

Effects of enzyme replacement therapy for cardiac-type Fabry patients with a Chinese hotspot late-onset Fabry mutation (IVS4+919G>A)

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ABSTRACT

Objective: Current studies of newborn screening for Fabry disease in Taiwan have revealed a remarkably high prevalence of cardiac-type Fabry disease with a Chinese hotspot late-onset Fabry mutation (IVS4+919G>A).

Design: Retrospective cohort study.

Setting: Tertiary medical centre.

Participants: 21 patients with cardiac-type Fabry disease (15 men and 6 women) as well as 15 patients with classic Fabry disease (4 men and 11 women) treated with biweekly intravenous infusions of agalsidase β (1 mg/kg) or agalsidase α (0.2 mg/kg) for at least 6 months.

Outcome measures: These data were collected at the time before enzyme replacement therapy (ERT) began and followed up after ERT for at least 6 months, including patient demographics, medical history, parameter changes of cardiac status and renal functions, plasma globotriaosylsphingosine (lyso-Gb3) and Mainz Severity Score Index.

Results: After 6–39 months of ERT, plasma lyso-Gb3 was found to be reduced in 89% (17/19) and 93% (14/15) of patients with cardiac-type and classic Fabry disease, respectively, which indicated an improvement of disease severity. For patients with cardiac-type Fabry disease, echocardiography revealed the reduction or stabilisation of left ventricular mass index (LVMI), the thicknesses of intraventricular septum (IVS) and left posterior wall (LPW) in 83% (15/18), 83% (15/18) and 67% (12/18) of patients, respectively, as well as 77% (10/13), 73% (11/15) and 60% (9/15) for those with classic type. Most patients showed stable renal function after ERT. There were statistically significant improvements ($p<0.05$) between the data at baseline and those after ERT for values of plasma lyso-Gb3, LVMI, IVS, LPW and Mainz Severity Score Index. No severe clinical events were reported during the treatment.

Conclusions: ERT is beneficial and appears to be safe for Taiwanese patients with cardiac-type Fabry disease, as well as for those with the classic type.

ARTICLE SUMMARY

Article focus

- Retrospectively reviewed the clinical findings of enzyme replacement therapy (ERT) in 21 Taiwanese patients with cardiac-type Fabry disease (IVS4+919G>A), along with 15 patients with the classic type.
- Evaluation of the safety and effects on disease stability for these patients under ERT.

Key messages

- ERT improved or stabilised cardiac status, stabilised renal function, improved microalbuminuria, stabilised or improved overall severity of signs and symptoms according to Mainz Severity Score Index, while reducing plasma globotriaosylsphingosine concentration.
- ERT is beneficial and appears to be safe for Taiwanese patients with cardiac-type Fabry disease (IVS4+919G>A), as well as for those with the classic type.

Strengths and limitations of this study

- The first report to demonstrate the efficacy and safety of ERT with agalsidase β or agalsidase α in patients with cardiac-type Fabry disease and a relatively large cohort study.
- Retrospective cohort study.

INTRODUCTION

Fabry disease (MIM 301500) is an X linked inherited condition caused by the absence or reduction of α -galactosidase A (α -Gal A) activity in lysosomes, leading to a progressive accumulation of globotriaosylceramide (Gb3) and other neutral glycosphingolipids in lysosomes of all cells in the body. It is a complex, multi-systemic disorder characterised clinically by acroparaesthesias, hypohydrosis, angiokeratomas, corneal opacities, cardiomyopathy, progressive renal impairment, gastrointestinal

disturbances and cerebrovascular lesions.¹ The first symptoms of classic Fabry disease usually appear in childhood, and by middle age, some degree of irreversible damage may already have occurred. Despite being an X linked disorder, heterozygous women can be as severely affected as hemizygous men, although the range of symptoms varies widely. Life-threatening complications may develop in treated and untreated patients. The estimated incidence of classic Fabry disease is 1 in 40 000–117 000 live births in the general population.^{1–3}

During the past decade, late-onset phenotypes of Fabry disease primarily involving the heart,^{4–6} kidneys^{7–9} or cerebrovascular system¹⁰ have been reported. Patients with the cardiac variant often lack the classic symptoms of Fabry disease and present with left ventricular hypertrophy (LVH), arrhythmias or hypertrophic cardiomyopathy in the fifth to eighth decades of life. Newborn screening for Fabry disease in Taiwan revealed a surprisingly high incidence (about 1 in 1500 men) of a cardiac variant *GLA* mutation, IVS4+919G>A, in our population, and also found this mutation in a number of adult patients with idiopathic hypertrophic cardiomyopathy. As a result, dozens of Taiwanese patients with cardiac-type Fabry disease were identified in the recent years.^{11–13}

There are two forms of enzyme replacement therapy (ERT) for Fabry disease: agalsidase α (Replagal; Shire Human Genetic Therapies, Lexington, Massachusetts, USA) and agalsidase β (Fabrazyme; Genzyme, Cambridge, Massachusetts, USA). Previous studies showed that ERT was an effective treatment for neuropathic pain¹⁴ and can stabilise renal function or at least slow the decline of renal function in many patients with Fabry nephropathy^{15–22} and stabilise or improve surrogate parameters like cardiac size in those with cardiomyopathy.^{18 23–26} However, most study participants were Caucasian patients with classic Fabry disease. Information on ERT in patients with cardiac-type Fabry disease as well as in Asian patients is limited.^{27–29} In this study, we retrospectively reviewed the clinical findings of ERT in 21 Taiwanese patients with cardiac-type Fabry disease (IVS4+919G>A), along with 15 patients with the classic type. Our aim was to evaluate the safety and effects on disease stability for these patients under ERT.

