

## Anderson-Fabry disease: Ten-year outcome of enzyme replacement therapy in a renal transplant patient

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### ■ ABSTRACT

Anderson-Fabry disease (AFd) is a rare disorder characterised by the deficiency or absence of lysosomal enzymatic alpha-galactosidase A activity ( $\alpha$ -Gal A) that leads to progressive and systemic accumulation of glycosphingolipids. The clinical manifestations are variable but kidney disease usually manifests before the fourth decade of life and chronic renal failure rapidly progresses to end-stage renal disease (ESRD), requiring dialysis and kidney transplantation (KT). In patients with a definite diagnosis, enzyme replacement therapy (ERT) is recommended as soon as there are early clinical signs of kidney, heart or brain involvement. We present a case of a kidney transplant patient who was diagnosed with AFd nine years after KT, confirming the difficulty that may exist in an early diagnosis of this disease even among high-risk groups. At this stage, in addition to renal damage, the patient already had advanced disease and established organ injury, including ocular, pulmonary, cerebrovascular and cardiac. He started agalsidase beta (Fabrazyme<sup>®</sup>) intravenously every two weeks at a dose of 1 mg/kg body weight. During ten years of treatment no major adverse events were reported and our experience indicates that ERT is a safe and effective treatment for extra-renal Fabry manifestations in KT patients.

**Key-Words:** Anderson-Fabry disease; end-stage renal disease; enzyme replacement therapy; kidney transplant.

### ■ INTRODUCTION

Anderson-Fabry disease (AFd) is a rare X-linked recessive metabolic disorder characterised by the deficiency or absence of lysosomal enzymatic alpha-galactosidase A activity ( $\alpha$ -Gal A). The enzyme defect leads to progressive accumulation of glycosphingolipids, particularly globotriaosylceramide (GL-3; also abbreviated Gb3), in all kinds of cells<sup>1</sup>. The clinical manifestations are variable and range from the severe phenotype in males to an asymptomatic disease course occasionally observed in females, with a variety of clinical presentations in between. In the classic phenotype, the first clinical symptoms typically begin in childhood and adolescence and are characterised by myalgia, arthralgia,

acroparesthesia, fever, cutaneous angiokeratomas and corneal opacities. Later, severe renal impairment and involvement of the cerebrovascular and cardiovascular systems occur<sup>2</sup>.

The estimated incidence of AFd is 1 in 40,000 to 100,000 live births, excluding the polymorphisms and mutations of uncertain significance<sup>1</sup>. Still the diagnosis may be delayed for many years or even missed, and this underestimates the true prevalence of the disease<sup>3</sup>.

Nephropathy in Fabry disease is characterised by GL-3 deposition in all glomerular cell types, particularly in podocytes; the results of Tøndel *et al.*<sup>4</sup>, using

ultrastructural morphologic studies on human kidney biopsies, suggests that podocyte foot process effacement represents a very early sign of kidney injury in Fabry disease, preceding the onset of clinically overt urinary protein loss. As proteinuria is a strong predictor of progression to end-stage renal disease in Fabry disease, these early morphological findings in Fabry nephropathy are clinically significant. Later, deposition of glycosphingolipids in other kidney cells (tubular epithelial cells, endothelial and vascular smooth muscle cells) leads to microvascular dysfunction, occlusion and ischaemia, with subsequent development of tubular atrophy, segmental and global sclerosis and interstitial fibrosis<sup>5,6</sup>. Proteinuria usually manifests before the fourth decade of life and chronic renal failure rapidly progresses to end-stage renal disease (ESRD) requiring dialysis and kidney transplantation (KT)<sup>7</sup>. Several reports show that KT can be safely proposed to Fabry patients<sup>5,8-11</sup> and, in spite of heart and cerebrovascular complications which may reduce long-term patient survival, KT should be recommended as a first choice in renal replacement therapy for ESRD patients<sup>7,10</sup>.

Enzyme replacement therapy (ERT) with either agalsidase alfa or agalsidase beta has been developed for AFd treatment, and was approved in 2001. In 2015, the European Fabry Working Group published a consensus document with recommendations for initiation and cessation of ERT in patients with AFd<sup>12</sup>, where they stated that in patients with a definite diagnosis, ERT is recommended as soon as there are early clinical signs of kidney, heart or brain involvement. Also treatment should not be withheld from patients with severe renal insufficiency (GFR < 45 mL/min/1.73 m<sup>2</sup>).

