

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.

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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

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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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 5th–8th 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 pain¹² 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 Index³⁷ 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 ≥ 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.

Table 1
Baseline demographics of nine Taiwanese patients with Fabry disease who were switched from agalsidase beta to agalsidase alfa.

Patient No.	1	2	3	4	5	6	7	8	9
Type	Classic	Classic	Classic	Renal	Renal	Cardiac	Cardiac	Cardiac	Cardiac
Sex	M	M	M	M	M	M	M	M	M
Age at diagnosis (y)	14.2	33.0	49.4	30.7	34.7	42.7	53.3	62.6	65.4
Age at ERT (y)	14.4	33.0	49.4	31.3	35.4	42.8	53.4	63.4	66.7
GLA mutation	W204X	E398DfsX6	E398DfsX6	R112H	R112H	IVS4+919G>A	IVS4+919G>A	IVS4+919G>A	IVS4+919G>A
Plasma α -Gal A enzyme activity (nmol/h/mL) ^a	0	0.027	0.02	1.3	3.0	0.65	0.88	1.2	0.95
Plasma lyso-Gb3 (nM) ^b	178.4	54.95	71.48	1.48 ^c	1.62 ^d	4.44	5.19	3.49	7.8
Height (cm)	166	169	181	174	167	171	166	172	163
Body weight (kg)	78	63	64	90	75	94	65	78	59
Cardiac symptoms	N	N	N	Y	Y	Y	Y	Y	Y
LVM (gm)	225.2	282.2	151.6	165.3 ^c	232.1 ^f	392.1	378.8	383.6	195.6
LVMI (g/m ^{2.7})	57.3	68.5	30.5	37.1 ^g	58 ^h	92.1	76	88.7	52.3
IVS (mm)	10.1	13	10.5	10.5	11.2	16.7	14.6	19.4	15.4
LPW (mm)	11.7	11	7	7.5	8.2	12	15.2	13.3	8
Ejection fraction (%)	84	75	75	67	69	84	78	84	64
Fractional shortening (%)	54	44	44	37	39	53	46	53	34
Pacemaker	N	N	N	N	N	N	N	N	N
Urine ACR (mg/mmol)	0.99	171.68	111.84	2.36	68.43	0.35	0.84	5.65	1.07
Serum creatinine (mg/dL)	0.8	1.12	2.33	1	3	0.8	0.84	0.83	0.65
eGFR (mL/min/1.73 m ²)	133.	85.7	31.5	99.6	25.6	109.6	99.7	93.4	100.9
Hemodialysis	N	N	N	N	Y ⁱ	N	N	N	N
Acroparesthesia	Y	Y	Y	N	N	N	N	N	N
Angiokeratoma	Y	Y	Y	N	N	N	N	N	N
Hypohidrosis	N	N	Y	N	N	N	N	N	N
Cerebrovascular disorders	N	N	N	N	N	N	Y	N	N
Dysacusis	N	Y	Y	Y	N	N	N	N	N
Gastrointestinal symptoms	N	N	Y	Y	N	N	N	Y	Y
Respiratory symptoms	N	N	N	Y	N	Y	N	N	N
Agalsidase beta									
Start date	28 Aug 2009	15 Aug 2010	17 Nov 2010	20 Dec 2002	20 Dec 2002	6 Jan 2009	13 Dec 2008	1 May 2009	18 Aug 2009
Treatment (mo)	7	3.5	0.7	88.6	88.6	16.8	14.2	11.3	7.5
Adverse effects	Y	Y	N	N	N	N	N	N	Y
Agalsidase alfa									
Start date	26 Mar 10	29 Nov 10	8 Dec 10	31 Mar 10	31 Mar 10	25 May 10	11 Feb 10	5 Apr 10	31 Mar 10
Treatment (mo)	>12	>12	>12	>12	>12	>12	>12	>12	>12
Adverse effects	N	Y	N	N	N	N	N	N	Y

ACR = albumin-to-creatinine ratio; α -Gal A = α -galactosidase A; eGFR = estimated glomerular filtration rate; ERT = enzyme replacement therapy; IVS = intraventricular septum; LPW = left posterior wall; lyso-Gb3 = globotriaosylsphingosine; LVM = left ventricular mass; LVMI = left ventricular mass index.

