Dialysis and Transplantation in Fabry Disease: Indications for Enzyme Replacement Therapy

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ESRD is a major cause of morbidity and premature mortality in Fabry disease, particularly in classically affected males. The decline of renal function in Fabry nephropathy is adversely affected by male gender, advanced chronic kidney disease (CKD), and severe proteinuria. The diagnosis of Fabry nephropathy may be missed if not specifically addressed in progressive CKD and patients have been first identified in screening programs of dialysis patients. Fabry patients have worse 3-year survival rates on dialysis as compared with nondiabetic controls. The 5-year survival rate of transplanted Fabry patients is also lower than that of controls. However, because Fabry nephropathy does not recur in the allograft and transplanted Fabry patients appear to have better overall outcomes than those maintained on dialysis, kidney transplantation should be recommended as a first choice in renal replacement therapy (RRT) for Fabry disease. Appropriately designed and powered studies are not available to answer the question whether enzyme replacement therapy (ERT) influences outcomes, the course of cardiomyopathy, events, or survival in Fabry patients on RRT. The authors are not aware of compelling indications for ERT in RRT patients because progression of cardiomyopathy was documented during ERT. Whether the excess mortality risk of Fabry patients on RRT can be prevented by ERT is unknown. Despite observational reports of symptomatic improvement, the available evidence supporting ERT for such patients is not compelling enough. To clarify this issue, studies are needed to test the effectiveness of agalsidases in preventing cardiac and cerebrovascular complications in Fabry patients with ESRD.

This article summarizes the current knowledge about the effect of ERT in Fabry patients requiring dialysis therapy or who have received a kidney transplant. A second goal is to address important research questions in the field.

What Do We Know?

Progression of Fabry Nephropathy

Proteinuria and progressive renal deterioration may develop rapidly in Fabry disease. Schifffman et al. re-examined the natural history of Fabry nephropathy with a retrospective analysis of 279 men and 168 women. In men with an estimated GFR (eGFR) of more than 60 ml/min/1.73 m², the slope of renal function was −0.3 and for women was −0.9 ml/min/1.73 m² per year; for men with eGFR <60 ml/min/1.73 m², it was −6.8 and for women it was −2.1 ml/min/1.73 m² per year. Patients with proteinuria >1 g/24 h had a worse prognosis (13). Therefore, clinical experiences addressed to evaluate the role of ERT (14–17) should be compared with this study and not only with small-scale study results (2). Of interest, women who progress...
to ESRD do so at the same mean age as men (18). Another recent analysis of the Fabry registry showed that 14% of male and 2% of female patients included in this survey had a history of RRT (19).

Since the availability of ERT, its long-term protective effect on the progressive deterioration of kidney dysfunction has not been fully established. Open-label extension studies of the pivotal clinical trials have demonstrated that renal function remained stable in the long-term in most patients with Fabry disease who were treated with agalsidase alfa or beta for more than 4 years (15,20). However, baseline renal function was normal in most of these patients. In contrast, patients with impaired renal function presented with a continuous decline of renal function despite conventionally dosed ERT (14,15,20,21).

Epidemiology, Case-Finding Studies, and Outcomes in Patients on RRT

Four reports described the prevalence and outcomes of Fabry disease among ESRD patients. In Europe (22) and in the United States (11), the prevalence of Fabry disease among patients on RRT was 0.0188 (83/440,665 patients) and 0.0167 (42/250,352 patients), respectively. Importantly, 12% of ESRD patients with Fabry disease were female in both registries. In the meantime, several case-finding studies among ESRD populations have shown a more than 10 times higher prevalence of Fabry disease as compared with the U.S. Renal Data System or European Renal Association-European Dialysis and Transplant Association registries (Table 1) (23,24).

Some of these patients did not present with the typical dermatologic, neuropathic, and ocular features of classical Fabry disease and have a more limited renal phenotype, which may be difficult to recognize clinically (25), particularly in the absence of a known family history of Fabry disease or if a diagnostic kidney biopsy has not been done.

Three-year survival of dialysis patients with Fabry disease was worse as compared with nondiabetic dialysis patients in Europe (60%) and in the United States (63%) (11,22). Among kidney transplant recipients, 3-, 5-, and 10-year graft and patient survival was similar in patients with Fabry disease and matched patients without Fabry disease as compared with the United States (26). Most recently, Shah et al. examined outcomes of 197 (0.085%) patients with Fabry disease among 233,280 U.S. kidney transplant recipients (12). Although 5-year graft survival was similar in patients with or without Fabry disease, Fabry disease conferred a higher risk of death as compared with a matched control population (hazard ratio, 2.15; 95% confidence interval, 1.52 to 3.02).

