], much has been learned about its diagnosis, progression and management [6,7]. As end-stage renal failure

occurs in the majority of male patients [8], kidney transplantation has become increasingly relevant in the management of patients with Fabry disease. However, data on kidney transplantation in these patients are scarce. This study therefore set out to examine the clinical characteristics of kidney transplant recipients (KTRs) enrolled in the Fabry Outcome Survey (FOS) and to compare the clinical characteristics of KTRs receiving or not receiving enzyme replacement therapy (ERT).

Materials and methods

Fabry outcome survey

The Fabry Outcome Survey (FOS) is a global outcomes survey for patients with Fabry disease who may receive ERT with agalsidase alfa (Replagal®; Shire Human Genetic Therapies, Danderyd, Sweden) [9]. At entry into FOS, each patient's medical history is documented, including the year of diagnosis of Fabry disease, details of Fabry disease-related signs and symptoms and previous treatment. Patients within FOS are followed longitudinally with regard to the data obtained from routine physical and laboratory examinations, and adverse events. All patients enrolled in FOS have given their written, informed consent.

Data extraction and study design

All European patients in FOS with a history of kidney transplantation were included in this study. Each patient's age, gender, onset of symptoms, and time since last kidney transplantation at entry into FOS were ascertained from the database. Data on renal function (serum creatinine, estimated glomerular filtration rate [eGFR] using the short Modification of Diet in Renal Disease equation [10], and proteinuria), as well as echocardiographic findings in these patients before and during ERT (Replagal® at 0.2 mg/kg of body weight, every 2 weeks) were also obtained from FOS. Disease severity was estimated using the FOS adaptation of the Mainz Severity Score Index (FOS-MSSI), which is a clinical scoring system for Fabry disease [11].

Statistical methods

Continuous data are presented as medians and percentiles, and categorical data as counts and frequencies. Student's *t*-test or Wilcoxon's rank-sum test were used for comparison of continuous variables, and Fischer's exact test was used for binomial data. SAS® software (SAS Institute Inc., Cary, NC, USA) was used for all analyses. All statistical tests were two-sided and no multiplicity correction was conducted.

Results

Patients

As of March 2006, 36 (4.3%) of 837 patients enrolled in FOS were reported to be KTRs (Fig. 1). The mean age of these 34 male and 2 female patients was 44.2 ± 8.6 years, and the mean time since transplantation was 7.7 ± 6.4 years. The mean age at diagnosis of Fabry disease was 31.1 ± 13.1 years and the mean age at transplantation was 37.6 ± 10.9 years. Four patients (all male) died after receiving a transplant. The cause of death was recorded as bronchopneumonia ($n = 1$), sepsis ($n = 2$) and endocarditis/septicaemia/renal failure ($n = 1$). Patients received standard immunosupressant therapy, most commonly, cyclosporin. Three male patients experienced graft failure, one associated with cyclosporin toxicity.

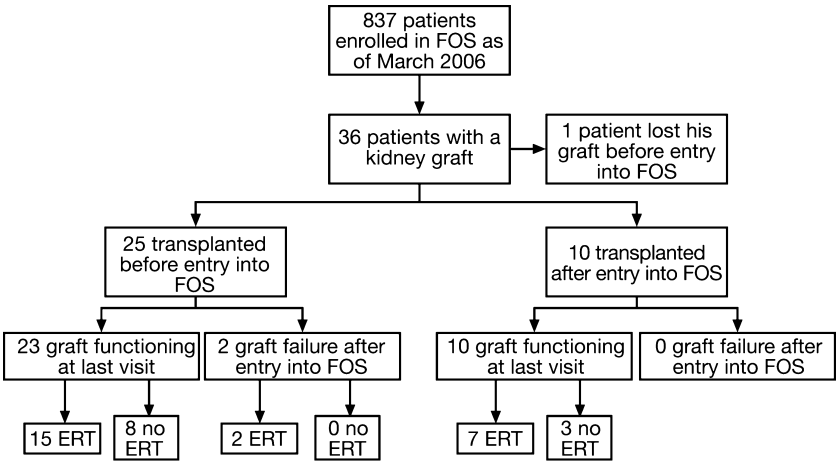

Figure 1 Patient disposition in FOS – the Fabry Outcome Survey. ERT, enzyme replacement therapy.

