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Safety and effectiveness of enzyme replacement therapy with agalsidase alfa in patients with Fabry disease: Post-marketing surveillance in Japan

Hiroaki Sasa*, Munehiko Nagao, Koichi Kino

Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan

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ABSTRACT

Fabry disease is a rare X-linked inherited multisystem disorder resulting from deficiency of the lysosomal enzyme alpha-galactosidase A. Currently, specific therapies, including enzyme replacement therapies, are available for Fabry disease, but clinical trials provide limited information on long-term safety and effectiveness.

Agalsidase alfa was approved in Japan in 2006. The post-marketing surveillance study of all patients receiving agalsidase alfa to evaluate its long-term safety and effectiveness as a mandatory condition for its approval had been conducted for 8 years (from February 2007 to March 2015).

A total of 493 patients were included in this analysis of safety and effectiveness. The overall mean follow-up period was 3.5 years (range, 0.0–7.9 years). The percentage of patients with adverse drug reactions was 24.5% (121/493) and 12.6% had infusion-related reactions (62/493). In the 256 patients without prior enzyme replacement therapy whose IgG antibody data were available, 17 were IgG antibody positive (6.6%). However, the chronological correlation between seroconversion and the incidence of infusion-related reactions was not clear.

The mean brief pain inventory score of the worst pain decreased in patients with moderate and severe pain at baseline. Plasma Gb_3 and urine sediment Gb_3 in males with classical Fabry disease without prior enzyme replacement therapy significantly decreased. The mean yearly changes in eGFR (mL/min/1.73 m^2) ranged from −2.88 to +1.00 in males with classical Fabry disease, from −2.04 to −0.95 in males with non-typical variant and from −2.64 to −1.02 in females. The lower eGFR or the more proteinuria at baseline, the faster the decrease in eGFR of the patients was observed. There was no substantial difference in cardiac parameters (left ventricular mass index, E/A wave ratio, ejection fraction, and QRS duration).

In conclusion, agalsidase alfa, 0.2 mg/kg every other week, was well tolerated and controlled the progression of symptoms (especially renal and cardiac) of Fabry disease in adults. Enzyme replacement therapy should be started in Japanese patients before cardiac and/or renal symptoms of Fabry disease develop.

1. Introduction

Fabry disease (OMIM 301500) is a rare X-linked inherited multisystem disorder resulting from deficiency of lysosomal enzyme alpha-galactosidase A. This leads to the progressive accumulation of glycosphingolipids, especially globotriaosylceramide (Gb_3), in the cells of various tissues and organs. Male patients with absent or nearly no alpha-galactosidase A activity (classic phenotype) have various clinical manifestations, such as acroparesthesia, hypohidrosis, and angiokeratoma, during childhood or adolescence and as they age develop serious manifestations such as renal failure, cardiac dysfunction, and stroke. Male patients with residual alpha-galactosidase A activity (non-typical variant) do not have the early clinical manifestations of classic phenotype but may develop renal failure, cardiac dysfunction and/or stroke with increasing age. Clinical manifestations in heterozygous females range from asymptomatic to many symptoms as severe as that in male patients because of random X-chromosomal inactivation [1,2].

Enzyme replacement therapy (ERT) is a specific treatment for Fabry disease. Although ERT can stabilize the progression of the disease, concomitant treatments such as analgesics, diuretics, and implantable cardiac devices may also be required. Infusion-related reactions (IRRs) and generation of anti-agalsidase antibodies have been reported with ERT for Fabry disease [3].

In 2006, agalsidase alfa (Replagal, Shire) was approved in Japan. Its

Abbreviations: BPI, Brief pain inventory; EQ-5D, European Quality of Life-5 Dimensions; ERT, Enzyme replacement therapy; ADR, Adverse drug reaction; IRR, Infusion-related reaction; eGFR, Estimated glomerular filtration rate; Gb_3, Globotriaosylceramide (ceramide trihexoside); LVMI, Left ventricular mass index

* Corresponding author at: Sumitomo Dainippon Pharma Co., Ltd., 6-8 Doshomachi, 2-Chome, Chuo-ku, Osaka 541-0045, Japan.
E-mail address: hiroaki-sasa@ds-pharma.co.jp (H. Sasa).

