Successful Management of Enzyme Replacement Therapy in Related Fabry Disease Patients with Severe Adverse Events by Switching from Agalsidase Beta (Fabrazyme®) to Agalsidase Alfa (Replagal®)

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Abstract *Background:* Enzyme replacement therapy (ERT) is the only approved therapy for Fabry disease. In June 2009, there was a worldwide shortage of agalsidase beta, necessitating dose reductions or switching to agalsidase alfa in some patients.

Case presentation: We present two cases of Fabry disease (a parent and a child) who received agalsidase beta for 27 months at the licensed dose and 10 months at a reduced dose, followed by a switch to agalsidase alfa for 28 months.

Case 1, a 26-year-old male had severe coughing and fatigue during ERT with agalsidase beta requiring antitussive and asthmatic drug therapy. After switching to agalsidase alfa, the coughing gradually resolved completely.

Case 2, a 62-year-old female had advanced cardiac manifestations at the time of diagnosis. Despite receiving ERT with the approved dose of agalsidase beta, she experienced aggravation of congestive heart failure and was hospitalized. After switching to agalsidase alfa with standard care in heart disease, BNP level, echocardiographic parameters, eGFR rate and lyso-Gb3 levels were improved or stabilized.

Conclusions: We report on two Fabry disease patients who experienced severe adverse events while on approved and/or reduced doses of agalsidase beta. Switching to agalsidase alfa associated with standard care in heart disease led to resolution or improvement in the cardiorespiratory status. And reduction in dose associated with standard care in respiratory disease was useful for decrease in cough and fatigue. Plasma BNP level was useful for monitoring heart failure and the effects of ERT.

Background

Fabry disease (OMIM 301500) is an X-linked, inherited lysosomal storage disorder caused by a deficiency of the enzyme α -galactosidase A (Nagueh 2003). α -Galactosidase deficiency results in the accumulation of globotriaosylceramide (Gb3 or ceramide trihexoside) and other neutral glycolipids in many tissues and cell types throughout the body, ultimately leading to cellular abnormalities and triggering inflammation and fibrosis (Zarate and Hopkin 2008). The consequences of these biochemical changes can be wide-ranging, and include acroparesthesias, hypohidrosis, angiokeratomas, corneal opacities, cerebrovascular lesions, cardiac disorders and renal dysfunction (Nagueh 2003; Fabry 2002). Organ dysfunction and pain are usually the first clinical manifestations of Fabry disease and, at this stage, some degree of irreversible damage may already have occurred. The onset of symptoms generally starts during childhood, and by middle-age life-threatening complications often develop in untreated patients (Zarate and Hopkin 2008).

Enzyme replacement therapy (ERT) is currently the only approved therapy for Fabry disease (Lidove et al. 2007).

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Two preparations of the enzyme α -galactosidase A are now available in Japan: agalsidase alfa (Replagal®; Dainippon Sumitomo Pharma) and agalsidase beta (Fabrazyme®; Genzyme). Since June 2009, there had been a worldwide shortage of agalsidase beta as a result of viral contamination in the manufacturer's production facility. This shortage led to a series of recommendations including dosage reductions (i.e., spreading the usual dose over a longer time period). These guidelines were reviewed by a consensus group of treating physicians, with the outcomes reported by the European Medicines Agency in October 2010 (European Medicines Agency 2011; Sirrs 2011; Linthorst et al. 2011). At this meeting it was noted that there was a steady increase in the number of adverse events reported, presumably because of clinical deterioration in patients receiving the reduced dose of agalsidase beta. Currently, the general consensus is that patients should receive only the licensed dose of agalsidase beta (1 mg/kg once every 2 weeks), and if this is not possible, then switching to treatment with agalsidase alfa (0.2 mg/kg once every 2 weeks) is an option (European Medicines Agency 2011). However, only limited clinical data are available regarding patients in whom treatment has been switched between the different forms of α -galactosidase A enzyme (European Medicines Agency 2011; Sirrs 2011; Linthorst et al. 2011).

Recently, an observational study involving 11 patients with Fabry disease who were switched from agalsidase beta to agalsidase alfa showed that indices of renal function, cardiac mass, pain and quality of life were maintained after switching (Tsuboi and Yamamoto 2012). Another study found that a reduced dose of agalsidase beta was not associated with an increase in the incidence of clinical events compared with the full dose, and neither was a switch to agalsidase alfa (Smid et al. 2011).

In this report, we present two cases with Fabry disease, a parent and child, who received 27 months of treatment with agalsidase beta at the registered dose and 10 months of treatment at the reduced dose, followed by a switch to 28 months of treatment with agalsidase alfa. We analyzed cardiac involvement using echocardiography and plasma brain natriuretic peptide (BNP) levels, renal function (estimated glomerular filtration rate; eGFR), and plasma Gb3 and lyso-Gb3 levels.