Data on the use of ERT in patients with a functioning KT is scarce and, therefore, whether ERT is safe and effective in treating extra-renal manifestations in this population<sup>5,10</sup> requires additional studies with a higher number of patients and a longer follow-up time.

We present a case of a KT patient with a functioning allograft and over 10 years of successful ERT. It also underlines the difficulty that may exist in an early diagnosis in this lysosomal storage disease.

## ■ CASE REPORT

A 36-year-old male patient was first referred for a pre-transplant consultation in our Nephrology department in 1995.

In September 1994 he presented to the accident and emergency (A&E) department of his local hospital with severe hypertension (blood pressure 200/110 mmHg) and renal dysfunction (serum creatinine 11.5 mg/dL). He had sought no prior medical contact. Ultrasound scan showed small and hyperechoic kidneys. In spite of blood pressure control he progressed to renal failure and started maintenance haemodialysis by central catheter on October 4th 1994.

The first pre-transplant consultation was held in December 1995. The patient had been on dialysis for about a year via arteriovenous fistula and without significant complications. Blood pressure was controlled with an angiotensin-converting-enzyme inhibitor (enalapril 10 mg once a day) and a dihydropyridine calcium channel blocker (nifedipine 20 mg twice a day). He still had residual diuresis of about 1000 mL/day. There was no family history of Fabry's disease, although his brother had advanced renal failure and had died one year earlier in another hospital. The post-mortem examination indicated ischaemic leukoencephalopathy as cause of death. The patient reported mild vision decrease and occasional acroparesthesias. He did not have angiokeratomas or hypohidrosis. On physical examination the blood pressure was 120/74 mmHg and the heart rate was regular, at 70 beats/min. Cardiac auscultation revealed a systolic murmur at the left sternal border. Electrocardiography was unremarkable. Echocardiographic evaluation assessed normal cardiac ejection fraction (80%) with mild dilatation of both the left atrium (40 mm, for a normal of 22-38 mm) and of the left ventricular end-diastolic diameter (58 mm, for a normal of 34-54 mm); the valves were normal. There was no history of previous transfusions. He was evaluated by vascular surgery and urology and no contraindication to kidney transplant was found.

Deceased renal transplant was performed on June 22nd 1996. The recipient presented three HLA A, B, DR mismatches with the donor. The induction immunosuppressive agents were cyclosporine and methylprednisolone. He had immediate diuresis. At discharge, he was immunosuppressed with prednisolone 25 mg/day, azathioprine 50 mg/day and cyclosporine 2.8 mL twice a day. Blood pressure was controlled with nifedipine 20 mg twice a day; his serum creatinine was 1.5 mg/mL and decreased to 1.0 mg/dL one month later.

After transplant, he continued evaluation at routine post-transplant assessments, maintaining good graft function. He developed progressive vision loss and was referred to an ophthalmology appointment. Five years

after renal transplantation, in 2001, he underwent cataract surgery and corneal deposits were observed at that time. He also developed respiratory symptoms (shortness of breath and wheezing) so he performed a lung function test (spirometry) which indicated a moderate obstructive airway limitation.

At this stage, taking the history of chronic kidney disease with hypertension and proteinuria, corneal opacities (cornea verticillata) and family medical history including early death of his brother who had as diagnosis at the time of death chronic kidney disease and ischaemic leukoencephalopathy, allowed the doctors who followed the patient to consider AFd as a diagnosis. In September 2002 biochemical diagnosis of Fabry's disease was made, using enzymatic activity measurement. The leukocyte-specific activity of alpha-galactosidase A was low at 0.8 nmol/h/mg of protein (normal range: 36-80 nmol/h/mg). The genetic study identified a nonsense mutation (R220X) in the alpha-Gal A gene, associated with the classic phenotype of AFd. Family screening was performed in another hospital. As mentioned earlier, the patient had one brother who died, and has two sisters as well. One sister has AFd and is under ERT. He also has a nephew (son of the affected sister) who was also diagnosed with AFd and treated in Geneva, Switzerland. In 1994, this nonsense mutation (R220X) was reported for the first time<sup>13</sup>: it is predominantly renal and causes disease in both genders.