Table 1. Renal function of 27 kidney transplant recipients with Fabry disease at entry into the Fabry Outcome Survey.

	n	Mean ± SD or median (Q1–Q3)
Gender (male/female)	25/2	25/2
Age at transplantation (years)	25	37.3 ± 9.7
Serum creatinine (mg/dl)	27	1.7 (1.3–2.2)
eGFR (ml/min/1.73 m^2)	27	44.4 (33.6–64.0)
Proteinuria (mg/24 h)	14	296 (100–1210)
Time on ERT (months)	25	42.4 (31.0–56.8)

eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; Q, quartile.

Renal function and comorbid conditions

Data on renal function were available for 27 patients. Serum creatinine concentrations, eGFR and levels of proteinuria are given in Table 1. Of these 27 patients, 16 (59%) were reported to have hypertension, 19 (71%) left ventricular hypertrophy, six (22%) cardiac valve disease, eight (30%) arrhythmia, six transient ischaemic attacks (22%) and four stroke (15%). Of the patients receiving ERT, 50% were also given angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers. Two of the seven patients (29%) not receiving ERT were given ACE inhibitors.

Enzyme replacement therapy

Twenty patients (56%, two female patients, 18 male patients) received ERT with agalsidase alfa (Fig. 2). The median duration of treatment was approximately 3.5 years. Five patients received ERT before transplantation. There were no differences in age or time since transplantation between the treated and untreated patients (Table 2). ERT was well tolerated, with mild infusion-related reactions reported in only one patient.

Table 2. Comparison of kidney transplant recipients enrolled in the Fabry Outcome Survey (FOS) with and without enzyme replacement therapy (ERT). Values are means ± SD or medians and quartiles (Q1–Q3).

	ERT (*n* = 20)	No ERT (*n* = 7)
Gender (male/female)	18/2	7/0
Age at transplantation (years)	38.4 ± 9.3	33.6 ± 10.8
Age at first creatinine measurement (years)	43.3 ± 8.6	36.9 ± 12.1
Serum creatinine (mg/dl)	1.4 (1.3–2.0)	2.2 (1.6–3.6)*
eGFR (ml/min/1.73 m^2)	59.2 (36.5–65.2)	35.1 (19.9–51.7)
Proteinuria† (mg/24 h)	240 (200–885)	420 (100–1300)
FOS-MSSI at baseline	34.7 ± 9.2	31.6 ± 6.3
Duration from transplantation until last visit (years)	9.2 (3.6–12.0)	3.3 (1.7–5.9)

*$P < 0.05$ compared with patients receiving ERT (two-sample Wilcoxon's test, two-sided).
†Measurements of proteinuria were taken from nine patients on ERT and from five patients not on ERT.
eGFR, estimated glomerular filtration rate; FOS-MSSI, FOS adaptation of the Mainz Severity Score Index.

At entry into FOS/start of ERT, median eGFRs were 59 and 35 ml/min/1.73 m^2 and the median levels of proteinuria were 240 and 420 mg/24 h in patients receiving or not receiving ERT respectively (Table 2).

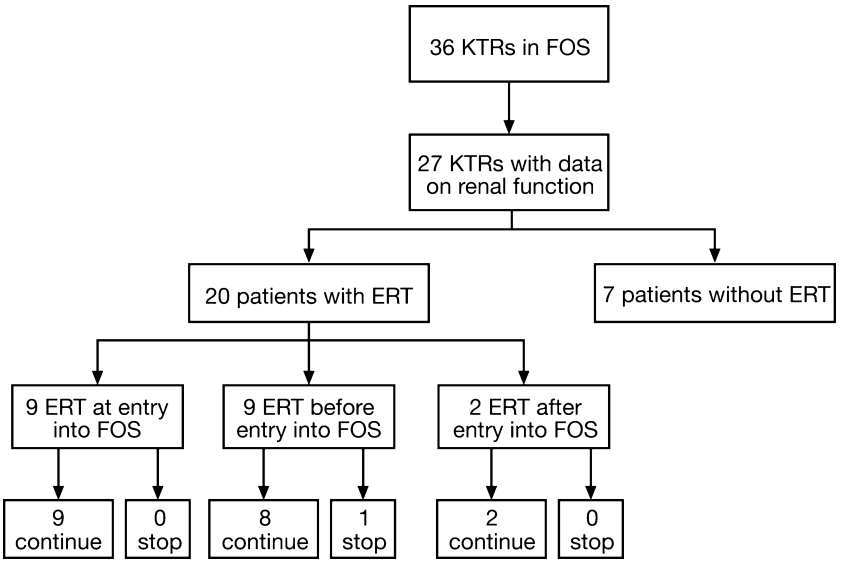

Figure 2 Enzyme replacement therapy (ERT) before and after enrolment in FOS – the Fabry Outcome Survey – in 36 kidney transplant recipients (KTRs).