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marketing authorization holder, Sumitomo Dainippon Pharma Co., Ltd., conducted the post-marketing survey study for all patients receiving Replagal to evaluate its long-term safety and effectiveness as a mandatory condition for its approval.

In Japan, clinical studies generally provide only limited data for large number of patients due to Fabry disease being rare, and patients being treated at various hospitals. This survey was conducted from February 2007 to March 2015 for the purpose of proving the long-term safety and effectiveness for all agalsidase alfa-treated patients in Japan.

2. Materials and methods

2.1. Study design

As a mandatory condition for approval, all patients treated with Replagal in Japan were enrolled in this non-interventional observational post-marketing surveillance (PMS). Patients were diagnosed with Fabry disease by physicians according to deficient alpha-galactosidase A activity or the identification of alpha-galactosidase A gene mutation.

This survey protocol was designed based on the clinical trial protocol of Replagal in Japan and reviewed as necessary by the Institutional Review Board at each medical facility. The registration and survey period was from February 2007 (the launch date of Replagal in Japan) to March 2015. Agalsidase alfa was administered at a dose of 0.2 mg/kg every 2 weeks by intravenous infusion over 40 min as by authorized dose regimen.

This study was conducted in compliance with the Japanese regulatory requirements of the Good Post-Marketing Study Practice with physician agreement on data publication. Since this was a mandatory surveillance study, informed consent from individual patients was not necessary as per Japanese health authority regulations.

2.2. Data collection

Each physician entered each patient's data into a case report form using patient medical records. Case report forms were collected at baseline and at the following intervals after the first Replagal dose: 6 months, 1, 2, 3, 4, 5, 6, 7, and 8 years. Follow-up continued until end of study, death or the withdrawal of Replagal for any reason. Data included patient demographics, dosing conditions of agalsidase alfa, concomitant medications, adverse drug reactions (ADRs), clinical laboratory tests, Brief Pain Inventory (BPI) scores, European Quality of Life-5 Dimensions (EQ-5D) scores, Gb_3 in plasma and urine sediment, serum anti-agalsidase alfa antibodies, and the following organ examinations:

- Cardiac: electrocardiography, echocardiography, cardiac magnetic resonance imaging, and cardiac catheterization with coronary and left ventricular angiography
- Renal: inulin clearance
- Cerebrovascular: magnetic resonance imaging of the brain
- Auditory: pure-tone air and bone conduction audiometry and tympanometry

2.3. Measurement and assessment

2.3.1. BPI

The BPI contains a series of questions related to pain and its interference with life. Each question is answered by circling a number between 0 and 10 [4].

2.3.2. EQ-5D

The European Quality of Life questionnaire (Euro-QOL) covers five dimensions: mobility, pain/discomfort, self-care, anxiety/depression, and usual activities. Each dimension comprises three levels (no problems, some/moderate problems, extreme problems) [5]. In this study, the modified EQ-5D for Japanese was used [6].

2.3.3. Gb_3 in plasma and urine sediment

Plasma samples (4 mL of whole blood) and 24-h urine collection samples were obtained for plasma Gb_3 and urine sediment Gb_3, respectively. Quantitative analysis of Gb_3 was performed by HPLC. The results of urine sediment Gb_3 were expressed as nmol/g of urinary creatinine.

2.3.4. Serum anti-agalsidase alfa antibodies

Serum samples (4 mL of whole blood) were obtained for anti-agalsidase alfa IgG and IgE antibodies. Analysis of anti-agalsidase alfa antibodies was performed using enzyme-linked immunosorbent assay, colorimetric reaction, and spectrophotometry. The titer of the sample at each point was determined at the same time as that at baseline. The results of IgG and IgE antibody testing were expressed as positive when the absorbance of each point sample was two times more than the baseline sample.