PATIENTS AND METHODS

Selection of patients

Data from 21 patients with cardiac-type Fabry disease (15 men and 6 women; age range, 25–67 years) and 15 patients with classic Fabry disease (4 men and 11 women; age range, 14–79 years) treated with biweekly intravenous infusions of agalsidase β (1 mg/kg) or agalsidase α (0.2 mg/kg) for at least 6 months between December 2008 and June 2012 in Taipei Veterans General Hospital were retrospectively reviewed for this study. Of these 36 patients, 7 (patients no. 2, 3, 12, 15, 16, 18, 19) initially received agalsidase β (1 mg/kg) treatment. However, since June 2009, viral contamination of

Genzyme's production facility resulted in a worldwide shortage of agalsidase β leading to the switch to agalsidase α for these seven patients with Fabry disease in Taiwan.³⁰ All other 29 patients received only agalsidase α (0.2 mg/kg) throughout the treatment course. The patients' ages when treatment began ranged widely, from 14 to 79 years, and the duration of ERT ranged from 6 to 39 months. Written informed consent was obtained from parents for patients who were children and from patients themselves who were above 18 years of age. The study was approved by the medical ethics committee of Taipei Veterans General Hospital, Taiwan.

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.^{11 12} Data were collected retrospectively at the time before ERT began and followed up after ERT for at least 6 months, including patient demographics, such as gender, genotype, age at ERT, height and body weight and medical history. Together with 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,^{31–34} urine albumin-to-creatinine ratio (ACR), estimated glomerular filtration rate (eGFR; based on serum creatine concentration),³⁵ plasma globotriaosylsphingosine (lyso-Gb3) concentration^{36 37} and severity of signs and symptoms of Fabry disease using the Mainz Severity Score Index (MSSI)³⁸ were recorded. LVM was calculated according to the American Society of Echocardiography simplified cubed equation. LVM was indexed (LVMI) by height^{2.7} to normalise heart size to body size. LVH was defined as an LVMI higher than the upper normal limit (men, >51 g/m^{2.7}; women, >48 g/m^{2.7}).^{31–34} Microalbuminuria was defined as urinary ACR ratio ≥ 2.0 mg/mmol for men and ≥ 2.8 mg/mmol for women on at least two occasions, based on the National Kidney Foundation's Kidney Disease Outcome Quality Initiative working group definition.³⁹ Adverse events were assessed by history; physical examination, including vital signs during treatment; patient records of side effects; laboratory tests (chemistry, haematology, urinalysis); and ECG.

Data analysis and statistics

Descriptive statistics, including means, SD and percentage change over time, were calculated. Changes in plasma lyso-Gb3, eGFR, urine ACR, LVM, LVMI, IVS, LPW and MSSI before and after treatment were analysed using Student's paired t test. SPSS V.11.5 (SPSS Inc, Chicago, Illinois, USA) was used, and differences were considered to be statistically significant when the p value was <0.05.

RESULTS

Demographics

Details of the 36 patients' backgrounds and clinical characteristics are shown in [table 1](#). The age at start of ERT was 53.4 ± 14.4 years. For cardiac-type Fabry patients, the mean plasma α -Gal A activity for men and women were 1.16 and 6.24 nmol/h/mL, respectively (reference range: 7.9–16.9 nmol/h/mL). For classic Fabry patients, those were 0.01 and 4.66 nmol/h/mL, respectively. No patient underwent haemodialysis. Thirty-two patients suffered from cardiac symptoms, and three of them underwent pacemaker implantation. Among 15 classic Fabry patients, 4 men and 7 women had acroparaesthesia, 3 men had angiokeratoma and 1 woman and 4 men had hypohydrosis. Cerebrovascular disorders were present in one cardiac man, one classic man and two classic women. Dysacusis, gastrointestinal symptoms and respiratory symptoms were described in 2, 8 and 17 patients, respectively. Among 28 patients receiving slit-lamp examinations of the eye, 13 and 10 patients were found with cornea verticillata and Fabry cataract, respectively.