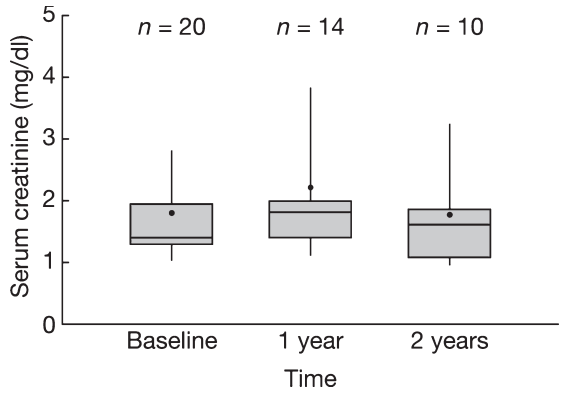

Figure 3 Serum levels of creatinine at baseline and after 1 and 2 years of enzyme replacement therapy with agalsidase alfa in kidney transplant recipients with Fabry disease. Plots show means (dots), medians (horizontal lines) and 10th, 25th, 75th and 90th percentiles (box and whiskers).

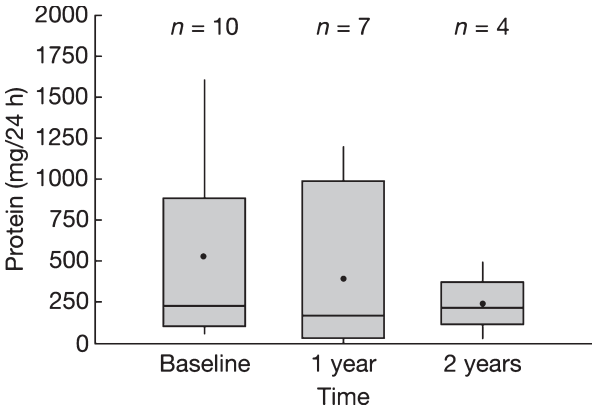

Figure 5 Proteinuria at baseline and after 1 and 2 years of enzyme replacement therapy with agalsidase alfa in kidney transplant recipients with Fabry disease. Plots show means (dots), medians (horizontal lines) and 10th, 25th, 75th and 90th percentiles (box and whiskers).

During 2 years of ERT, there was a slight increase in serum creatinine (1.4 mg/dl at baseline vs. 1.6 mg/dl at 2 years; Fig. 3) and a decrease in eGFR (59.2 ml/min/1.73 m^2 at baseline vs. 51.1 ml/min/1.73 m^2 at 2 years; Fig. 4). Proteinuria remained stable over this period (225 mg/24 h at baseline vs. 219 mg/24 h at 2 years; Fig. 5).

With respect to cardiac disease, ventricular mass was somewhat greater in untreated patients ($n = 4$) compared with patients on ERT ($n = 9$) (86.5 g/$m^{2.7}$ vs. 64.9 g/$m^{2.7}$; not significant). Arrhythmia was detected in five patients prior to the start of ERT. No additional arrhythmia occurred during the study period.

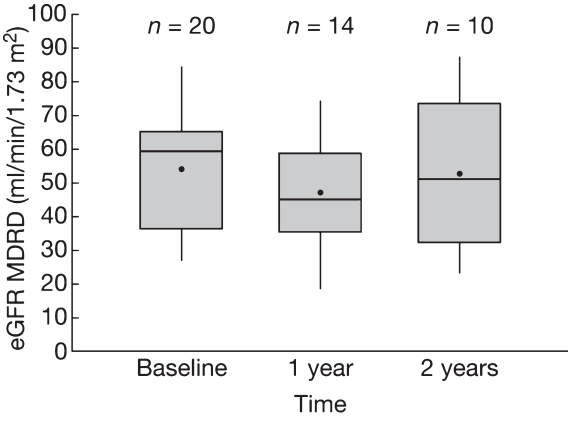

Figure 4 Estimated glomerular filtration rate [eGFR; using the Modification of Diet in Renal Disease (MDRD) equation] at baseline and after 1 and 2 years of enzyme replacement therapy with agalsidase alfa in kidney transplant recipients with Fabry disease. Plots show means (dots), medians (horizontal lines) and 10th, 25th, 75th and 90th percentiles (box and whiskers).