2.3.5. Other examinations

Other examinations in adults (age 19 and older) were determined by each medical facility on a regular basis. The value of the estimated glomerular filtration rate (eGFR) in adults was calculated from serum creatinine data using the modified IDMS-MDRD study equation [7]. The value of the left ventricular mass index (LVMI) in adults was calculated from echocardiography data and height using the Devereux formula [8,9]. The value of the E/A wave ratio in adults was calculated from echocardiography data. The value of the ejection fraction in adults was calculated from echocardiography data using the Teichholz formula [10]. Mortality and morbidity were evaluated from fatality and IRR data using Kaplan-Meier analyses.

2.3.6. Limitations

Cardiac catheterization with coronary and left ventricular angiography, inulin clearance, magnetic resonance imaging of the brain, and auditory functions could not be assessed because available data were very limited.

2.4. Statistical analysis

The safety analysis population included all patients from whom a case report form was collected. The ADRs for which a causal relationship to Replagal could not be ruled out were recorded during agalsidase alfa treatment, and each physician judged whether there were IRRs. Each ADR was summarized by preferred term (MedDRA/J version 19.0).

The effectiveness analysis population included all patients from whom a case report form was collected, with baseline and any later dosing point data for any one of the parameters. In this analysis, the parameters, excluding BPI, EQ-5D, Gb_3, and antibodies were not assessed in children (< 19 years old). Since Gb_3 and antibody data were influenced by whether the patient had received ERT before entry, for this analysis, the patients were divided into separate groups based on the presence and absence of prior ERT.

Paired *t*-tests were used for statistical analyses at a significance level of $p < 0{\cdot}05$. The data analysis was conducted using SAS (version 9.4).

3. Results

3.1. Demographics and characteristics

All 495 patients treated with Replagal from February 2007 to March 2015 in Japan were registered in this study (363 medical facilities). A total of 493 patients were included in this analysis of safety and effectiveness because two patients' case report forms could not be collected.

Table 1
Demographics and patient characteristics.

Parameter	Total		Males (Classic phenotype)		Males (Non-typical variant)		Females	
Total number of patients	493	(100)	238	(48.3)	56	(11.4)	198	(40.2)
Age category at enrollment (years)								
< 10	4	(0.8)	2	(0.8)	0	(0.0)	2	(1.0)
10– < 20	60	(12.2)	45	(18.9)	1	(1.8)	14	(7.1)
20– < 30	55	(11.2)	39	(16.4)	2	(3.6)	13	(6.6)
30– < 40	91	(18.5)	64	(26.9)	9	(16.1)	18	(9.1)
40– < 50	101	(20.5)	52	(21.8)	12	(21.4)	37	(18.7)
50– < 60	100	(20.3)	24	(10.1)	15	(26.8)	61	(30.8)
60– < 70	57	(11.6)	9	(3.8)	10	(17.9)	38	(19.2)
70-	25	(5.1)	3	(1.3)	7	(12.5)	15	(7.6)
Age category at Fabry diagnosis (years)								
< 10	17	(3.4)	14	(5.9)	1	(1.8)	2	(1.0)
10– < 20	89	(18.1)	68	(28.6)	2	(3.6)	19	(9.6)
20– < 30	67	(13.6)	47	(19.7)	4	(7.1)	15	(7.6)
30– < 40	86	(17.4)	51	(21.4)	10	(17.9)	25	(12.6)
40– < 50	83	(16.8)	26	(10.9)	10	(17.9)	47	(23.7)
50– < 60	84	(17.0)	19	(8.0)	13	(23.2)	52	(26.3)
60– < 70	43	(8.7)	5	(2.1)	11	(19.6)	27	(13.6)
70-	15	(3.0)	2	(0.8)	5	(8.9)	8	(4.0)
Unknown	9	(1.8)	6	(2.5)	0	(0.0)	3	(1.5)
Time from diagnosis to ERT (years)								
< 5	403	(81.7)	185	(77.7)	47	(83.9)	171	(86.4)
5– < 10	27	(5.5)	10	(4.2)	4	(7.1)	13	(6.6)
10– < 20	35	(7.1)	25	(10.5)	4	(7.1)	6	(3.0)
20– < 30	12	(2.4)	10	(4.2)	1	(1.8)	1	(0.5)
30– < 40	4	(0.8)	1	(0.4)	0	(0.0)	3	(1.5)
Unknown	12	(2.4)	7	(2.9)	0	(0.0)	4	(2.0)
Agalsidase alfa treatment duration (years)								
−0.5	35	(7.1)	15	(6.3)	3	(5.4)	17	(8.6)
> 0.5–1	31	(6.3)	8	(3.4)	8	(14.3)	15	(7.6)
> 1–2	48	(9.7)	24	(10.1)	6	(10.7)	18	(9.1)
> 2–3	69	(14.0)	27	(11.3)	9	(16.1)	32	(16.2)
> 3–4	86	(17.4)	41	(17.2)	10	(17.9)	35	(17.7)
> 4–5	132	(26.8)	68	(28.6)	16	(28.6)	48	(24.2)
> 5–6	55	(11.2)	31	(13.0)	2	(3.6)	22	(11.1)
> 6–7	20	(4.1)	10	(4.2)	2	(3.6)	8	(4.0)
> 7–8	17	(3.4)	14	(5.9)	0	(0.0)	3	(1.5)
Prior ERT								
Without	278	(56.4)	112	(47.1)	38	(67.9)	128	(64.6)
With	198	(40.2)	118	(49.6)	17	(30.4)	62	(31.3)
Unknown	17	(3.4)	8	(3.4)	1	(1.8)	8	(4.0)
Patients with conventional treatment at baseline								
Dialysis	57	(11.6)	39	(16.4)	11	(19.6)	7	(3.5)
Renal transplantation	6	(1.2)	3	(1.3)	3	(5.4)	0	(0.0)
Pacemaker	32	(6.5)	12	(5.0)	9	(16.1)	11	(5.6)
n (%)								