After diagnosis, during 2003 and 2004, the renal function was stable with serum creatinine around 1.4 mg/dL, estimated glomerular filtration rate (eGFR) according to MDRD formula of 55 mL/min/1.73 m<sup>2</sup>, and no proteinuria was detected. Electrocardiography showed asymptomatic bradycardia (58 beats per minute) and criteria for left ventricular hypertrophy. An echocardiographic study was also performed and revealed left ventricular hypertrophy with an interventricular septum of 18 mm (N < 12) and a posterior wall thickness of 15 mm (N < 11). Brain magnetic resonance imaging (MRI) exhibited periventricular white-matter lesions and deep lacunar infarcts.

Enzyme replacement therapy was initiated on April 2005, by injection of recombinant alpha-galactosidase (Fabrazyme – agalsidase beta) at 1 mg per kg body-weight once every two weeks. The treatment infusions were well tolerated and the patient has now been under treatment for over 10 years.

During these 10 years of treatment, diagnosis of neurosensory deafness was made and, in 2009, cochlear

implants were implanted in the patient. Further, in 2014, asymptomatic bradycardia was detected (heart rate at rest 35-38 beats per minute). Electrocardiography revealed prolongation of the PR interval, culminating in a non-conducted P wave, with 2:1 pattern, leading to the diagnosis of atrioventricular block 2nd degree, Mobitz I. After excluding the main causes of secondary aetiologies for atrioventricular block (beta-blockers, digoxin, amiodarone, inferior myocardial infarction, myocarditis), permanent pacing was placed.

Nineteen years after renal transplant and ten years after ERT initiation, the patient maintained serum creatinine of 1.5 mg/dL, and eGFR (MDRD) of 48 mL/min/1.73 m<sup>2</sup>. Proteinuria was stable at 0.35 g/g and minimum cyclosporine A level was 118 ng/mL. Renal ultrasonography showed graft with normal longitudinal size, normal parenchymal thickness and mild echogenicity increase. Lung function test showed a mixture of restrictive and obstructive airflow limitation, both mild. A two-dimensional Doppler echocardiographic study performed revealed left ventricular hypertrophy with an interventricular septum 19 mm (18 mm before ERT) and a posterior wall thickness of 17 mm (15 mm before ERT). A stress myocardial perfusion scan (pharmacologic intervention) revealed normal function with left ventricular ejection fraction estimated of 56%. A brain MRI showed severe multifocal leukoencephalopathy and lacunar ischaemic lesions located in the deep arterial territory (basal ganglia and the brainstem), similar to those previously observed.

## ■ DISCUSSION

Anderson-Fabry disease results in kidney damage and leads to progressive impairment of renal function in almost all male patients and in a significant percentage of females<sup>14</sup>. According to the data of Schiffmann *et al.*<sup>15</sup>, patients with proteinuria of at least 1 g/day had a worse prognosis.

More than 600 variants in the  $\alpha$ -galactosidase A gene have been described, generating considerable variability in age at disease onset and in disease progression rate<sup>12</sup>. Patients with ESRD have been shown to have an increased prevalence of AFd and case-finding studies among this population<sup>16-18</sup> suggest a much higher prevalence than that reported in the general population<sup>1</sup>. Some patients do not present with the typical and classical features of AFd and have a more limited renal phenotype, which may be difficult to recognise<sup>16</sup>,

particularly in the absence of previously identified family members. This phenotype may be referred to as non-classical AFd or attenuated phenotypes. Patients with non-classical AFd may present one single non-specific symptom, such as chronic kidney disease or left ventricular hypertrophy (LVH)<sup>12</sup>. In 2009, an Austrian study with 1306 patients from 30 kidney transplant centres that uncovered two previously unrecognised cases with AFd was published<sup>18</sup>. This study was the first to show that this diagnosis can be missed even in patients who undergo kidney transplantation. Therefore, given the increased risk of adverse cardiovascular and cerebrovascular events in patients with AFd, the availability for treatment with ERT, and the diagnosis and genetic counselling that can be offered to them and their extended families, is a diagnosis that is worth considering and cannot be overlooked. The diagnostic confirmation relies on the demonstration of a deficient activity of alpha-galactosidase activity in plasma or leukocytes in males, whilst in heterozygous females, in whom alpha-galactosidase A activity is highly variable, genotyping is essential for a diagnosis. Genotyping can also be useful in male patients to assist with tracing family history of the disease<sup>1,12</sup>.