^aReference range, 7.9–16.9.

^bReference range < 0.01–0.5.

^{c–h} These data were only available after enzyme replacement therapy for specific time intervals: ^{c,d} 108 months

^{e–h} 100 months.

ⁱPatient No. 5 had undergone hemodialysis since September 2009 and renal transplantation in November 2010.

The switch of ERT to agalsidase alfa was started in March 2010. The patient then underwent renal transplantation in November 2010.

3.2. Cardiac status, renal function, and lyso-Gb3 concentration

Table 2 shows the parameter changes in cardiac status, renal function, and plasma lyso-Gb3 concentrations of these nine patients after 12–112 months of ERT, comparing with the baseline data prior to ERT. Among the six patients with available echocardiographic data at baseline and after ERT, all six experienced reductions of the LVMI (Fig. 1), six had decreasing or stable thickness of the IVS, and four had decreasing thickness of the LPW. For four patients with microalbuminuria (urine ACR ≥ 2.0 mg/mmol for men)³⁸ prior to ERT, three patients revealed improvement after ERT. Among the eight patients with available data for eGFR, all eight showed stable renal function after ERT (Fig. 2). Five of seven patients had a decrease in plasma lyso-Gb3 concentration, indicating improvement in disease severity (Fig. 3). However, because of the small sample size, there were no

statistically significant differences after ERT for these six parameters ($p > 0.05$).

3.3. Mainz Severity Score Index

Mainz Severity Score Index scores revealed that all nine patients had mild-to-moderate Fabry disease (Mainz Severity Score Index ≤ 40) at the preswitch baseline.³⁷ The disease remained stable at 12 months after switching to agalsidase alfa, with mild improvements in cardiac or renal scores in three patients (patients Nos. 6–8), and a slight deterioration in general score in patient No. 9 (Table 3).

3.4. Adverse events

Three patients had hypersensitivity reactions (shortness of breath, skin itching/urticaria, fever) at some point during their treatment (Table 1).

3.4.1. Patient No. 1

Fever and chills were only noted at the time of first agalsidase beta infusion in August 2009. However, no adverse

Table 2
Parameter changes in cardiac status, renal function, and plasma lyso-Gb3 before and after enzyme replacement therapy in nine Taiwanese patients with Fabry disease.

Patient No.	1	2	3	4	5	6	7	8	9
Baseline LVMI (g/m ^{2.7})	57.3	68.5	30.5	37.1 ^a	58 ^b	92.1	76	88.7	52.3
ERT duration (mo)	32	13	NA	NA	NA	39	39	35	32
LVMI after ERT	47.5	44.1	NA	NA	NA	63.4	50.4	77.7	51.1
LVMI change (%)	-17	-36	NA	NA	NA	-31	-34	-12	-2
<i>p</i>	0.073								
Baseline IVS (mm)	10.1	13	10.5	10.5	11.2	16.7	14.6	19.4	15.4
ERT duration (mo)	32	13	NA	NA	NA	39	29	35	21
IVS after ERT	8.9	9.5	NA	NA	NA	13.7	12.8	17.7	15.4
IVS change (%)	-12	-27	NA	NA	NA	-18	-12	-10	0
<i>p</i>	0.348								
Baseline LPW (mm)	11.7	11	7	7.5	8.2	12	15.2	13.3	8
ERT duration (mo)	32	13	NA	NA	NA	39	29	35	21
LPW after ERT	8.9	10.6	NA	NA	NA	12.2	11.7	8.2	10.6
LPW change (%)	-24	-4	NA	NA	NA	2	-23	-35	33
<i>p</i>	0.228								
Baseline urine ACR (mg/mmol)	0.99	171.68	111.84	2.36	68.43	0.35	0.85	5.65	1.07
ERT duration (mo)	27	18	18	108	NA	41	39	37	34
Urine ACR after ERT	1.11	206.32	23.44	1.89	NA	0.43	0.39	0.34	0.30
ACR change (%)	13	20	-79	-20	NA	23	-54	-94	-72
<i>p</i>	0.830								
Baseline eGFR (ml/min/1.73 m ²)	133.8	85.7	31.5	99.6	25.6	109.6	99.7	93.4	100.9
ERT duration (mo)	33	15	15	112	NA	41	35	37	34
eGFR after ERT	141.2	83.1	31.6	100.6	NA	115.1	92.5	89.7	98.4
eGFR change (%)	6	-3	0	1	NA	5	-7	-4	-2
<i>p</i>	0.987								
Baseline plasma lyso-Gb3 (nM)	178.4	54.95	71.48	1.48 ^c	1.62 ^d	4.44	5.19	3.49	7.8
ERT duration (mo)	27	16	12	NA	NA	30	35	31	12
Plasma lyso-Gb3 after ERT	75.64	45.13	58.80	NA	NA	3.36	4.18	4.17	10.80
Plasma lyso-Gb3 change (%)	-58	-18	-18	NA	NA	-24	-19	19	38
<i>p</i>	0.524								