Pharmacokinetics of ERT in Dialysis and Transplant Patients

Pastores et al. (27) determined pharmacokinetics in 22 Fabry patients (two women) receiving either hemodialysis (n = 9) or who had a functioning renal transplant (n = 13; eGFR 64.5 ± 6.0 ml/min/1.73 m²). Agalsidase alfa was infused biweekly at a dose of 0.2 mg/kg. A typical biphasic plasma elimination profile was seen in dialysis and transplant patients, similar to that observed in 18 Fabry patients with normal GFR. The serum clearance profiles for dialysis and transplant patients were comparable with 18 Fabry patients with normal renal function.

In a study of 10 Fabry patients receiving agalsidase beta at a dose of 1 mg/kg infused biweekly over 4 hours during and off dialysis, Kosch et al. investigated the effect of the dialysis procedure on enzyme activity (28). The rise in plasma activity of α-galactosidase A during infusion and steady-state levels were comparable for enzyme administrations with (high-flux and low-flux) or without dialysis.

These results confirmed the theoretical assumption that the recombinant agalsidases are not cleared by hemodialysis filters.

ERT in Dialysis Patients

To date, only limited data are available on Fabry patients receiving ERT and undergoing dialysis therapy at the same time. The efficacy of ERT, which has been shown in patients with preserved renal function or at early stages of renal disease (9,10,21), could be hampered by the multiple pathogenic factors and comorbidities in patients on maintenance hemodialysis therapy.

The clinical outcome of nine patients with Fabry disease after 2 years of treatment with agalsidase beta undergoing dialysis treatment (six hemodialysis, three peritoneal dialysis) was first reported in an open-label, nonrandomized Italian study (29). Six of nine patients enrolled underwent clinical and Doppler echocardiography assessment at baseline and after 24 months by means of physical examination, a questionnaire on typical Fabry manifestations, and two-dimensional echocardiography. Echocardiography parameters were also available for 2 years before study entry. An overall amelioration of clinical symptoms was noted; in particular gastrointestinal pain improved in all patients and the use of analgesic medication could be reduced. No patient experienced cardiovascular or cerebrovascular events during follow-up. Notably Fabry patients had a significant higher left ventricular (LV) mass at baseline compared with control groups of healthy subjects and dialysis patients (healthy: 40 ± 5.7 g/height²; ESRD: 63 ± 9.7; ESRD and Fabry: 73 ± 29g; P < 0.5 versus healthy subjects). During follow-up echocardiography data were available in all six patients and showed an increase in LV mass index of 6% in the 2 years before study entry and of 3% after the 2 years of ERT. Indeed, the mean slope of LV mass index decreased from 0.98 ± 0.01 in the pretreatment period to 0.46 ± 0.96 in the ERT period (P = 0.06) (29).

Mignani and colleagues conducted a nationwide survey in Italy to elucidate the cardiac status in patients on RRT receiving ERT (30). A total of 33 patients could be included, 16 (one female) receiving dialysis treatment. Patients were followed over a mean of 61 months and ERT duration was 45 months. At 3 years of ERT, the mean LV mass index had increased by 19% (from 210.9 to 251.0 g/m²; P = NS) in the 7 patients with available two-dimensional Doppler echocardiography data. Strikingly, 6 years after the start of the survey, 6 of 16 patients had died (all receiving dialysis treatment) and 6 had received a renal transplant with only 4 survivors remaining on dialysis and on ERT. Nine severe cardiac and cerebrovascular events were recorded during follow-up in dialysis patients (10.8
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<th>Author and Citation</th>
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HD, hemodialysis; PD, peritoneal dialysis; KTR, kidney transplant recipients; P, plasma; L, leukocyte; WB, whole blood; DBS, dried blood spot.

Table 1. Overview of 18 case-finding studies among patients with CKD.
in allograft recipients (3.12 events per 100 person years).