Case Presentation

Case 1 (Male, 26 Years Old)

This patient was diagnosed with Fabry disease in 2005 at the age of 19. He was initially suspected of having the disease because of a history of peripheral pain and sweating abnormality since the age of approximately 5 years, and

Fig. 1 Familial tree for cases 1 and 2

because of a definitive diagnosis of Fabry disease in his older sibling (Fig. 1). The level of α -galactosidase A activity in a dried blood spot analysis was 2.4 AGal U, which is below the male cut-off level (17.0 AGal U). A genetic analysis showed a missense mutation of the α -galactosidase A gene (D299V in exon 6). Consequently, ERT with the registered dose of agalsidase beta (1 mg/kg every other week) was initiated in February 2006. The patient had coughing from the time of initiation of ERT, and IgG anti-agalsidase beta antibody was detected, with a titre of 1/3,200 to 1/6,400.

In August 2007, Case 1 was transferred to Nagoya Central Hospital voluntarily. An extensive work-up revealed neuropathic pain, dermatological symptoms (angiokeratoma and sweating abnormality), gastrointestinal symptoms (diarrhoea and abdominal pain) and ocular manifestations (cornea verticillata and vessel tortuosity). ERT with agalsidase beta was continued. He had coughing and fatigue at night, and a steroid (betamethasone 1 mg/day) and an antihistamine (chlorpheniramine maleate 8 mg/day) were administered to suppress these symptoms. As this was not successful, an anti-leukotriene agent (montelukast 10 mg/day) and a beta-agonist (tulobuterol 2 mg/day) were co-administered for approximately 1 month from September 2009, followed by a switch to inhalation of fluticasone propionate 0.2 mg twice/day from October 2009 (Fig. 2).

During the supply shortage of agalsidase beta, Case 1 preferred to remain on agalsidase beta at the reduced dose of 0.7 mg/kg every other week from November 2009 to July 2010. Despite the reduction in dose of agalsidase beta, his coughing did not improve and inhaled fluticasone remained necessary.

Because the supply shortage of agalsidase beta continued and his mother (Case 2) was switched from agalsidase beta onto agalsidase alfa, Case 1 also switched onto agalsidase alfa at 0.2 mg/kg every other week. His coughing gradually resolved completely and administration of fluticasone was stopped in August 2010. Administration of betamethasone and chlorpheniramine were also stopped in December 2011. IgG anti-agalsidase alfa antibody was not detected at any point of determination following the switch.

Fig. 2 Case 1: clinical course (Agal β = agalsidase beta; Agal α = agalsidase alfa)

Cardiac structure, function and renal function were maintained during ERT with both agalsidase beta and alfa (data not shown). Changes in plasma lyso-Gb3 and Gb3 levels are shown in Fig. 2; both increased at 12 months after switching to agalsidase alfa, but decreased to their original levels by 24 months.

Case 2 (Female, 62 Years Old)

This patient was diagnosed with Fabry disease in 2005 at the age of 55 years. The diagnosis was suspected because of the presence of left ventricle hypertrophy and the definitive diagnosis of her older son. The level of α -galactosidase A activity in a dried blood spot test was 12.6 AGal U, below the female cut-off level (20.0 AGal U). Genetic analysis confirmed the diagnosis of Fabry disease (D299V in exon 6 of the α -galactosidase A gene). Consequently, ERT with agalsidase beta at 1 mg/kg every other week was initiated in April 2006.

In August 2007, Case 2 was transferred to Nagoya Central Hospital voluntarily. An extensive work-up revealed advanced organ manifestations including heart, kidney and eyes (cornea verticillata). Electrocardiography showed ST segment depression with a negative T wave in leads I, II, aVL, aVF and V₄–V₆. Left ventricular mass (LVM) index was 54 g/m^{2.7}. eGFR was 65.7 mL/min/1.73 m² (indicating chronic kidney disease stage 2) and proteinuria was present. ERT with agalsidase beta was continued. In contrast to Case 1, Case 2 generally tolerated

treatment with agalsidase beta well, and no infusion-related reaction was observed.

Plasma BNP level was monitored during ERT with the registered dose of agalsidase beta (Fig. 3a). Plasma BNP level increased gradually from approximately 200 pg/mL in November 2007 to 500 pg/mL in September 2009. Case 2 was hospitalized for congestive heart failure twice between September 2009 and December 2009. Plasma BNP level increased rapidly to >700 pg/mL in September 2009 and ejection fraction decreased to 42.5% in November 2009. Case 2 was treated for congestive heart failure with a loop diuretic (furosemide 10–30 mg/day), beta-blocker (carvedilol 2.5 mg/day), amiodarone 100 mg/day and an angiotensin-converting enzyme (ACE) inhibitor (perindopril 2 mg/day). Plasma BNP level decreased and ejection fraction improved with this treatment (Fig. 3a, b).

