Fabry Disease: Multidisciplinary Evaluation After 10 Years of Treatment with Agalsidase Beta

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Abstract Fabry disease is an X linked disorder of metabolism due to deficient α -galactosidase A activity. Enzyme replacement therapy (ERT) with agalsidase Beta was approved by EMA in 2001 and FDA in 2003.

Patients and methods: Six patients were enrolled. Baseline data was measured for renal, cardiac, and cerebrovascular functioning. We compared baseline quality of life scales with the current results. These parameters were assessed during the 10 years of follow-up period.

Results: Before ERT four patients showed normal eGFR, one stage 2 of CKD, and one hyperfiltration stage. All presented microalbuminuria and just two cases showed proteinuria. After 10 years of ERT, no patient showed decrease in renal functioning. One patient decreased from proteinuria to microalbuminuria range. Before treatment one case showed left ventricular (LV) hypertrophy and LV Mass Index was abnormal in two female patients. After 10 years echocardiographic values did not present progres-

sion to LVH and one female showed regression to normal values of LV posterior wall and interventricular septum. Brain MRI showed ischemic lesions in one female and vertebrobasilar dolichoectasia in one male. From baseline and during the follow-up period MRI did not progress to new ischemic lesions and there were no clinical signs of cerebrovascular damage. After 10 years quality of life showed improvement in all domains measured.

Conclusion: Early treatment of agalsidase Beta is related to a better outcome regarding stability and regression of signs and symptoms in Fabry disease. Our results in patients with mild organ involvement showed good outcomes and support an early and continuous ERT.

Introduction

Fabry disease (FD) is the result of deficient lysosomal α -galactosidase A (alpha-Gal A) activity, which leads to excessive deposition of glycosphingolipids, predominantly Globotriaosylceramide (GL₃). The incidence of this X chromosome-linked disorder is estimated at 1/40,000 live births in its classic phenotype and according to recent reports the incidence of the late-onset variant may be as high as 1/3,100 (Germain 2010; Spada et al. 2006). The deposition of GL₃ occurs in endothelial, perithelial, smooth muscle cells of the blood vessels, neurons, podocytes, cardiomyocytes, etc. The first symptoms appear in hemizygous males during childhood with distal neuropathic pain in the four limbs and hypohidrosis, associated with skin lesions known as angiokeratomas. During adolescence further symptoms include GL₃ deposition in the cornea (cornea verticillata), autonomic dysfunctions, fatigue, depression, and reduced hearing ability, followed by signs

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of kidney and heart failure and cerebrovascular accidents during the third decade (Germain 2010).

Subsequent to the approval of enzyme replacement therapy (ERT) in Europe in 2001 and in the USA in 2003, FD has taken a significant turn, arousing the interest of a large number of specialists (Eng et al. 2001; Schiffmann et al. 2001).

ERT with agalsidase Beta has returned positive results, reducing neuropathic pain (Hilz et al. 2004), stabilizing the renal and auditory functions (Germain et al. 2007; Sergi et al. 2010), preventing the development of cardiac complications (Weidemann et al. 2009), in addition to improving quality of life and reversing angiokeratomas in certain cases (Watt et al. 2010; Furujo et al. 2013). These findings are more evident in relation to early initiation of ERT.

Objective

To describe the results of the multidisciplinary evaluation in six patients suffering from FD after 10 years of treatment with agalsidase Beta.