Cardiac status, renal function, plasma lyso-Gb3 concentration and MSSI at baseline and after ERT

[Table 2](#) shows the parameter changes of cardiac status, renal function, plasma lyso-Gb3 concentrations and MSSI of these patients at baseline and after 6–39 months of ERT. LVH was present at baseline in 13 women (13/16, 81%) and 16 men (16/21, 76%). The median ERT duration was 16 months. After ERT, plasma lyso-Gb3 was reduced in 89% (17/19) and 93% (14/15) of patients with cardiac and classic types, respectively, indicated the improvement of the disease severity. For patients with cardiac-type Fabry disease, echocardiography revealed the reduction or stabilisation of LVMI, the thicknesses of IVS and LPW in 83% (15/18), 83% (15/18) and 67% (12/18) of patients, respectively, along with 77% (10/13), 73% (11/15) and 60% (9/15) for those with the classic type. For 16 patients with microalbuminuria at baseline, 15 patients (94%) showed some degree of improvement after ERT. Among 35 patients with available data for eGFR, most showed stable renal function after ERT. There were statistically significant differences ($p < 0.05$) between the data at baseline and those after ERT for values of plasma lyso-Gb3, LVM, LVMI, IVS, LPW and MSSI. No significant differences were found for values of eGFR and urine ACR after ERT ([table 2](#)). We also subdivided these 21 cardiac and 15 classic Fabry patients into four groups according to the gender ([table 3](#)). For the values of plasma lyso-Gb3, LVM, LVMI, LPW and MSSI, the results after ERT revealed improvements compared with those of baseline. However, owing to the small sample size in each group, only some items showed statistically significant differences ($p < 0.05$) in certain groups. MSSI scores revealed that all 36 patients (range, 5–38) had mild-to-moderate Fabry disease at baseline (< 20 , mild; 20–40, moderate and > 40 , severe). After ERT, the total scores showed mild improvement or

stabilisation in all patients. All scores in general, neurological, cardiovascular and renal components revealed mild improvements or stabilisation after ERT except a slight worsening in the general score for men with the cardiac type ([table 4](#)).

In addition, we also presented the renal and cardiac data for all the men together and women together and did statistical analysis again on these data ([table 5](#), [figure 1A,B](#)). For the values of urine ACR, LVMI, IVS and LPW, the results after ERT revealed improvements compared with those of baseline. However, owing to the small sample size in each group, only some items (LVMI, IVS and LPW in women) showed statistically significant differences ($p < 0.05$).

Adverse events

Twelve patients (12/36, 33%) experienced at least one adverse event (tachycardia, dyspnoea, chest pain, urticaria, diarrhoea, fever) since the start of ERT ([table 2](#)). However, with premedication with oral antihistamines, steroids and antipyretics, they were able to tolerate the ERT. With continued treatment, including premedication, the reactions all abated. No severe clinical events were reported during the treatment.

DISCUSSION

There are numerous clinical reports describing the beneficial effects of ERT for patients with classic Fabry disease; however, there is limited literature reporting those for patients with cardiac-type Fabry disease. In order to clarify this point, we subdivided these 21 cardiac and 15 classic Fabry patients into four groups according to the gender. For the values of plasma lyso-Gb3, LVM, LVMI, LPW and MSSI, the results after ERT all revealed improvements compared with baseline, including both cardiac and classic types of different genders. However, owing to the small sample size in each group, only some items showed statistically significant differences ($p < 0.05$) in certain groups ([table 3](#)). The results which showed ERT for cardiac-type Fabry disease also had beneficial effects as well as that for classic Fabry disease.

To the best of our knowledge, this is the first report to demonstrate the efficacy and safety of ERT with agalsidase β or agalsidase α in patients with cardiac-type Fabry disease. For most patients in this study, including both cardiac and classic types, ERT reduced plasma lyso-Gb3 concentration, stabilised or improved surrogate parameters, such as LVM, LVMI, the thicknesses of IVS and LPW in those with LVH, improved microalbuminuria, stabilised renal function in those with Fabry nephropathy, and stabilised or improved the overall severity of signs and symptoms according to MSSI. Our results were consistent with those of the previous studies for classic Fabry patients.^{15–26 38 40}

Beck *et al*¹⁸ reported a 20% reduction in LVM after 12 months of agalsidase α treatment with the standard

Table 1 Baseline demographics and clinical characteristics of 36 Taiwanese patients with Fabry disease received enzyme replacement therapy (ERT) with agalsidase β (1 mg/kg/biweekly) or agalsidase α (0.2 mg/kg/biweekly) for 6–39 months