During the supply shortage of agalsidase beta, this patient preferred to remain on agalsidase beta at a reduced dose of 0.7 mg/kg every other week from September 2009 to July 2010. During the initial 27-month period of ERT with the registered dose of agalsidase beta 1 mg/kg, LVM index was maintained at around 50–56 g/m^{2.7}; but after the dose reduction, LVM index increased to 62 g/m^{2.7} by June 2010 (Fig. 3b). Interventricular septum thickness and left ventricular posterior wall thickness showed similar changes (data not shown). During ERT with agalsidase beta, IgG anti-agalsidase beta antibody was not detected at any point.

The supply shortage of agalsidase beta continued and Case 2 decided to switch to agalsidase alfa 0.2 mg/kg every other

Fig. 3 Case 2: clinical course (Agal β = agalsidase beta; Agal α = agalsidase alfa)

week in August 2010. Administration of an ACE inhibitor (perindopril) continued. Plasma BNP level decreased gradually from >300 pg/mL in August 2010 (before switching) to <200 pg/mL by December 2012 after 28 months' treatment with agalsidase alfa (Fig. 3a). LVM index and ejection fraction were maintained after 6 months' treatment.

Changes in eGFR are shown in Fig. 3c. During 36 months' ERT with agalsidase beta, eGFR decreased from around 78.6 mL/min/1.73 m² in November 2007 to 44.5 mL/min/1.73 m² by June 2010. Two years after switching to agalsidase alfa, eGFR remained at around 50 mL/min/1.73 m².

During ERT with agalsidase alfa, IgG anti-agalsidase alfa antibody was not detected.

Changes in plasma lyso-Gb3 and Gb3 levels are shown in Fig. 3d. Both increased slightly 12 months after switching to agalsidase alfa, but then decreased to a level below that seen while the patient was on agalsidase beta.

Discussion

In this report, we present two cases with Fabry disease (a parent and a child) who received 27 months of treatment with agalsidase beta at the registered dose and 9 months of treatment at a reduced dose, followed by a switch to 28 months of treatment with agalsidase alfa. For both patients the switch was performed because of severe adverse events while receiving the registered dose of agalsidase beta and also because of a worldwide shortage of agalsidase beta.

Case 1 was thought to have an allergic tendency when he was transferred to Nagoya Central Hospital. He had severe coughing and fatigue, and therefore antitussive and antiasthmatic drugs were prescribed for about 4.5 years. After switching to agalsidase alfa because of the shortage of agalsidase beta, the coughing gradually resolved and anti-allergic drugs were no longer needed. These results suggest that Case 1 had severe coughing and fatigue due to an infusion-related reaction to agalsidase beta.

Case 1 developed a high titre of IgG anti-agalsidase beta antibody, but no IgG anti-agalsidase alfa antibody during ERT with the alternative drug. IgE anti-agalsidase beta antibody was not determined. Although the mechanism underlying coughing as an infusion-related reaction to agalsidase beta has not been elucidated, immunological reactions are thought to be involved.

There are significant differences in the frequencies of immunoglobulin responses and infusion-related reactions between agalsidase alfa and beta (Lidove et al. 2007, 2010; Deegan 2012). According to data from Shire HGT and Genzyme Corp held on file with the European Medicines Agency, 24% of men treated with agalsidase alfa develop

IgG antibodies and 89% of patients treated with agalsidase beta develop IgG antibodies (European Medicines Agency 2006a, b). An IgE antibody response to ERT has only been reported for patients treated with agalsidase beta (Banikazemi et al. 2007; Bodensteiner et al. 2008), not in those receiving agalsidase alfa (Pastores et al. 2007; Schiffmann et al. 2006; Tesmoingt et al. 2009). The frequency of infusion-related reactions is also higher with agalsidase beta than agalsidase alfa, at about 67% and 13.7%, respectively (European Medicines Agency 2006a, b). Agalsidase alfa seems to be less immunogenic than agalsidase beta, although it should be noted that these frequencies came from different trials using different methods for detecting antibodies in plasma. Tanaka et al. reported that IgE antibodies against agalsidase beta which developed in a male patient with Fabry disease showed no cross-reactivity to agalsidase alfa (Tanaka et al. 2010). This suggests that IgE anti-agalsidase beta antibody could be determined in order to clarify differences between adverse events.

Our case studies showed that decrease in cough and fatigue started at lower dose of agalsidase beta with standard and effective care in respiratory disease, and switching to agalsidase alfa can be helpful for resolving severe infusion-related reactions while maintaining various indices of cardiac and renal function. However, the licensed dose of agalsidase beta is only 1 mg/kg once every 2 weeks and its reduced dose should be used carefully because it has not clarified to be effective in various symptoms of Fabry disease.