Materials and Methods

Six adult patients (four males) from Buenos Aires, Argentina were included in this study. All the patients were diagnosed with FD via an enzyme activity test and a molecular test with a mutation search. All the patients had been treated with agalsidase Beta (Fabrazyme[®]) at 1 mg/kg every 14 days for the last 10 years without interruption. Due to a temporary shortage of agalsidase Beta, three patients were given a dose of 0.3 mg/kg every 14 days for a period of 10 consecutive months in the year 2010. The evaluation of the renal function was conducted by means of the estimated glomerular filtration rate (eGFR) using the MDRD formula, measurement of microalbuminuria (>30 mg/24 h) and proteinuria (>300 mg/24 h); kidney disease was broken down into five stages in accordance with the eGFR: (1) between 120 and 90 mL/min, (2) between 90 and 60 mL/min, (3) between 60 and 30 mL/min, (4) between 30 and 15 mL/min, and (5) <15 mL/min. The evaluation of the cardiac function was conducted by measuring the thickness of the interventricular septum (IVS) and the left ventricle posterior wall (LVPW) and the left ventricular mass index (LVMI) measured by echocardiography. The normal values for IVS and LVPW were 6–11 mm in both genders; the normal LVMI was 43–95 g/m² in females and 49–115 g/m² in males (Lang et al. 2005). The presence of cerebrovascular compromise was assessed by means of brain magnetic resonance imaging (MRI) using a 1.5T Signa Echo Speed (GE) MRI system with data

acquisition techniques standardized for cerebrovascular diseases (conventional FLAIR, T1, T2, diffusion and proton density) and a magnetic resonance angiogram of the intracranial vessels. Quality of life was evaluated using the SF36 scale, which, similar to MRI, describes the findings prior to commencement of ERT and after 10 years of treatment. The SF36 scale is a tool which has been validated in several languages and is used to assess the quality of life of the population as a whole and patients with chronic diseases. It can be conducted via the telephone or by instructing the patient to conduct a self-assessment; the assessment of eight independent items related to the day-to-day life of the individual: physical functioning, limitations due to physical problems (or physical role), bodily pain, general health perceptions, vitality, social functioning, limitations due to emotional problems (or emotional role) and mental health. All the items are given a score of between 0 and 100, whereby the higher the score, the better the quality of life. The reference value was based on the average registered for the general population of the USA (Ware et al. 1993), ranging from 64 to 87 points in males and 58 to 82 points in females for each item. An increase of more than seven points between one assessment and another is regarded as a significant improvement in all the items, with the exception of vitality, where a five-point difference is regarded as a significant improvement. Informed consent was obtained from all patients for being included in the study.

Statistical Analysis

Given the characteristics of this study, no official statistical analysis of the sample in question was conducted. The data is expressed as an average, mean, or percentage, as applicable.

Results

The demographic data is set forth in Table 1. Six patients from two different unrelated families were assessed initially. All the patients registered deficient enzyme activity measured in leukocytes. The mutation study revealed the same mutation in all the patients. A subsequent study of the family tree revealed a common origin in the fourth generation prior to the cases under analysis. The eGFR prior to commencement of ERT was normal in four patients and one patient registered stage 2 baseline CKD. All the patients registered microalbuminuria before beginning of ERT, whereby proteinuria was two cases only. After 10 years of treatment with agalsidase Beta, the state of CKD remained in all the patients (Fig. 1). Microalbuminuria values remained stable throughout the study period,

Table 1 Demographic data

Patient	Gender	Age when symptoms commenced	Age on diagnosis	Age on commencement of ERT	Alpha-Gal A activity in leukocytes	Mutation
1	M	12	17	17	2.2	L415P
2	M	5	18	19	1.1	L415P
3	M	6	18	20	1.9	L415P
4	M	10	29	30	0.7	L415P
5	F	10	49	50	2.6	L415P
6	F	35	45	46	1.4	L415P

Alpha-Gal A activity in leukocytes. Normal values: 30.5–57.7 nmol/h/mg

Fig. 1 Evaluation of eGFR after 10 years of treatment **Fig. 2** Evaluation of microalbuminuria after 10 years of treatment

whereby one patient registered a reduction in microalbuminuria at values of less than 30 mg/24 h (Fig. 2). The proteinuria results revealed no increases whatsoever, whereby one of the two patients with baseline values of 300 mg/24 h concluded the study with a value of 224 mg/24 h (Fig. 3).