ACR = albumin-to-creatinine ratio; eGFR = estimated glomerular filtration rate; ERT = enzyme replacement therapy; IVS = intraventricular septum; LPW = left posterior wall; LVMI = left ventricular mass index; lyso-Gb3 = globotriaosylsphingosine; NA = not available.

^{a-d} These data were only available after enzyme replacement therapy for specific time intervals: ^{a,b} 100 months.

^{c,d} 108 months.

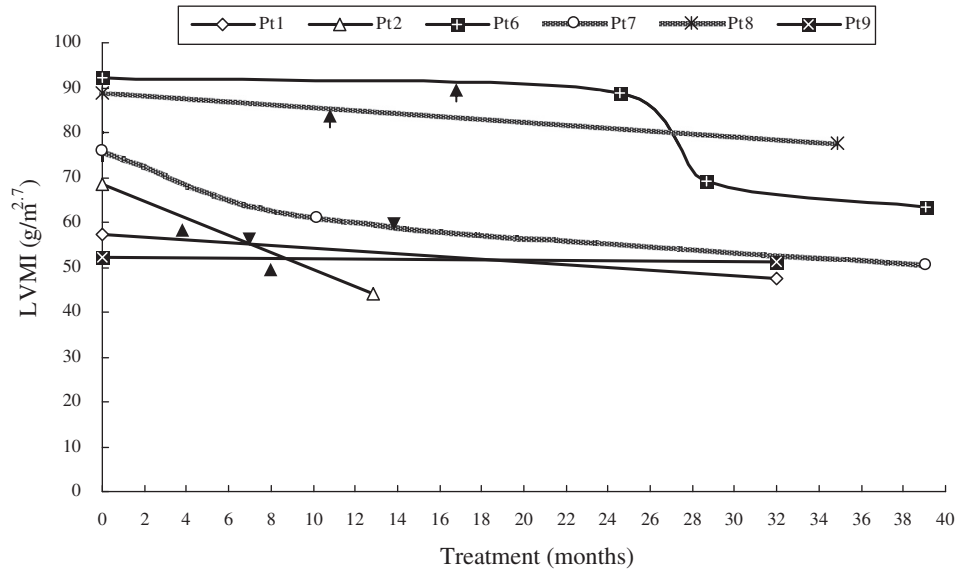


Fig. 1. Left ventricular mass index (LVMI) versus treatment month for six patients with Fabry disease receiving enzyme replacement therapy for 13–39 months. Arrowheads indicate the switch time of agalsidase beta to agalsidase alfa treatment for each patient.

effects occurred after that, including the switch to agalsidase alfa treatment beginning March 2010.