No.	Type	Age at ERT (year)	Gender	Genotype	Plasma α -Gal A activity (nmol/h/mL)*	Haemodialysis	Cardiac symptoms	Pacemaker	Acroparaesthesia	Angiokeratoma	Hypohidrosis	Cerebrovascular disorders	Dysacusis	Gastrointestinal symptoms	Respiratory symptoms	Cornea verticillata	Fabry cataract
1	Cardiac	25	M	IVS4+919G>A	0.93	-	-	-	-	-	-	-	-	-	-	-	-
2	Cardiac	43	M	IVS4+919G>A	0.65	-	+	-	-	-	-	-	-	-	+	NA	NA
3	Cardiac	53	M	IVS4+919G>A	0.88	-	+	-	-	-	-	+	-	-	+	NA	NA
4	Cardiac	54	M	IVS4+919G>A	1.39	-	+	-	-	-	-	-	-	+	+	-	-
5	Cardiac	55	M	IVS4+919G>A	1.3	-	+	-	-	-	-	-	-	-	+	-	-
6	Cardiac	55	M	IVS4+919G>A	1.32	-	-	-	-	-	-	-	-	+	+	+	-
7	Cardiac	57	M	IVS4+919G>A	1.13	-	+	-	-	-	-	-	-	-	+	-	-
8	Cardiac	59	M	IVS4+919G>A	1.02	-	+	+	-	-	-	-	-	-	-	-	-
9	Cardiac	60	M	IVS4+919G>A	0.79	-	+	-	-	-	-	-	-	-	-	-	+
10	Cardiac	62	M	IVS4+919G>A	1.48	-	+	-	-	-	-	-	-	-	-	-	+
11	Cardiac	63	M	IVS4+919G>A	1.47	-	+	-	-	-	-	-	-	-	-	-	+
12	Cardiac	63	M	IVS4+919G>A	1.2	-	+	-	-	-	-	-	-	+	-	NA	NA
13	Cardiac	64	M	IVS4+919G>A	1.15	-	+	+	-	-	-	-	-	-	+	-	-
14	Cardiac	65	M	IVS4+919G>A	1.71	-	+	-	-	-	-	-	-	-	+	-	-
15	Cardiac	67	M	IVS4+919G>A	0.95	-	+	-	-	-	-	-	-	-	-	NA	NA
16	Classic	14	M	W204X	0	-	+	-	+	+	+	-	-	-	-	NA	NA
17	Classic	23	M	E398DfsX6	0	-	+	-	+	-	+	+	-	-	+	+	-
18	Classic	33	M	E398DfsX6	0.027	-	+	-	+	+	+	-	+	-	-	+	-
19	Classic	49	M	E398DfsX6	0.02	-	+	-	+	+	+	-	+	+	-	+	+
20	Cardiac	44	F	IVS4+919G/A	7.67	-	+	-	-	-	-	-	-	-	-	-	-
21	Cardiac	53	F	IVS4+919G/A	4.4	-	+	-	-	-	-	-	-	-	-	-	-
22	Cardiac	58	F	IVS4+919G/A	4.03	-	+	-	-	-	-	-	-	-	+	-	+
23	Cardiac	59	F	IVS4+919G/A	5.17	-	+	-	-	-	-	-	-	-	-	-	-
24	Cardiac	63	F	IVS4+919G/A	9.63	-	+	-	-	-	-	-	-	-	+	-	+
25	Cardiac	67	F	IVS4+919G/A	6.51	-	+	-	-	-	-	-	-	-	+	+	-
26	Classic	33	F	G132R	2.4	-	-	-	-	-	-	-	-	-	-	+	+
27	Classic	34	F	S345X	3.34	-	-	-	+	-	-	-	-	-	-	+	-
28	Classic	48	F	W204X	5.59	-	+	-	+	-	-	+	-	+	+	+	+
29	Classic	53	F	W204X	9.19	-	+	-	+	-	-	-	-	-	-	NA	NA
30	Classic	54	F	W204X	2.54	-	+	-	-	-	-	-	-	-	+	NA	NA
31	Classic	56	F	E398DfsX6	7.73	-	+	-	+	-	-	-	-	-	-	+	-
32	Classic	58	F	G132R	1.26	-	+	-	-	-	-	-	-	-	+	+	+
33	Classic	58	F	W204X	5.04	-	+	+	+	-	+	-	-	+	+	+	-
34	Classic	66	F	E398DfsX6	6.91	-	+	-	+	-	-	-	-	+	-	+	+
35	Classic	76	F	E398DfsX6	3.91	-	+	-	+	-	-	-	-	-	+	+	-
36	Classic	79	F	W204X	3.31	-	+	-	-	-	-	+	-	+	+	NA	NA

*Reference range: 7.9–16.9.

 α -Gal A, α -galactosidase A; NA, not available.

Table 2 Parameter changes of cardiac status and renal function, plasma lyso-Gb3 and Mainz Severity Score Index (MSSI) at baseline and after 6–39 months of enzyme replacement therapy (ERT) for 36 Taiwanese patients with Fabry disease