The patient demographics and characteristics are shown in Table 1. The clinical phenotypes of Fabry disease were based on the physicians' judgment in the males. The clinical phenotype of one male patient was unknown. Treatment of Fabry disease was initiated within 5 years after diagnosis in 81.7% (403 patients) of patients and > 30 years after diagnosis in 0.8% (4 patients). A total of 198 patients were treated with agalsidase alfa (for example, in clinical trials of Replagal in Japan) or agalsidase beta before participating in this survey. The percentages of patients who started dialysis and received renal transplantation before registration were 11.6% and 1.2%, respectively. The ages at which the patients started dialysis or received renal transplantation before registration and ERT were 41.5 years (mean, n = 53) and 41.9 years (mean, n = 44), respectively. However, the ages at which the patients started dialysis or received renal transplantation during agalsidase alfa treatment in this survey and ERT were 48.7 years (mean, n = 21) and 46.0 years (mean, n = 30), respectively. The overall mean follow-up period and dose of agalsidase alfa were 3.5 years (SD of the mean 1.8 years, range 0.0 to 7.9 years) and 0.2 mg/kg every 2 weeks, respectively.

The manifestations in the patients at baseline are shown in Fig. 1. The major involvement was neurological and cardiac in the male patients and the most frequent involvement was cardiac in the female patients.

3.2. Safety

Of the 493 patients in this survey, 121 (24.5%) had 812 ADRs including IRRs. Common ADRs reported (50 events or more) were rash (128 events in 6 patients), malaise (103 events in 14 patients), erythema (90 events in 3 patients), and extremity pain (63 events in 10 patients). Of those, while 2 events of "extremity pain" and 1 event of "malaise" were serious, the outcomes were "resolving" or "resolved" with treatments (for example, antibiotics, analgesics, steroids, and/or antihistamines). ADRs that resulted in death as an outcome were reported for 7 events in 4 male patients. These events were not IRRs. One patient died from septic shock, abnormal hepatic function, decreased platelet count, and cerebral infarction. In the other three cases, the cause of death was unknown or cardiac failure.