3.4.2. Patient No. 2

Urticaria and dyspnea were seen after the fifth administration of agalsidase beta. These symptoms improved with intravenous antihistamine and steroids, and the reactions were noted twice under agalsidase beta infusion after that. After switching to agalsidase alfa treatment from November 2010, adverse effects did not occur initially. However, after the 30th instance of agalsidase alfa infusion, mild dyspnea was seen. No reaction occurred after the 32nd administration of agalsidase alfa.

3.4.3. Patient No. 9

Itching red plaques on the extensor aspects of all four limbs and diarrhea were noted throughout both the whole courses of agalsidase beta therapy and then after switching to agalsidase alfa infusion. The symptoms were partially relieved following oral antihistamines, topical steroids, and oral antidiarrheal agents.

4. Discussion

This is the first report to demonstrate the efficacy of ERT and the safety of switching from agalsidase beta to agalsidase alfa in Taiwanese patients with Fabry disease. For most

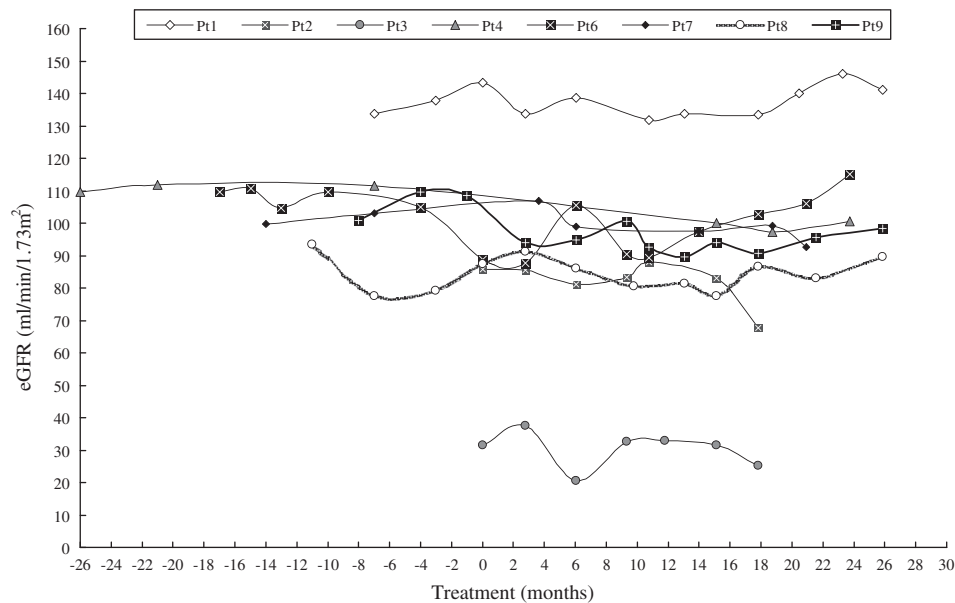


Fig. 2. Individual estimated glomerular filtration rate (eGFR) values in eight patients with Fabry disease treated with agalsidase beta (from months –26 to 0 if available) prior to being switched to agalsidase alfa treatment (months 0–26 if available).