No.	Type	Age at ERT (year)	Gender	ERT duration (months)	Plasma lyso-Gb3 (nM)*		eGFR (mL/min/1.73 m ²) (CKD-EPI)		Urine ACR (mg/mmol)		LVM (g)		LVMI (g/m ^{2.7})		IVS (mm)		LPW (mm)		MSSI (max score=76)		Adverse effects
					Baseline	After ERT	Baseline	After ERT	Baseline	After ERT	Baseline	After ERT	Baseline	After ERT	Baseline	After ERT	Baseline	After ERT	Baseline	After ERT	
1	Cardiac	25	M	14	4.1	1.8	73.3	101.1	0.46	0.49	221.3	NA	48.8	NA	8.7	NA	10	NA	9	9	N
2	Cardiac	43	M	39	4.44	3.36	109.6	115.1	0.35	0.48	392.1	270	92.1	63.4	16.7	13.7	12	12.2	21	17	N
3	Cardiac	53	M	39	5.19	4.18	99.7	92.5	0.85	0.30	298.5	198	76	50.4	14.6	12.8	15.2	11.7	24	20	N
4	Cardiac	54	M	10	6.13	4.71	93.9	93.3	1.70	0.28	303.0	304	74.5	74.8	14.7	12	14.7	12	16	16	N
5	Cardiac	55	M	17	8.22	8	72.2	80.1	13.31	0.66	272.1	342.8	66.5	83.8	15.2	14	12.8	12	27	27	N
6	Cardiac	55	M	19	5.44	3.67	71.3	69.9	2.43	0.27	188.8	148	50.5	39.6	12.7	12.5	7.3	9.5	24	24	N
7	Cardiac	57	M	13	6.77	NA	94.9	97.8	3.94	3.28	148.2	138.7	43.8	41.0	15.4	9.9	6.4	7	20	21	N
8	Cardiac	59	M	12	13.51	9.86	67.9	63.2	0.30	0.43	185.3	244.3	51.2	67.5	13.3	13.3	9	10.7	25	25	N
9	Cardiac	60	M	12	5.06	4.38	86.7	96	1.97	0.49	204.1	130	50.6	32.2	10.5	9	9.3	9.5	16	14	N
10	Cardiac	62	M	15	11.52	3.79	92.5	95.9	0.81	1.07	276.9	403.9	75.9	110.7	18.6	12	10.1	10	20	20	N
11	Cardiac	63	M	18	14.54	8.19	94.8	90	1.07	0.25	340.8	302.1	88.2	78.2	12	15.3	14	13.3	17	17	N
12	Cardiac	63	M	35	3.49	4.17	93.4	89.7	5.65	0.47	383.6	336	88.7	77.7	19.7	17.7	12.6	8.2	25	21	N
13	Cardiac	64	M	6	9.77	8.66	66.8	82.8	0.67	0.51	544.8	439	136.4	109.9	30	22.3	28.6	16.6	31	31	N
14	Cardiac	65	M	8	8.08	4.49	76.1	83.5	0.25	3.67	179.1	NA	55.2	NA	16	NA	8	NA	22	22	N
15	Cardiac	67	M	32	7.8	10.8	100.9	98.4	1.07	0.15	195.6	191	52.3	51.1	15.4	20.2	8	10.7	23	24	Y
16	Classic	14	M	27	178.4	75.64	133.8	141.2	0.99	0.74	225.2	NA	57.3	NA	10.1	9.9	11.7	9.9	17	17	Y
17	Classic	23	M	9	203.68	74.51	108	119.7	1.14	0.68	323.3	242	57.1	42.8	12	11.3	11.3	10.7	19	17	N
18	Classic	33	M	16	54.95	45.13	85.7	83.1	171.68	NA	282.2	181.9	68.5	44.2	13	9.5	11	10.6	27	25	Y
19	Classic	49	M	16	71.48	58.8	31.5	25.3	111.84	11.53	151.6	227.1	30.5	45.7	10.5	13.3	7	7.3	32	34	Y
20	Cardiac	44	F	8	2.23	1.34	106.7	112.7	0.77	0.89	204.6	104	57.5	29.2	11	5	9.5	8	17	15	N
21	Cardiac	53	F	15	2.59	1.29	103.6	NA	0.66	0.74	143.0	NA	45.4	NA	9	NA	6.4	NA	15	15	N
22	Cardiac	58	F	24	2.60	1.20	26	12.1	286.24	117.22	186.5	114	59.2	36.2	12.5	9.9	13	8.8	25	19	Y
23	Cardiac	59	F	17	3.49	3.11	77.2	94.3	13.11	4.09	169.0	133.8	53.4	42.3	13.3	11	8	6.5	21	15	N
24	Cardiac	63	F	9	4.24	1.47	96.2	96.6	6.14	0.67	179.0	94.4	52.1	27.5	11.5	7.6	11.5	7.6	17	11	N
25	Cardiac	67	F	12	3.67	NA	91.1	99.1	0.76	0.33	194.7	193.8	64	63.7	12	12.7	12.7	11.8	18	18	N
26	Classic	33	F	16	11.74	7.08	114.7	117.4	0.73	0.52	124.5	131.7	35.6	37.7	9.1	8	9.1	6	5	4	Y
27	Classic	34	F	25	24.8	12.57	107.9	120.2	355.33	105.94	122.2	155.7	38.1	48.5	7	8.6	8.2	9.5	18	20	Y
28	Classic	48	F	17	8.97	6.85	108.2	106	2.03	3.43	168.7	155.7	55.9	51.6	15.7	9.3	8.8	8.8	29	29	Y
29	Classic	53	F	6	4.66	4.56	97.2	100.1	40.08	55.31	195.6	158	62.6	50.6	12	9.5	10	10.8	21	21	N
30	Classic	54	F	26	17.26	11.70	105.6	104.2	4.10	1.81	216.8	182	72.5	60.9	15	10.1	14	10.8	27	15	N
31	Classic	56	F	12	11.41	12.16	109	84.1	0.69	1.86	211.8	233	51.1	56.2	9.3	16.3	9.9	11.5	22	26	Y
32	Classic	58	F	16	20.12	17.17	77.1	82.3	3.79	2.81	123.9	101.2	58.7	35.1	10.5	9.5	8.6	8	25	23	Y
33	Classic	58	F	20	31.77	21.00	86.7	78.1	5.53	0.31	255.7	250.4	82.6	80.8	16.4	14.3	11.1	11.3	38	38	Y
34	Classic	66	F	11	18.38	14.03	77	74.3	13.57	2.03	468.3	431.1	146.5	134.8	24.5	22.5	16.3	14.4	35	35	N
35	Classic	76	F	8	28.12	23.32	54.7	60.9	4.19	0.58	352.4	272	120.1	92.7	18	18.3	18	14.5	34	34	Y
36	Classic	79	F	12	11.55	10.36	72.5	73.2	36.34	1.41	NA	NA	NA	NA	21	16	9	11	34	34	N
	Mean	53.4		17	24.1	14.2	87.9	89.5	30.4	9.3	247.2	219.7	68.2	60	14.3	12.6	11.5	10.3	22.7	21.5	
	SD	14.4		8.8	44.9	19.6	22	24.6	79.4	27.2	102.9	97.1	26.9	26.1	4.6	4.2	4.1	2.4	7.1	7.7	
	p value†				0.043		NS		NS		0.015		0.008		0.006		0.024		0.019		
	N				34		35		35		31		31		33		33		36		