Kidney transplantation should be endorsed as a first choice in renal replacement therapy for patients suffering from ESRD, since graft and patient survival are similar in patients without AFd, at three and five years post-transplant<sup>19,20</sup>. In 2009, a study examined 197 kidney transplant recipients with AFd and showed that AFd patients had a 40% lower risk of returning to dialysis compared to both matched and unmatched cohorts of patients with other causes of ESRD, but had a higher risk of death (hazard ratio 2.15; 95% confidence interval 1.52-3.02) compared to a matched cohort of patients with other causes of ESRD<sup>11</sup>.

Agalsidase beta (Fabrazyme®) is a recombinant form of human  $\alpha$ -Gal A used for ERT in Fabry disease and is given intravenously every two weeks at a dose of 1 mg/kg body weight. Agalsidase alfa (Replagal®) is also available in some countries for treatment of Fabry disease (0.2 mg/kg/2 weeks)<sup>12</sup>. Both seem to be safe and well tolerated in renal transplant patients, but this data needs to be confirmed by randomised controlled studies with an appropriate sample size<sup>8</sup>. One randomised open-label study<sup>21</sup> compared the effect of agalsidase alfa with that of agalsidase beta, using the same dose of 0.2 mg/kg every other week in both treatment arms, on the primary endpoint, defined as a reduction in left ventricular mass (LVM) after 12 and 24 months. After 12 and 24 months of treatment no reduction in LVM

was observed in either treatment arm. A systematic review published in 2009<sup>22</sup> concluded that data available were more robust for enzyme replacement therapy in patients with AFd at 1 mg/kg compared with 0.2 mg/kg every other week. Beneficial effects with either dose or preparation were variable. In this systematic review, the lack of reporting of the review process, unclear study quality, and the possibility of missing studies mean these conclusions should be viewed with caution.

Recently, Germain *et al.* reported a study evaluating the ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with AFd<sup>23</sup>. The study enrolled 52 patients with median agalsidase beta treatment duration of 10 years (25th-75th: 7.3-10.3 years) and they evaluated the following outcomes: severe clinical events, renal function and cardiac structure. The study concluded that agalsidase beta is effective and safe, as most patients remained alive and event-free during follow-up time: 42/52 patients did not experience any severe clinical event during the treatment interval and 49/52 patients were alive at the end of the study period. They also reported that patients who initiated treatment at a younger age and with less kidney involvement benefited the most from therapy. However, it is important to note that patients were excluded if their serum creatinine concentration exceeded 2.2 mg per decilitre (194.5  $\mu$ mol per litre), if they were undergoing dialysis, or if they had undergone kidney transplantation<sup>24</sup>.

Limited data are available on the effects of ERT after kidney transplantation. Although kidney graft produces  $\alpha$ -Gal A, most studies show globotriaosylceramide deposition in tissues and organs, leading to some functional damage of the organ. Hence extra-renal symptoms are important and have prognostic impact, since renal transplantation does not correct the underlying metabolic defect in other organs.

Anecdotal studies have suggested that ERT therapy may have a beneficial effect in kidney transplant patients with Fabry disease. Mignani *et al.*<sup>25</sup> assessed ERT treatment in three kidney transplant patients with Fabry and severe cardiac involvement. After 18 months, the extra-renal symptoms disappeared and renal function was preserved. In 2007, Pastores *et al.*<sup>26</sup>, in a phase II open-label trial, assessed the safety of agalsidase alfa (0.2 mg/kg every other week) in a population of 9 dialysis patients, 13 kidney transplant patients, and 22 non-ESRD patients with Fabry disease, over a median follow-up period of 42 weeks (the study was stopped

early by the sponsor when ERT became commercially available). The authors concluded that agalsidase alfa administration was safe in this population.