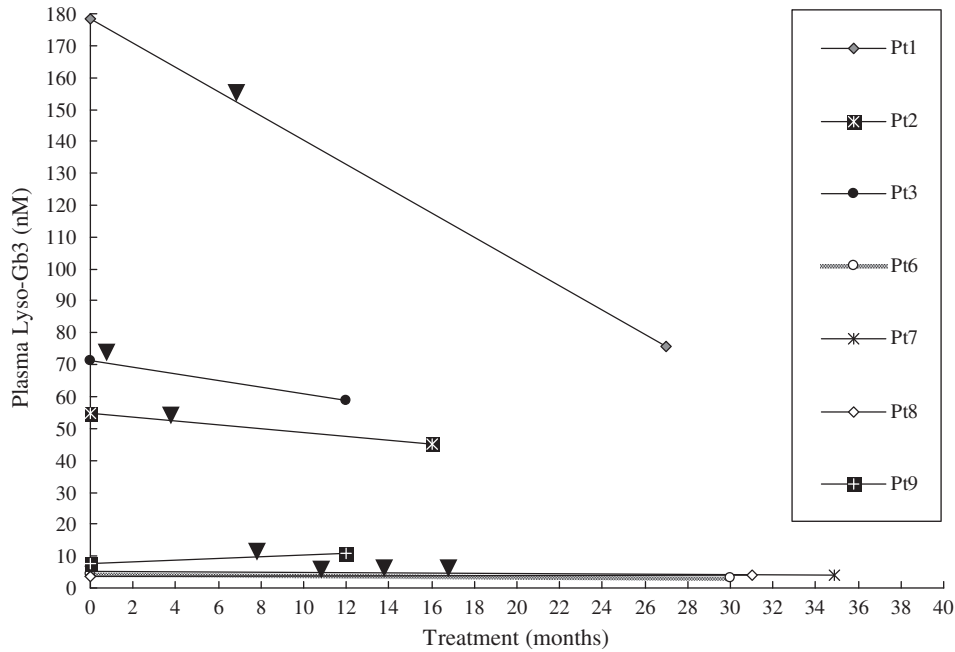


Fig. 3. Plasma globotriaosylsphingosine (lyso-Gb3) versus treatment month for seven patients with Fabry disease receiving enzyme replacement therapy for 12–35 months. Arrowheads indicate the switch time of agalsidase beta to agalsidase alpha treatment for each patient.

patients in this study, ERT decreased plasma lyso-Gb3 concentration, stabilized or improved surrogate parameters (e.g., LVM) and the thicknesses of IVS and LPW in those with LVH, improved microalbuminuria, and stabilized renal function in those with Fabry nephropathy. Our results were consistent with those of previous studies.^{13–24}

In this study, we report data from nine male patients with Fabry disease (three with classic type, two with renal type, and four with cardiac type) who had received at least 12 months of treatment with agalsidase alfa after switching from agalsidase beta. Agalsidase alfa and agalsidase beta have several differences in structure, including glycosylation, sialylation, and phosphorylation of mannose residues, which may cause differences in tissue distribution and antibody production. Moreover, agalsidase alfa and agalsidase beta are produced by

expression of the *GLA* gene in modified human cells derived from fibroblasts and Chinese hamster ovary cells, respectively. Patients are usually treated with the established protocol of agalsidase alfa at 0.2 mg/kg and agalsidase beta at 1.0 mg/kg, administered intravenously every 2 weeks. However, comparison between the two enzymes is difficult, mainly because in the Phase III pivotal studies, evaluations of agalsidase alfa and agalsidase beta were based predominantly on clinical and histological primary end-points, respectively.^{12,39–41} Meanwhile, there have been few studies regarding the safety and efficacy of ERT for patients who switched from one enzyme to the other.^{25–27} Tsuboi and Yamamoto²⁷ in Japan recently reported findings involving 11 patients with Fabry disease who switched from agalsidase beta to agalsidase alfa with standard doses. They found that all patients maintained disease stability

Table 3
Mainz Severity Scores at the preswitch baseline and 12 months after switching from agalsidase beta to agalsidase alfa in nine male patients with Fabry disease.

Patient No.	Max score	Score (baseline at switch)					Score (12 mo)				
		General	Neuro	Cardio	Renal	Total	General	Neuro	Cardio	Renal	Total
		18	20	20	18	76	18	20	20	18	76
1	Classic	1	5	11	0	17	1	5	11	0	17
2	Classic	5	8	11	4	28	5	8	11	4	28
3	Classic	6	10	9	8	33	6	10	9	8	33
4	Renal	4	1	10	4	19	4	1	10	4	19
5	Renal	3	1	12	18	34	3	1	12	18	34
6	Cardiac	3	1	16	0	20	3	1	12	0	16
7	Cardiac	3	4	16	0	23	3	4	12	0	19
8	Cardiac	4	1	16	4	25	4	1	16	0	21
9	Cardiac	5	1	16	0	22	6	1	16	0	23
Mean		3.78	3.56	13.00	4.22	24.56	3.89	3.56	12.11	3.78	23.33