*Reference range: <0.01–0.5.

†Paired t test, significance at p<0.05.

ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; IVS, intraventricular septum; LPW, left posterior wall; LVM, left ventricular mass; LVMI, left-ventricular mass index; lyso-Gb3, globotriaosylsphingosine; NA, not available; NS, not significant.

Table 3 Parameter changes of cardiac status and renal function, plasma lyso-Gb3 and Mainz Severity Score Index (MSSI) at baseline and after enzyme replacement therapy (ERT) for 36 Taiwanese patients with Fabry disease subdivided into four groups according to the gender and the type (cardiac or classic)

Gender	Type	Gender	Plasma lyso-Gb3 (nM)		eGFR (mL/min/1.73 m ²) (CKD-EPI)		Urine ACR (mg/mmol)		LVM (g)		LVMI (g/m ^{2.7})		IVS (mm)		LPW (mm)		MSSI (max score=76)	
			Baseline	After	Baseline	After	Baseline	After	Baseline	After	Baseline	After	Baseline	After	Baseline	After	Baseline	After
Male	Cardiac	Mean	7.66	5.72	86.3	90	2.3	0.9	287.2	265.2	72.8	67.7	16.1	14.2	12.3	11	21.3	20.5
		SD	3.53	2.79	13.7	12.8	3.4	1.1	109.9	100.8	25.3	25	4.9	3.8	5.7	2.4	5.4	5.5
		n	14		15		15		13		13		13		13		15	
		p*	0.020		NS		NS		NS		NS		NS		NS		NS	
	Classic	Mean	127.13	63.52	89.8	92.3	37.99	4.32	252.4	217	52.1	44.2	11.4	11	10.3	9.6	23.8	23.3
		SD	74.82	14.47	43.5	50.7	63.96	6.25	89.7	31.3	19.5	1.5	1.3	1.7	2.2	1.6	7	8.1
n		4		4		3		3		3		4		4		4		
	p*	NS		NS		NS		NS		NS		NS		NS		NS		
Female	Cardiac	Mean	3.03	1.68	79.4	83	51.28	20.66	186.8	128	57.2	39.8	12.1	9.2	10.9	8.5	18.8	15.5
		SD	0.82	0.8	31.7	40.3	115.21	47.33	13.8	39.6	4.8	14.6	0.9	3	2.1	2	3.6	2.8
		n	5		5		6		5		5		5		5		6	
		p*	0.028		NS		NS		0.031		0.028		NS		0.025		0.042	
	Classic	Mean	17.16	12.8	91.9	91	42.4	16	224	207.1	72.4	64.9	14.4	12.9	11.2	10.6	26.2	25.4
		SD	8.48	5.85	19.4	19.6	104.73	33.91	111.3	95.5	35.6	30.3	5.4	4.8	3.4	2.5	9.5	10.2
n		11		11		11		10		10		11		11		11		
	p*	0.005		NS		NS		NS		NS		NS		NS		NS		

*Significance at p<0.05.

ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio; LVM, left ventricular mass; LVMI, left ventricular mass index; IVS, intraventricular septum; LPW, left posterior wall; MSSI, Mainz Severity Score Index; NS, not significant.

Table 4 Mainz Severity Scores Index (MSSI) at baseline and after 6–39 months of enzyme replacement therapy (ERT) for 36 Taiwanese patients with Fabry disease subdivided into four groups according to the gender and the type (cardiac or classic)

Gender	Max score	n	ERT	General 18	Neuro 20	Cardio 20	Renal 18	Total 76
Male	Cardiac	15	Baseline	2.8 (1.3)	1.6 (1.1)	13.7 (3.1)	3.2 (3.8)	21.3 (5.4)
			Follow-up	2.9 (1.4)	1.6 (1.1)	13.1 (3.1)	2.9 (3.8)	20.5 (5.5)
	Classic	4	Baseline	3.5 (1.7)	6.8 (2.8)	10.5 (1)	3 (3.8)	23.8 (7)
			Follow-up	3.5 (1.7)	6.8 (2.8)	10 (1.2)	3 (3.8)	23.3 (8.1)
Female	Cardiac	6	Baseline	2.8 (0.8)	1.7 (0.5)	11 (1.1)	3.3 (3.9)	18.8 (3.6)
			Follow-up	2.8 (0.8)	1.7 (0.5)	9.7 (1.5)	1.3 (2.1)	15.5 (2.8)
	Classic	11	Baseline	4 (2.2)	4 (2.4)	13.1 (4.2)	5.1 (3.6)	26.2 (9.5)
			Follow-up	4 (2.2)	4 (2.4)	12.6 (4.4)	4.7 (3.5)	25.4 (10.2)

Data are mean (SD).
Cardio, cardiovascular; Max, maximum possible score; Neuro, neurological.

dose (0.2 mg/kg/biweekly). Our results showed similar improvements. For cardiac-type Fabry patients, there was an average decrease of 12% (68.5 to 60 g/m^{2.7}) in LVMI for 18 patients after ERT, as well as 14% (15–12.8 mm) and 13% (11.9–10.3 mm) decreases in the thicknesses of IVS and LPW, respectively, along with 11% (67.7–60.1 g/m^{2.7}), 9% (13.6–12.4 mm) and 5% (10.9–10.3 mm) decreases for those with the classic type. Schifmann *et al*¹⁶ described stabilisation in patients with preserved renal function, but gradual worsening in advanced kidney disease following 4–4.5 years of agalsidase α therapy. In our study, most patients revealed stable renal function after ERT. Microalbuminuria occurs when the kidney leaks small amounts of albumin into the urine, and it is a marker of vascular endothelial dysfunction. There is a handful of literature reporting the change of urine ACR after ERT. In our study, 15 of the 16 patients showed an improvement of microalbuminuria after treatment, with the average urine ACR decreased from 56.6 to 19.27 mg/mmol (–66%). These results show that ERT has a potentially positive effect for kidney disease of these patients. Plasma lyso-Gb3 elevation is a hallmark of Fabry disease,

and is associated with clinical manifestations.^{36–37} The average baseline plasma lyso-Gb3 concentration values of 14 male cardiac-type patients and four male classic patients were 7.66 and 127.13 nM, respectively (reference range <0.01–0.5 nM). Similar values were also seen in female patients. Plasma lyso-Gb3 is also a reliable marker for monitoring the therapeutic outcomes of ERT.^{41–43} In our study, plasma lyso-Gb3 showed reductions of 28% (6.4–4.7 nM) and 43% (46.5–26.3 nM) for patients with cardiac and classic types, respectively, suggesting the improvement in disease severity.

MSSI is a sensitive and useful tool for objectively assessing the severity of Fabry disease and for monitoring the effects of ERT. In our study, MSSI scores revealed the severity of signs and symptoms of Fabry disease remained stable or showed mild improvement after ERT in both cardiac and classic types with average scores of 20.6–19.1, and 25.5–24.8, respectively (maximum score=76). Given the progressive nature of Fabry disease, stabilisation can be seen as a positive outcome following treatment. Our results were in accordance with those of previous studies.^{38–40}

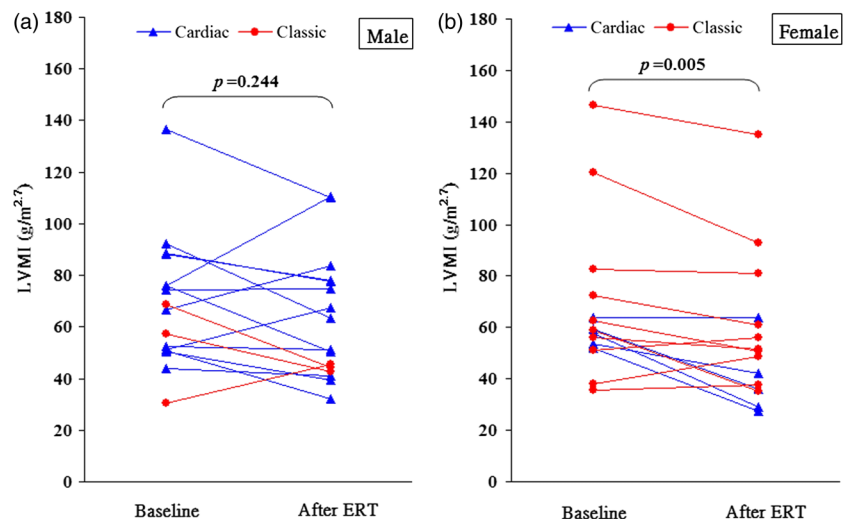
Table 5 Parameter changes of cardiac status and renal function at baseline and after enzyme replacement therapy (ERT) for 36 Taiwanese subdivided into two groups according to the gender