Cardiac assessment prior to start of ERT demonstrated only one patient with an increased thickness of the IVS and

LVPW. There were no cases of progression to left ventricular hypertrophy (LVH) after the study, whereby the only patient with abnormal values returned to the normal range for these parameters (Figs. 4 and 5). The LVMI was normal in four male patients and pathological in the female patients on commencement of the study. No progression to abnormal values was registered in the male patients after 10 years of ERT. One of the heterozygous

Fig. 3 Evaluation of proteinuria after 10 years of treatment

Fig. 4 Evaluation of the interventricular septum after 10 years of treatment

Fig. 5 Evaluation of the left ventricle posterior wall after 10 years of treatment

patients showed no change and the other a clear reduction in LVMI, but without registering normal values (Fig. 6).

The brain MRI prior to beginning of ERT revealed punctate periventricular ischemic lesions in one patient and vertebrobasilar dolichoectasia in another. Monitoring after

10 years of ERT revealed no progression to the lesions described in both cases nor the appearance of new images in the normal baseline assessment cases.

The SF36 scale registered significant improvements in the eight domains analyzed in all the patients (Fig. 7). Compared

Fig. 6 Evaluation of the left ventricular mass index after 10 years of treatment

Fig. 7 Evolution of the SF36 scale before (gray bars) and after 10 years of treatment (black bars)

with the reference values registered for the general population, before ERT four items were below the lower limit in females and three in males, those being: limitations due to physical problems, bodily pain, and general health perceptions in both genders and social functioning in females only. All the scores in relation to 10 years of treatment fell within the normal reference values.

Discussion

ERT with agalsidase Beta has been shown to change the natural history of FD. Histopathological studies conducted prior to commencement and months or years before the use of agalsidase Beta showed a significant reduction of Gl₃ in the renal, cardiac, and dermal capillary endothelium (Eng

et al. 2001). It has recently been reported that a 1 mg/kg dose of agalsidase Beta every 14 days has resulted in the clearance of substrate in the podocytes (Tøndel et al. 2013). A dose of 0.2 mg/kg failed to show any statistically significant results in relation to a reduction of Gl_3 in renal tissue, and recent evidence has revealed no change with regard to podocytes in renal biopsies of young patients on comparing histological results with those in relation to 5 years of treatment with the aforementioned dose (Tøndel et al. 2013).

This patient's cohort is part of the same family as the lineage showed us. The L415P mutation is related to severe classical phenotype and enhancement with chemical chaperones showed no significant response. Recently, one study showed that this mutation overexpressed the mutant alpha-Gal A in the cells, notably above the endogenous level at the expected size of 46 kDa. Thus, the protein is evidently processed, but it is not catalytically active (Lukas et al. 2013). Clinical signs and symptoms were shared in all patients as dysmorphic features, gastrointestinal complaints, and neuropathic pain before 10 years old and presence of proteinuria before third decade. Female patients were under ACEi treatment before ERT and maintained same doses during the study period.

The results of our case series showed a stable renal function measured using eGFR and no increase in proteinuria. We decided to include microalbuminuria as a separate parameter, because it is assumed that the prognostic effect in patients with FD is relatively large and that increased microalbuminuria is also associated with a poor renal prognosis.

One of the factors which may have influenced this response is early initiation of ERT in the hemizygous patients (all of an age ≤ 30). Although the heterozygous patients commenced treatment in the fourth decade of life, the phenotypic expression of the same was less severe than normally registered (Wang et al. 2007). The current evidence of unsatisfactory results in relation to male patients who started ERT at the average age of 40 years (Weidemann et al. 2013a; Rombach et al. 2013) has been one of the main reasons for justifying therapy at an early age. Furthermore, evidence of agents causing cellular hypertrophy in cardiomyocytes and vascular smooth muscle cells, such as markers associated with fibrosis in different tissues, has clearly demonstrated the need for early treatment (Weidemann et al. 2013b). Previously, the Phase IV study showed in patients with reduced GFR treated with agalsidase Beta there was a 61% reduction in renal, cardiac, and cerebrovascular events when corrected for baseline proteinuria when compared to placebo (Banikazemi et al. 2007).