Overall disease severity, as expressed by the FOS-MSSI, was similar between the treated and untreated groups at baseline (Table 2).

Discussion

This study shows that KTRs represent an important minority of patients with Fabry disease enrolled in FOS. According to a previous study from the European Dialysis and Transplant Association/European Renal Association Registry, graft survival at 3 years in 33 patients with Fabry disease was not considered as inferior to that of patients with other nephropathies (72% vs. 69%), and patient survival after transplantation was comparable to that of patients aged under 55 years with non-Fabry nephropathies [12]. Excellent graft and patient survival were also reported from the US Renal Data System Registry [13,14]. Fabry disease is therefore not considered a contraindication for renal transplantation [15,16]. Although a case study has shown that the disease may recur in the transplanted organ [17], another case study has shown no evidence of disease recurrence in a renal biopsy 8 years after transplantation [18]. A further case study showed extensive Fabry-related renal changes in a renal biopsy from a patient who had received a graft from his sister who was heterozygous for the disease [19].

Enzyme replacement therapy (ERT) was introduced some 5 years ago to correct the metabolic defect in Fabry disease [20,21]. As of 2006, more than 50% of patients enrolled in international patient registries receive ERT with agalsidase alfa or agalsidase beta (Fabrazyme®; Genzyme Corp., Cambridge, MA, USA) [22]. However, data on the use of ERT in KTRs are scarce. A case series

of three patients suggested that ERT using agalsidase beta is well tolerated [23]. Plasma Gb_3 decreased by 23–50%, pain in the extremities resolved within 2 months, and left ventricular mass, end diastolic diameter, and cardiac contractility improved in two patients. Mild mitral insufficiency persisted in all patients, as did the atrial fibrillation in one individual. Renal function remained stable in all patients [23].

This study provides the first report on treatment of KTRs with agalsidase alfa. Among the 36 KTRs in FOS, 20 had received ERT with agalsidase alfa. Patients receiving ERT tended to be older than those not receiving treatment, which may suggest that transplant physicians may be reluctant to use ERT in younger KTRs who present with mild renal insufficiency. However, ERT may be indicated in all patients to reduce the rate of progression of the non renal aspects of Fabry disease and also to reduce the prospect of recurrence of glycosphingolipid deposition in the transplanted organ.

Renal function remained stable during 2 years of ERT (Figs 3–5). This is consistent with the results of a study by Schwarting *et al.* [24] who showed that ERT with agalsidase alfa was associated with some preservation of renal function in a large cohort of non-transplanted patients. Similarly, another observational study described stable renal function among 25 patients treated with agalsidase alfa for more than 5 years [25]. This is of particular interest because a previous study suggested that untreated male patients with Fabry disease show a yearly decrease in GFR of about 10–15 ml/min/1.73 m^2 [8]. There was also no increase in proteinuria in KTRs in this study, which is consistent with the findings of Schwarting *et al.* [26] on the effect of ERT with agalsidase alfa in patients with chronic kidney disease. A recent placebo-controlled study of the effects of agalsidase beta in patients with mild to moderate kidney disease indicated a delay in the onset of composite clinical outcomes [27].

Treatment with agalsidase alfa is generally well tolerated in patients with Fabry disease. A detailed report of the FOS database revealed few serious adverse events in a total of 401 patients receiving long-term treatment; as in this study, most adverse events consisted of mild infusion reactions [25].

Limitations of this study, which apply generally to registry studies, include the observational nature of the design, with no matched control group of untreated transplanted patients with Fabry disease during follow-up. Furthermore, the small sample size and the incompleteness of data, especially in untreated patients, make it difficult to draw definitive conclusions regarding the renal effectiveness of ERT in KTRs.

Conclusions

Kidney transplant recipients (KTRs) suffering from Fabry disease represent a significant minority of individuals enrolled in FOS. Approximately two-thirds of these patients have received ERT with agalsidase alfa. The data from this observational study indicate that ERT is well tolerated in patients with renal transplants. Although ERT appears to stabilize renal function, further data are required to confirm whether such treatment will confer long-term renoprotective effects on KTRs.

Authorship

All authors contributed to interpreting the data collected in FOS.

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