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Original Article

Clinical observations on enzyme replacement therapy in patients with Fabry disease and the switch from agalsidase beta to agalsidase alfa

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Abstract

Background: Fabry disease is an X-linked inherited lysosomal storage disease that can be treated with the enzymes of agalsidase beta (Fabrazyme) and agalsidase alfa (Replagal). Since June 2009, viral contamination of Genzyme's production facility has resulted in a worldwide shortage of agalsidase beta, leading to the switch to agalsidase alfa for patients with Fabry disease in Taiwan.
Methods: The medical records were retrospectively reviewed for nine male patients with Fabry disease from the start of agalsidase beta treatment until the switch to agalsidase alfa for at least 1 year.
Results: After 12–112 months of enzyme replacement therapy (ERT), decreased plasma globotriaosylsphingosine (lyso-Gb3) was found in five out of seven patients, indicating improvement in disease severity. Among the six patients with available echocardiographic data at baseline and after ERT, all six experienced reductions of left ventricular mass index. Renal function, including microalbuminuria and estimated glomerular filtration rate, showed stability after ERT. Mainz Severity Score Index scores revealed that all nine patients remained stable at 12 months after switching to agalsidase alfa. ERT improved or stabilized cardiac status and stabilized renal function, while reducing plasma lyso-Gb3. ERT was well tolerated, even among the three patients who had hypersensitivity reactions.
Conclusion: The switch of ERT from agalsidase beta to agalsidase alfa appears to be safe after 1 year of follow-up for Taiwanese patients with Fabry disease.

Keywords: agalsidase alfa; agalsidase beta; enzyme replacement therapy; Fabrazyme; Fabry disease; Replagal

1. Introduction

Fabry disease (MIM 301500) is an X-linked lysosomal storage disorder caused by a deficient α-galactosidase A (α-Gal A) activity, leading to progressive accumulation of globotriaosylceramide (Gb3) and other neutral glycolipids in the vascular endothelium of the skin, kidneys, heart, and brain. It is a complex, multisystemic disorder characterized clinically

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by acroparesthesias, hypohydrosis, angiokeratomas, corneal opacities, gastrointestinal disturbances, progressive renal impairment, cardiomyopathy, and cerebrovascular lesions.[1] The onset of symptoms generally starts during childhood, and by middle age, some degree of irreversible damage may already have occurred. Life-threatening complications often develop in untreated patients.[2] The estimated incidence of classic Fabry disease is one in 40,000–60,000 males in the general population.[1,3]

During the past decade, there have been reports of late-onset phenotypes of Fabry disease primarily involving the heart,[4–6] kidneys,[7–9] or cerebrovascular system.[10] Patients with the cardiac variant lack the classic symptoms of Fabry disease and present with left ventricular hypertrophy (LVH), arrhythmias, or hypertrophic cardiomyopathy in the 5^{th}–8^{th} decades of life. Patients with the renal variant develop proteinuria and may progress to end-stage renal disease, typically after 50 years of age.

Prior to 2001, treatment of patients with Fabry disease was exclusively supportive. The advancement of molecular genetic techniques led to the development of enzyme replacement therapy (ERT).[11] There are two forms of ERT: agalsidase alfa (Replagal; Shire Human Genetic Therapies, Lexington, MA, USA) and agalsidase beta (Fabrazyme; Genzyme, Cambridge, MA, USA). Previous studies showed that ERT was an effective treatment for neuropathic pain[12] and could stabilize renal function, or at least, slow the decline of renal function in many patients with Fabry nephropathy[13–20] and stabilize or improve surrogate parameters such as cardiac size in those with cardiomyopathy.[16,21–24]

Since June 2009, viral contamination of Genzyme's production facility has resulted in a worldwide shortage of agalsidase beta, leading to a switch to agalsidase alfa for patients with Fabry disease in Taiwan. However, information is limited regarding the clinical outcome of Fabry patients in whom the treatment was switched from agalsidase beta to agalsidase alfa.[25–27] In this study, we retrospectively reviewed the clinical findings of ERT in nine Taiwanese patients with Fabry disease enrolled in the Fabry Outcome Survey who switched from agalsidase beta to agalsidase alfa for at least 12 months. Our aim was to evaluate the safety and effects on disease stability for these patients under ERT as well as the effect of the switch of treatment.

2. Methods

2.1. Selection of participants

Data from nine male patients with Fabry disease (three with classic type, two with renal type, and four with cardiac type) who received agalsidase beta treatment (1 mg/kg/biweekly) initially and were then switched to agalsidase alfa (0.2 mg/kg/biweekly) for at least 1 year between December 2002 and June 2012 in Taipei Veterans General Hospital, Taipei, Taiwan, were retrospectively reviewed for this study. The patients' ages when treatment began ranged widely, from 14.4 years to 66.7 years, and the duration of agalsidase beta therapy ranged from 0.7 months to 88.6 months. Informed written consent was obtained from a parent for children and from patients older than 18 years. The study was approved by the medical ethics committee of Taipei Veterans General Hospital, Taiwan.

2.2. Baseline and follow-up biochemical and clinical evaluation

All patients had clinical manifestations of the disease, and diagnosis was confirmed by plasma α-Gal A enzyme activity assay and *GLA* gene mutation analysis.[28,29] Prior to each infusion, patients were premedicated with diphenhydramine (0.5 mg/kg body weight). The data were collected retrospectively prior to ERT and after the switch for at least 1 year, including patient demographics, such as gender, age at diagnosis, height and body weight, and medical history. Furthermore, the relevant data pertaining to the left ventricular mass (LVM), left ventricular mass index (LVMI), the thicknesses of the intraventricular septum (IVS), and left posterior wall (LPW) obtained by serial echocardiographic assessments,[30–33] urine albumin-to-creatinine ratio (ACR), estimated glomerular filtration rate (eGFR; based on serum creatinine concentration),[34] plasma globotriaosylsphingosine (lyso-Gb3) concentration,[35,36] and severity of signs and symptoms of Fabry disease using the Mainz Severity Score Index[37] were recorded. LVM was calculated according to the American Society of Echocardiography simplified cubed equation. LVM was indexed (LVMI) by height$^{2.7}$ to normalize heart size to body size. LVH was defined as an LVMI of $\geq$51 g/m$^{2.7}$ in males.[30–33] Adverse events were assessed by: history; physical examination, including vital signs during treatment; patient records of side effects; laboratory tests (chemistry, hematology, urinalysis); and electrocardiography.

2.3. Data analysis

Descriptive statistics, including means, standard deviations, and percentage change over time, were calculated. Changes in LVMI, IVS, LPW, urine ACR, eGFR, and plasma lyso-Gb3 prior to and after treatment were analyzed using the Mann–Whitney test. SPSS version 11.5 (SPSS Inc., Chicago, IL, USA) was used, and differences were considered statistically significant when $p < 0.05$.

3. Results

3.1. Demographics

Details of the nine patients' backgrounds and clinical characteristics are shown in Table 1. During the entire course of ERT, only one patient (patient No. 5) underwent hemodialysis and renal transplantation. The patient had been receiving ERT with agalsidase beta since December 2002. End-stage renal disease developed in 2004, and the patient started to receive continuous ambulatory peritoneal dialysis from October 2004. Because of infection of the catheter, the patient started to undergo hemodialysis from September 2009.