There was no sign of progression to LVH in any of the patients in relation to cardiac assessment after the study

period. Only one patient showed echocardiographical signs of LVH, whereby the thickness of the IVS and the LVPW after 10 years of ERT was normal. As is repeated in the bibliography, an increase in the thickness of the IVS, LVPW, and LVMI is related to age, justified by the fact that the only patient with signs of LVH was the oldest in our series (Germain et al. 2013). Agalsidase Beta has proved to be effective in reducing left ventricular mass in patients who commenced ERT between the ages of 18 and 30 according to a recent survey conducted by the Fabry Registry (Germain et al. 2013).

The analysis of the brain MRI revealed microangiopathic lesions in one female patient prior to starting ERT and vertebrobasilar dolichoectasia in one of the male patients. These lesions underwent no change during the study period. The remaining cases showed no change in the images, remaining free of lesions. To date ischemic lesions have been registered in many patients from the third decade of life on, with no major differences between the two genders (Fellgiebel et al. 2005). Moreover, certain series have shown a greater frequency of cerebrovascular compromise in heterozygous patients than in hemizygous patients. Our series of male cases commenced ERT ≤ 30 years of age, and this may be the reason for which the males did not develop white matter lesions, although there is still no clear evidence that ERT is capable of preventing the appearance of the same. Vertebrobasilar dolichoectasia seems to be the earliest finding in relation to cerebrovascular damage in patients with FD (personal observation in press). Certain authors have demonstrated that measuring the diameter of the basilar artery may be a useful monitoring tool, as this has been the only parameter which separated general population with a stroke (group control) from patients with FD and stroke (Fellgiebel et al. 2011).

Interference with daily activities due to neuropathic pain, fatigue, and other symptoms registered in patients with FD may be assessed using life quality scales such as SF36. Reports exist of significantly reduced quality of life in men and women with FD (Gold et al. 2002; Miners et al. 2002; Street et al. 2006), this being one of the reasons for the common occurrence of depression (Cole et al. 2007). Of the eight domains assessed using the SF36 scale, four were under the normal limit in the females and three in the males. All the domains showed a significant improvement after 10 years of ERT, including the domains where the score prior to treatment fell within the normal range. Changes in the SF36 scale after the use of agalsidase Beta for 3 years have been registered in a group of 71 men and 59 women belonging to the Fabry Registry (FR) population. In both our series and that conducted by the FR, the domain most affected in both genders was the physical role. Beginning of ERT at an early age may explain why five domains in the male patients registered scores within the normal range.

The FR report described a similar situation, where on dividing the male patients into two groups ($>0 < 30$ years of age), the older patients registered lower baseline values in all the domains.

Conclusions

The use of agalsidase Beta in our series has shown a significant improvement in quality of life, in addition to the stabilization of renal, cardiac, and cerebrovascular parameters. The determining factor in these results may be the early treatment with ERT, particularly in the hemizygous patients.

Take-Home Message

Early treatment with enzyme replacement therapy in Fabry disease is related to a better outcome.

Compliance with Ethics Guidelines

Conflict of Interest

Politei Juan has received speaker honorarium from Genzyme, Shire HGT and Amicus Therapeutics.

Amartino Hernan, Schenone Andrea Beatriz, Cabrera Gustavo, Michref Antonio, Tanus Eduardo, Dominguez Raul, Larralde Margarita, Blanco Mariana, Gaggioli Daniela, and Szlago Marina declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation of Juan Fernandez Hospital, Buenos Aires, Argentina and with the Helsinki Declaration of 1975, as revised in 2000.

Informed consent was obtained from all patients for being included in the study.

The informed consents are available if the journal needed them.

Details of the Contributions of Individual Authors

All authors have contributed in the planning, conduct, and reporting of the work described in the article.

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