Plasma lyso-Gb3 elevation is a hallmark of Fabry disease (Aerts et al. 2008) and is associated with clinical manifestations (Rombach et al. 2010). Recently, Smid et al. reported that an increase in lyso-Gb3 was found both in male patients who switched to agalsidase alfa for approximately 1 year and in patients who received a reduced agalsidase beta dose for approximately 1 year, although no correlation between the incidence of clinical events and an increase in lyso-Gb3 was found (Smid et al. 2011). In our study of Case 1, lyso-Gb3 also increased 12 months after switching to agalsidase alfa, but by 24 months after switching it had decreased to a level similar to that seen prior to switching. The mechanism of such a transient increase of lyso-Gb3 remains to be determined.

Case 2 had advanced cardiac manifestations at the time of her definitive diagnosis. Despite receiving ERT at the approved dose of agalsidase beta, this patient was hospitalized because of aggravation of congestive heart failure, which was treated appropriately. After that, she received a reduced dose of agalsidase beta for 9 months during the supply shortage, which led to an increase in LVM index. After ERT was subsequently switched to agalsidase alfa, all measured indices such as BNP level, echocardiographic parameters, eGFR and lyso-Gb3 level improved or stabilized. The registered dose of agalsidase beta stabilized heart

structure, but was not effective at stabilizing cardiac function. In contrast, switching to agalsidase alfa after receiving conventional treatment for congestive heart failure led to stabilization of both heart structure and cardiac function. In this patient, IgG anti-agalsidase beta antibody did not develop during ERT with agalsidase beta, and an immunological response is not thought to be involved in the events experienced by this patient.

BNP is a cardiac neurohormone specifically secreted from the ventricles (Daniels and Maisel 2007) by stimuli such as pressure overload or ventricular wall distension. A recent study showed that NT-proBNP was potentially useful as a biomarker in Fabry disease and correlated with changes in Mainz Severity Score Index (Torralba-Cabeza et al. 2011). BNP gene expression is stimulated by both mechanical strain (Liang et al. 1997; Liang and Gardner 1998) and autocrine/paracrine processes via angiotensin II (Liang and Gardner 1998). Renin–angiotensin system blockade reduces plasma NT-proBNP level and improves prognosis, which is most likely a reflection of improved cardiac function due to the treatment (Anand et al. 2003). Based on these reports, combination therapy with an ACE inhibitor and agalsidase alfa might be useful in achieving a good effect on plasma BNP levels and cardiac function.

Therapy with ACE inhibitors and/or angiotensin II receptor blockers is recommended in patients with renal disease, to treat proteinuria and prevent progression toward renal failure (Chobanian et al. 2003). The role of ACE inhibitors and angiotensin II receptor blockers in patients with Fabry disease is not solely antihypertensive; in combination with ERT, it also helps stabilize kidney function by slowing the progressive decline of eGFR and reducing urinary protein excretion to <500 mg/day (Eng et al. 2006; Warnock and West 2006). In Case 2, combination therapy with an ACE inhibitor and agalsidase alfa is likely to have been responsible for the beneficial effects recorded for renal function.

Plasma BNP level was useful for monitoring several clinical aspects, such as heart failure during Fabry disease, and for evaluating the effect of ERT and/or combination therapy. Our results showed that switching to agalsidase alfa was helpful for maintaining various indices reflecting both cardiac and renal function.

Conclusions

In conclusion, we report two clinical cases that experienced severe adverse events during therapy with the approved and/or reduced doses of agalsidase beta. Switching to agalsidase alfa associated with standard care in heart disease led to resolution or improvement in the cardiorespiratory status. And reduction in dose associated with

standard and effective care in respiratory disease was useful for decrease in cough and fatigue. Plasma BNP level was found to be useful for monitoring various clinical aspects, such as heart failure and the effect of ERT and/or combination therapy in patients with Fabry disease.

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Synopsis

Switching to agalsidase alfa can ameliorate adverse events experienced during treatment with agalsidase beta, while maintaining cardiac and renal function.

Conflict of Interest

Kazuya Tsuboi has received a speaker honorarium from Genzyme, Shire HGT and Dainippon Sumitomo Pharma.

Hiroshi Yamamoto has received a speaker honorarium from Genzyme.

Fuji Somura and Hiromi Goto declare that they have no conflict of interest.

Informed Consent

The study was approved by the institutional review boards and was conducted in accordance with the ethical provisions set out in the Helsinki Declaration of 1975 as revised in 2000, and all applicable local laws and regulations. Informed consent was obtained from all patients for being included in the study.

Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

Details of the Contributions of Individual Authors

Kazuya Tsuboi contributed the planning, conduct and reporting of the work described in the article.

Hiroshi Yamamoto contributed conduct and reporting of the work.

Fuji Somura and Hiromi Goto contributed conduct for cardiovascular treatment to patients and checking the draft of report.

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