Of the 493 patients in this survey, 62 (12.6%) had 661 IRRs. IRRs that were reported in 5 patients or more were pyrexia in 13 patients, malaise and nausea in 9 patients each, pruritus in 7 patients, extremity pain, urticaria, and chills in 6 patients each, and rash, headache, and chest discomfort in 5 patients each. The outcomes were "resolving" or "resolved" either without any treatment or with treatment (for example, steroids and/or antihistamines). Serious IRRs occurred in 6 patients (18 events). Two patients experienced their first IRRs 2 years or more after the start of treatment. These 6 patients experienced IRRs during infusion or within 1 h after infusion, and they were resolved or resolving within one day after treatment with supportive care. One of 62 patients with IRRs discontinued the Replagal treatment (non-serious). Fig. 2 shows the time to first onset of IRRs using the Kaplan-Meier method. Many of the first IRRs occurred within 6 months after treatment (69% of patients with IRRs; 43/62). However, 7 patients had their first IRRs 2 years or more after the start of treatment. Table 2 shows the percentage of the patients experiencing IRRs or other ADRs by patient characteristics (type of Fabry disease, IgG antibody status, and allergic constitution). IRRs and other ADRs in the males were both at higher percentages than in the females. In the patients with allergy to some antigens besides agalsidase beta, the percentage of patients with IRRs was higher than in the patients without allergy.

Six females became pregnant during the administration period of Replagal in this survey. Five underwent uneventful childbirth, and newborns were normal. One woman had a miscarriage in her first pregnancy, but a causal relationship to Replagal was ruled out by her physician. In her second pregnancy, she gave birth uneventfully, and the newborn was normal.

3.3. Anti-agalsidase alfa antibodies

In the 278 patients without prior ERT, IgG antibody data both before and after agalsidase alfa treatment was available for 256 patients (140 males and 116 females). Seventeen of the 256 patients were IgG antibody positive (6.6%), and one was female (11.4% of males and 0.9% of females). In 6 of the 17 IgG antibody positive patients (5 males and 1 female), the IgG antibody status converted to negative while agalsidase alfa treatment continued. The percentage of IRRs for the 17 IgG antibody positive patients tended to be higher than that of the IgG

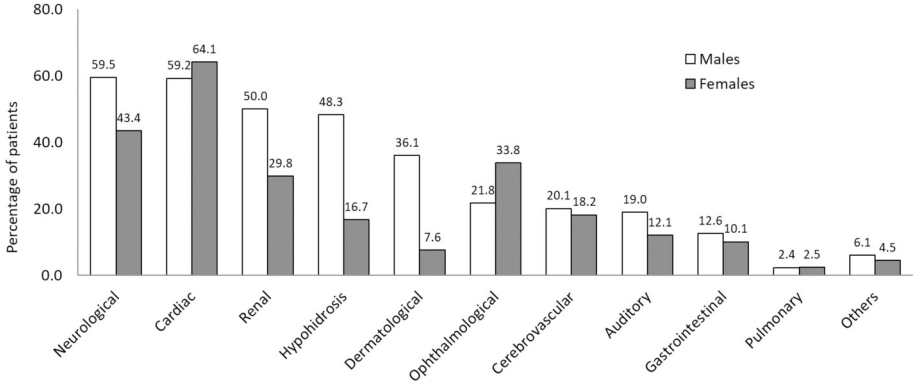

Fig. 1. Frequency of specific signs and symptoms of Fabry disease in males (n = 295) and females (n = 198) at baseline.

antibody negative patients (positive 23.5% and negative 13.8%; Table 2) but the chronological correlation between seroconversion and the incidence of IRRs was unclear. Plasma Gb_3 in the IgG antibody positive patients (classic type) decreased significantly by the last IgG antibody positive point from baseline (baseline 10.8 nmol/mL, the last IgG antibody positive point 5.8 nmol/mL, n = 15, p < .001). However, urine sediment Gb_3 did not decrease significantly by the last IgG antibody positive point from baseline (baseline 3039 nmol/g creatinine, the last IgG antibody positive point 2961 nmol/g creatinine, n = 10, p = .812). The chronological correlation between seroconversion and the changes in plasma Gb_3 and urine sediment Gb_3 levels was unclear.