Gender		eGFR (mL/min/1.73 m ²) (CKD-EPI)		Urine ACR (mg/mmol)		LVMI (g/m ^{2.7})		IVS (mm)		LPW (mm)	
		Baseline	After ERT	Baseline	After ERT	Baseline	After ERT	Baseline	After ERT	Baseline	After ERT
Male	Mean	87.63	90.96	8.0	1.5	68.9	63.3	15.0	13.5	11.8	10.7
	SD	21.2	23.1	25.3	2.6	25.2	24.3	4.7	3.7	5.1	2.3
	N	20		19		16		17		17	
	p Value*	NS		NS		NS		NS		NS	
Female	Mean	88.0	88.5	45.5	17.6	67.3	56.5	13.7	11.8	11.1	10.0
	SD	23.6	26.5	105.0	37.7	29.6	28.3	4.6	4.6	3.0	2.5
	N	16		17		15		16		16	
	p Value*	NS		NS		0.005		0.038		0.039	

*Significance at p<0.05.

ACR, albumin-to-creatinine ratio; CKD-EPI, chronic kidney disease epidemiology; eGFR, estimated glomerular filtration rate; IVS, intraventricular septum; LPW, left posterior wall; LVMI, left-ventricular mass index; NS, not significant.

Figure 1 Effects of enzyme replacement therapy (ERT) on left ventricular mass index (LVMI) in male (A) and female (B) patients with Fabry disease.



Adverse events, such as fever, dyspnoea and skin rash, were reported in clinical trials of agalsidase β and agalsidase α treatments for Fabry disease. However, the frequency and severity of adverse events diminish over time in most patients due to infusion rate optimisation, preinfusion medication and, possibly, increased tolerance to the exogenous protein since antibody titres often decline with time.^{15 16} Twelve of our 36 patients (33%) had similar symptoms after receiving ERT, but the reactions were easily managed. None of them had serious sequelae, and they were all able to continue with treatment. We were unable to measure IgG antibodies against these two products, but we assume that our patients' reactions occurred by the same mechanism.

Limitations

As an uncontrolled retrospective study, we could not compare the results of ERT in our patients with any untreated control patients. For seven patients who underwent the switch of ERT from agalsidase β (1 mg/kg) to agalsidase α (0.2 mg/kg), assessments for biochemical and clinical response were not available at regular time intervals during the treatment. Thus, partial parameters of cardiac status and renal function, and plasma lyso-Gb3 were not available for certain patients at the time point of switch. The results of ERT for these seven patients could only show the overall effects of ERT with agalsidase β (1 mg/kg) and agalsidase α (0.2 mg/kg). Meanwhile, the results were reported after 6–39 months of treatment. This period could not be enough to display the effects of ERT since 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 of each type reflected the rare nature of this genetic disorder, and the range of age at which treatment began was quite 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 problem that clinicians are likely to encounter when treating patients with Fabry disease, since each patient presents with a quite different condition.

CONCLUSION

In our study, for patients with cardiac-type Fabry disease, along with those with the classic type, ERT improved or stabilised cardiac status, stabilised renal function, improved microalbuminuria and stabilised or improved overall severity of signs and symptoms according to MSSSI, while reducing plasma lyso-Gb3 concentration. ERT was well tolerated, even among the patients who had hypersensitivity reactions. ERT for treatment of Fabry disease has been endorsed by the National Health Insurance programme in Taiwan since April 2002. Our clinical experience confirms that ERT is beneficial and safe for patients with a Chinese hotspot late-onset Fabry mutation (IVS4+919G>A) as well as for those with the classic type. Whether the stabilisation or improvement in disease severity and quality of life is durable remains to be seen on further follow-up.

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Contributors H-YL and H-CL performed acquisition, statistical analysis and interpretation of data, and drafting of the manuscript. D-MN and Y-HH participated in the design of the study, interpretation of the data and helped to draft the manuscript. H-CL, T-RH, C-KH and C-CC performed biochemical analyses and revised the manuscript. C-IS, S-TL, C-FL, L-HL, P-CL, C-YL and S-PL were responsible for patient screening. All authors contributed in interpreting data, revising drafts of the manuscript and in the approval of the final manuscript.

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