In conclusion, Fabry patients on hemodialysis therapy suffer from the primary Fabry-related cardiomyopathy and an additional cardiovascular risk related to uremia. ERT in this cohort of high-risk patients has the potential to alleviate typical manifestations of Fabry disease (e.g., recurrent pain crises and abdominal pain) and may therefore be considered in many patients. The increase in LV mass is a key feature of patients with Fabry disease and patients undergoing chronic dialysis therapy. Supposing a progressive worsening of LV mass in untreated patients, it can be speculated that the increase in LV mass in dialyzed Fabry patients may be slowed down but not reduced by ERT, as shown for Fabry patients not on dialysis therapy (32,33). Whether ERT is efficacious in reducing the cardiac and cerebrovascular mortality in patients with ESRD undergoing dialysis therapy has not been shown to date. This remains to be elucidated in prospective end-point studies in larger patient cohorts or by analyzing available registry data.

**ERT in Kidney Transplant Recipients**

Several studies have described the effects of ERT in patients with normal renal function or with mild-to-moderate chronic renal failure, but limited data are available on the effect of ERT after kidney transplantation. In a pilot clinical trial, Mignani et al. examined the safety and efficacy of ERT (agalsidase beta 1 mg/kg every other week for 18 months) in three kidney transplant patients with Fabry disease and severe cardiac involvement (34). In all patients, the extrarenal symptoms disappeared within 2 months after commencing ERT. Renal function was preserved until the end of the study without any variation of the immunosuppressive regimens.

To further explore renal function and cardiac disease after transplantation, a nationwide collaborative study was conducted in Italy (30). Thus far, one patient of this largest study received agalsidase alfa and 16 received agalsidase beta at the standard dose. After 48 months of ERT, no change in renal function was observed. Mean serum creatinine increased from 1.78 mg/dl at baseline to 1.92 mg/dl (+8%, P = NS) after 4 years of ERT, and mean creatinine clearance decreased from 52.9 to 45.2 ml/min (~15%, P = NS). The rate of decline in renal function from baseline to the last visit was ~1.92 ml/min per year. Proteinuria was less than 200 mg/d after 4 years of ERT and 14 of the 17 patients still had a functioning kidney allograft 6 years after the survey. Two patients suffered graft failure and returned to dialysis treatment, and ERT was stopped in one patient for reasons unrelated to the therapy. No significant change in Fabry cardiomyopathy was noted at study conclusion. The mean LV mass index varied by 6% (from 234.6 to 220.8 g/m², P = NS) after 3 years of ERT. However, cardiac response to agalsidase beta treatment was not uniform; echocardiography did not demonstrate an appreciable reduction in LV mass in 2 of 11 patients that reached the 4th year follow-up. Finally, only three cardiac or cerebrovascular events occurred in the allograft recipients (3.12 events per 100 person years).

More recently, Cybulla et al. (35) explored the effects of agalsidase alfa in transplant patients with Fabry disease. Allograft function of 20 patients from the Fabry Outcome Survey registry was analyzed after approximately 3.5 years (median) of agalsidase alfa therapy at the standard dose of 0.2 mg/kg every other week. After 2 years of ERT, there was a slight but NS increase in serum creatinine (1.4 mg/dl at baseline versus 1.6 mg/dl) and a decrease in eGFR (59.2 ml/min/1.73 m² at baseline versus 51.1 ml/min/1.73 m² at 2 years). Similar to the previously mentioned study, proteinuria remained stable during this time period.

In summary, agalsidase alfa and beta seem to be safe and well tolerated in renal transplant patients. However, the inability to perform a randomized controlled study, limited longitudinal follow-up given that ERT has been available for a relatively short time period, and the lack of a control group (nontreated Fabry patients or non-Fabry transplant patients) limit the relevance of this statement; therefore, further studies are needed to confirm these observations.

It may be tempting to hypothesize that a kidney graft in a patient with Fabry disease undergoes accumulation of globotriaosylceramide related to recipient-derived cells (e.g., endothelial progenitor cells), leading to some functional damage of the transplant. However, the retrospective study by Shah et al. has shown no worse graft survival in transplanted Fabry patients as compared with patients with other causes of ESRD. Their findings suggest that any theoretical compromise of the graft related to Fabry disease is not relevant in the context of clinical transplantation (12).

**Summary of What We Know**

Patients on hemodialysis therapy are a high-risk group for Fabry disease. Several case-finding studies using currently available technology have revealed a considerably high prevalence of Fabry disease among this population (Table 1). In the pre-ERT era, analyses of data from nontreated Fabry patients receiving dialysis have shown that ESRD is associated with significant morbidity and mortality as compared with diabetic or nondiabetic dialysis patients. Studies available to date on the effect of ERT in dialysis patients have suggested a possible stabilization or lower progression of cardiomyopathy in treated patients. However, the lack of a control group and the low number of patients investigated limit the relevance of this result.