IgE antibodies have been measured when the physician judged it necessary. There were no IgE antibody positive patients in all 68 tested patients (89 measurements).

3.4. Effectiveness

3.4.1. BPI and EQ-5D

No significant changes were observed in the overall mean BPI score of the worst pain from baseline to last visit (from 2.57 at baseline to 2.78, mean of 3.1 years after, n = 296, p = .209). The mean BPI score of the worst pain fell significantly from baseline to 0.5, 1, 2, and 3 years of treatment in the patients with moderate pain at baseline and from baseline to all time points in the patients with severe pain at baseline (Table 3). In the overall mean BPI score of pain intensity and pain interference with daily activities, no significant changes were observed from baseline to last visit (from 1.49 and 1.41 at baseline to 1.57 and 1.42, mean of 3.0 and 3.1 years after, n = 294 and 284, p = .436 and p = .939, respectively).

No significant changes were observed in the overall mean EQ-5D score from baseline to last visit (from 0.84 at baseline to 0.83, mean of 3.0 years after, n = 299, p = .064).

3.4.2. Gb_3 in plasma and urine sediment

The plasma Gb_3 levels at baseline in the classical Fabry disease males, non-typical Fabry disease males, and female patients without prior ERT were 9.1 ± 4.0, 4.1 ± 2.4, and 3.9 ± 1.5 nmol/mL (mean ± SD), and in those with prior ERT were 5.3 ± 2.4, 3.5 ± 1.4, and 3.8 ± 1.0 nmol/mL (mean ± SD), respectively. The changes from baseline in the mean plasma Gb_3 levels are shown in Fig. 3. In the patients without prior ERT, significant decreases were observed at all time points in the classical Fabry disease males and female patients and after 0.5, 1, 2, and 3 years of treatment in the non-typical Fabry disease males. In the patients with prior ERT, the plasma Gb_3 levels were almost maintained. However, the plasma Gb_3 levels increased within 1 year after treatment with agalsidase alfa (significant increase after 1 year of treatment, p = .024) but decreased after 2 years of treatment (significant decrease after 3 years of treatment, p = .007) in the classical Fabry disease males with prior ERT. In the classical Fabry disease males, non-typical Fabry disease males, and female patients without prior ERT, the plasma Gb_3 levels significantly decreased from baseline to last visit (from 9.1, 4.1, and 3.9 nmol/mL at baseline to 4.3, 3.1, and 3.2 nmol/mL; mean of 3.2, 2.3, and 2.8 years treatment; n = 100, 36, and 107; p < .001, p < .001, and p < .001; respectively).

The urine sediment Gb_3 levels at baseline in the classical Fabry disease males, non-typical Fabry disease males, and female patients

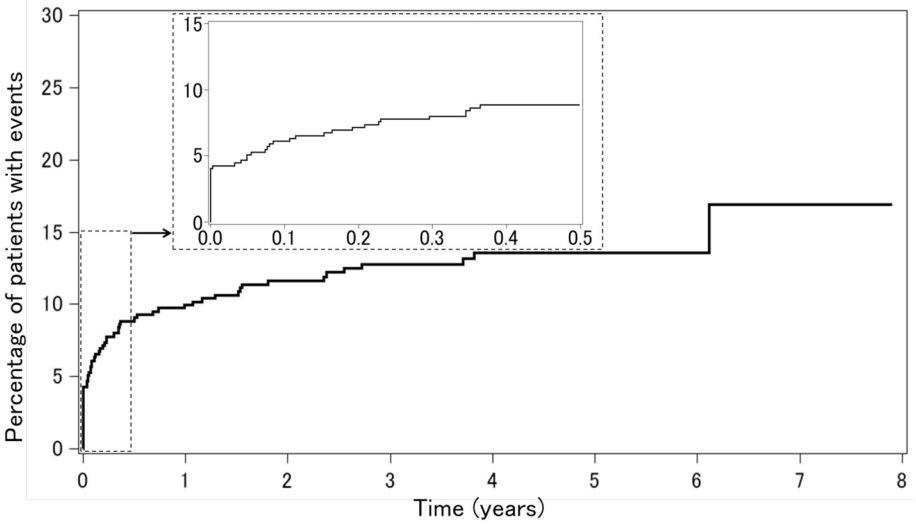

Fig. 2. Kaplan-Meier analyses for morbidity (first onset of any IRR). The first half-year is enlarged in the small graphs.