Cardio = cardiovascular; Max = maximum possible score; Neuro = neurological.

after switching to agalsidase alfa treatment throughout the 12 months of follow-up, as evidenced by LVMI, eGFR, pain scores, and quality-of-life indexes. In our study, besides the improvement or stability of the parameters for the assessments of cardiac status and renal function, Mainz Severity Score Index scores also revealed the severity of signs and symptoms of Fabry disease remained stable at 12 months after switching to agalsidase alfa treatment. Our results were in accordance with Tsuboi and Yamamoto's.²⁷

Beck et al¹⁶ reported a 20% reduction in LVM after 12 months of agalsidase alfa treatment with the standard dose (0.2 mg/kg/biweekly). Our study showed similar results, with an average decrease of 22% in LVMI for six patients after ERT, as well as 13% and 9% decrease in the thicknesses of IVS and LPW, respectively. Schiffmann et al¹⁴ described stabilization in patients with preserved renal function, but gradual deterioration in advanced kidney disease following 4–4.5 years of agalsidase alfa therapy. One patient in our study (patient No. 5) showed similarity to the latter outcome after ERT. However, the other eight patients showed stable renal function, and three of the four patients showed improvement of microalbuminuria after treatment. Plasma lyso-Gb3 elevation is a hallmark of Fabry disease and is associated with clinical manifestations.^{35,36} Thus, it was reasonable that the average baseline plasma lyso-Gb3 concentration values of three classic patients and four cardiac-type patients were 101.61 nM and 5.23 nM, respectively (reference range < 0.01–0.5 nM). Five of seven patients in our series showed an average reduction of 11% in plasma lyso-Gb3 after at least 12 months of ERT, suggesting improvement in disease severity.

Adverse events, such as pyrexia, dyspnea, and skin rash, were reported in clinical trials of agalsidase beta and agalsidase alfa treatments for Fabry disease. However, the frequency and severity of adverse events diminish over time in most patients due to infusion rate optimization, preinfusion medication, and, possibly, increased tolerance to the exogenous protein because antibody titers often decline with time.^{13,14} Three and two of our patients had similar symptoms after receiving agalsidase beta and agalsidase alfa treatment, respectively, but the reactions were easily managed. None of the three had serious sequelae, and all three were able to continue with treatment. We were unable to measure the immunoglobulin G antibodies against these two products, but we assume that our patients' reactions occurred by the same mechanism.

This research had some limitations. As an uncontrolled retrospective study, we could not compare the results of ERT in our patients with those of any untreated control individuals. Also, assessments for biochemical and clinical response were not available at regular time intervals among these patients during treatment. Thus, partial parameters of cardiac status and renal function, and plasma lyso-Gb3 were not available at the time point of the switch from agalsidase beta to agalsidase alfa. Given this situation, the results of ERT shown in Table 2 could only represent the overall outcome of the previous agalsidase beta and the later agalsidase alfa treatments. Meanwhile, the results were reported after more than 12

months of treatment. This period was not enough to display some differences between the two enzymes, because Fabry disease is a pleomorphic and long-lasting pathology and the clinical outcome requires a long time to be evaluated. In addition, the small sample size reflected the rare nature of this genetic disorder, and the range of age at which treatment began was wide, as was the degree of disease severity. Therefore, studies in larger cohorts with a longer follow-up are warranted. However, our experience reflects the problems that clinicians are likely to encounter when treating patients with Fabry disease, because each patient presents with a different condition.

In conclusion, in our study of Taiwanese patients with Fabry disease, ERT improved or stabilized cardiac status, and stabilized renal function, while reducing the plasma lyso-Gb3 concentration. ERT was well tolerated, even among the three patients who had hypersensitivity reactions. ERT for treatment of Fabry disease has been endorsed by the National Health Insurance program in Taiwan since April 2002. Our clinical experience confirms that ERT is beneficial for Taiwanese patients with Fabry disease, just as it is in other populations. The switch of ERT from agalsidase beta to agalsidase alfa appears to be safe after 1 year of follow-up.

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