By contrast, in non-ERT Fabry transplant patients, if compared with matched controls, graft survival is similar but kidney transplant recipients with Fabry disease share a higher risk of death. However, in general transplant outcomes are more favorable than dialysis outcomes.

Regarding specific therapy, ERT with agalsidase alfa or beta is safe in dialysis and transplant patients, and differences in pharmacokinetics or loss of enzyme activity have not been observed. With regard to the effects of ERT in ESRD, several confounding factors will have to be considered. In particular, volume overload, arterial hypertension, and uremic toxins are able to negatively influence the outcome of chronic kidney disease (CKD) patients.
What Do We Not Know?

The prevalence of Fabry disease among CKD stage I to IV patients is currently not known. Furthermore, the clinical variability of Fabry disease and the current causes of death in patients with various stages of CKD are enigmatic. No conclusive histologic evidence that Fabry nephropathy recurs in allografts from non-Fabry donors has ever been presented. However, we should strengthen the use of allograft biopsies to gain further knowledge on globotriaosylceramide deposits in transplanted Fabry patients.

We actually have a poor understanding of the course of the Fabry cardiomyopathy in untreated CKD patients versus CKD patients treated with ERT. Thus, it is largely unknown which Fabry patients respond to ERT in terms of slowing or halting progression of the systemic disease. Last but not least, we are not aware of compelling indications for ERT in RRT patients because progression of cardiomyopathy was documented during ERT. Although patients may clinically respond to treatment, we are currently not aware of a mechanism of improved survival in RRT patients on ERT.

Patients with Fabry disease are at excess risk of developing cardiovascular disease. Therefore, the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers to maximize cardioprotection is suggested to be prudent in this patient population, particularly if patients are on RRT. These treatments might also exert a renoprotective effect in kidney transplant recipients.

What Can We Do with What We Do Know?

In general, we endorse case-finding studies within an organized frame among high-risk populations, such as male ESRD patients. We should raise the awareness of this rare disease among nephrologists and other specialists that are likely to encounter unrecognized Fabry patients to improve early diagnosis. In ESRD patients, other typical clinical manifestations of Fabry disease may be useful diagnostic clues to specifically screen for α-galactosidase deficiency (36).

Regarding ERT and progression of Fabry nephropathy, we should focus our attention on some important points: ERT should be started early in male patients, although the body of evidence for prevention of ESRD by early initiation of ERT needs to be improved. Other factors of progression of renal diseases, including arterial hypertension and proteinuria, should be taken into account. If treatment effects are examined in clinical studies, patients should be stratified by the level of proteinuria, renal function, and blood pressure. In ESRD, the positive effects of ERT are blurred by the uremic state and kidney transplantation is the standard of care. Preemptive transplantation should be encouraged. In general, the indication for ERT can be considered on an individual basis (e.g., young patients versus patients with severe multiorgan manifestations).

Key Research Questions

High priority on the research agenda is to be given to the development of a reliable screening test for women and men to enable more effective case-finding strategies. Current causes of death in predialysis, dialysis, and transplant patients should be examined using Fabry registries to better understand the natural course of the disease in ESRD patients, including comparisons of morbidity and mortality of ERT-treated and ERT-naive patients on RRT. Finally, we have to improve the understanding of ERT outcomes in dialysis and transplant patients by conducting randomized controlled trials and using other designs, including nested case-control studies.

Appendix

Participants in the Symposium Session “Dialysis and Transplantation in Fabry Disease patients” at the Official Satellite of the World Congress of Nephrology titled “Focus on Fabry Nephropathy: Biomarkers, Progression, and Disease Severity”, held in Bergamo, Italy, on May 28, 2009, included the following: R. Mignani, Rimini, Italy; S. Fierozzi, Viterbo, Italy; R.M. Schaefer, Muenster, Germany; F. Breunig, Würzburg, Germany; J.P. Oliveira, Porto, Portugal; P. Ruggenenti, Bergamo, Italy; G. Sunder-Plassmann, Vienna, Austria; M. Beck, Mainz, Germany; A. Levin, Vancouver, Canada; I. Maya, Birmingham, Alabama; M. Banikazemi, New York; G. Biagini, Curitiba, Brazil; A. Delgado, Rio de Janeiro, Brazil; and B. Vučkovic, Ljubljana, Slovenia. In addition to the forenamed participants, Genzyme Corporation (one) and Shire Human Genetic Therapies (three) employees were present at the meeting but had no role in the presentations and did not influence the outcome of the discussions.

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