Mignani *et al.* in a registry-based cohort of AFd patients on renal replacement therapy receiving ERT, assessed left ventricular mass index (LVMI) and renal allograft function at baseline and at yearly intervals thereafter.<sup>27</sup> Thirty-four patients were included (17 had renal transplantation and 17 under dialysis). The mean ERT duration for dialysis and transplant patients was 45.1 and 48.4 months, respectively. The analysis after four years of ERT showed that LVMI increased in dialysis patients and had no change in transplant patients. Over the follow-up period, transplant patients showed stable renal function and an increase in proteinuria from 92 mg/day (baseline) to 180 mg/day. Cibulla *et al.*<sup>9</sup> evaluated all European patients in the Fabry Outcome Survey with a history of kidney transplantation. Thirty-six of 837 patients had a history of kidney transplantation and were included in the study. Of these, twenty patients received ERT with agalsidase alfa (at a standard dose of 0.2 mg/kg every other week) for a median duration of treatment of 3.5 years. During 2 years of ERT, renal function decreased slightly (eGFR 59.2 ml/min/1.73 m<sup>2</sup> at baseline and 51.1 ml/min/1.73 m<sup>2</sup> at 2 years) and proteinuria remained stable. There were no reports of interactions between ERT and other medications, particularly immunosuppressive agents<sup>10</sup>.

As time goes by, damage to vital organ systems progresses leading to cardiovascular and cerebrovascular complications that limit life-expectancy<sup>1</sup>.

Fabry cardiomyopathy is related to the storage of globotriaosylceramides in myocytes<sup>28</sup> with subsequent concentric hypertrophy and myocardium remodelling, resulting in irreversible fibrosis, conduction abnormalities, valvulopathy and myocardial infarction<sup>29</sup>. Recently a retrospective uncontrolled study was published analysing the effectiveness of agalsidase alfa enzyme replacement on Fabry-associated cardiomyopathy, evaluating the outcomes after approximately 10 years of treatment<sup>30</sup>. Forty-five adult patients were included and the authors reported heart failure improvement by at least one class in 22/42 patients, and angina scores were stable or improved in 41/42 patients. Of note, this type of analysis, presenting the proportion of patients with/without a beneficial effect of the intervention, instead of analysing the whole group, has a high risk of bias. No patient with left ventricular hypertrophy (LVH) at treatment initiation showed a decline in left ventricular mass. The authors concluded that 10

years of agalsidase alfa treatment appeared to have beneficial effects for controlling progression and improving some symptoms of Fabry-associated cardiomyopathy.

Cerebrovascular involvement can lead to a wide variety of symptoms such as dizziness, transient ischaemic attacks, ischaemic strokes, vascular dementia and constitute a major burden in both untreated and treated patients<sup>31</sup>. The prevalence of strokes in AFd is about 6.9% in males and 4.3% in females, much higher than in the general population<sup>1</sup>. The majority of strokes are due to microvascular disease and brain imaging can be used to diagnose white matter lesions before they manifest clinically<sup>31</sup>. Data on agalsidase alfa therapy reducing or preventing the cerebrovascular complications associated with AFd is scarce<sup>1</sup>. Fellgiebel *et al.* reported recently the first evidence of clinically significant stabilisation of, or reduction in, white matter lesions in patients treated with agalsidase-beta ERT<sup>31</sup>. The authors analysed 41 AFd patients (25 on ERT, 16 on placebo) over 27 months of follow-up (12-33 months) and concluded that burden in patients on ERT was more likely to remain stable, compared with patients on placebo. These data had more power if ERT was started at younger ages.

We report a successful case of 19 years' kidney transplant in which the last 10 were under ERT and with no major adverse events reported. We emphasise the fact that at the beginning of ERT the patient had already advanced disease and established organ injury, such as ocular, pulmonary, cerebrovascular, cardiac and renal, and organ injury remained stable under agalsidase beta (Fabrazyme®) given intravenously every two weeks at a dose of 1 mg/kg body weight.

## ■ CONCLUSION

In the case reported we highlight the importance of awareness of this rare disease, since the diagnosis is sometimes delayed for many years. This is especially true among high-risk groups with cardiomyopathy, juvenile strokes and chronic kidney disease, including those on dialysis or those who have undergone a kidney transplant. Early recognition of the disease is important to prevent the late life-threatening cardiac and cerebrovascular manifestations.

Kidney transplantation is recommended for AFd patients suffering from end-stage renal disease. Current



experience with renal transplantation in AFd patients also indicates that ERT is a safe and effective treatment for extra-renal Fabry manifestations and one that slows disease progression, although randomized controlled studies with longer follow-up are needed.

**Disclosure of Potential Conflicts of Interest:** None declared

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