Table 2
Percentage of patients experiencing IRRs or ADRs by patient characteristics.

	n	IRR		Serious IRR		ADR except for IRR		Serious ADR except for IRR	
Type of Fabry disease									
Males (Classic phenotype)	238	33	(13.9)	3	(1.3)	36	(15.1)	7	(2.9)
Males (Non-typical variant)	56	8	(14.3)	1	(1.8)	13	(23.2)	4	(7.1)
Females	198	21	(10.6)	2	(1.0)	20	(10.1)	4	(2.0)
IgG antibody status of patients without prior ERT									
Positive	17	4	(23.5)	0	(0.0)	2	(11.8)	0	(0.0)
Negative	239	33	(13.8)	6	(2.5)	41	(17.2)	10	(4.2)
Allergy to some antigens besides agalsidase beta									
With	86	23	(26.7)	1	(1.2)	16	(18.6)	3	(3.5)
Without	394	38	(9.6)	5	(1.3)	50	(12.7)	12	(3.0)

n (%)

without prior ERT were 2362 ± 1250, 688 ± 1502, and 420 ± 636 nmol/g creatinine (mean ± SD), and in those with prior ERT were 1336 ± 1983, 186 ± 113, and 184 ± 64 nmol/g creatinine (mean ± SD), respectively. The changes from baseline in the mean urine sediment Gb_3 levels are shown in Fig. 4. In the patients with all disease types of Fabry disease without prior ERT, the urine sediment Gb_3 levels significantly decreased from baseline to last visit (from 2362, 688, and 420 nmol/g creatinine at baseline to 954, 316, and 208 nmol/g creatinine; mean of 3.4, 2.6, and 2.8 years treatment; n = 67, 26, and 80; $p < .001$, $p = .017$, and $p = .002$; respectively).

3.4.3. Renal evaluations

Proteinuria and eGFR were calculated.

The changes in the mean proteinuria during agalsidase alfa treatment are shown in Table 4. Significant increases were observed after 4 and 5 years of treatment in the male patients. However, no significant changes were observed in other time points in the male patients and in all time points in the female patients.

The changes in the mean eGFR during agalsidase alfa treatment are shown in Table 5. Significant decreases were observed at multiple time points in the classical Fabry disease males and females, and the mean annual changes in eGFR (mL/min/1.73 m^2) ranged from −2.88 to +1.00 in the classical Fabry disease males, from −2.04 to −0.95 in the non-typical Fabry disease males and from −2.64 to −1.02 in the females. Table 6 shows the changes in the mean eGFR during agalsidase alfa treatment by patient characteristics (baseline eGFR, baseline proteinuria, and the presence or absence of hypertension). The mean annual changes in eGFR ranged from −2.22 to −0.92 in the males whose baseline eGFR were over 60 but from −4.45 to −2.76 in the males whose baseline eGFR were under 60. The mean yearly changes in eGFR ranged from −1.38 to −0.95 in the males and females whose baseline proteinuria was under 300 mg/day and from −4.52 to −2.14 in the males and females whose baseline proteinuria was over 300 mg/day. The mean annual changes in eGFR were − 1.64 in the males without hypertension and − 0.98 in the females without hypertension but were − 3.92 in the males with hypertension and − 1.93 in the females

Table 3
Change in mean BPI score of worst pain during treatment with agalsidase alfa.

	n	Mean baseline BPI score of worst pain		Mean BPI score of worst pain at each year		Mean change in BPI score of worst pain from baseline		p value
Patients with mild pain at baseline (BPI score of worst pain: 1–4)								
Year0.5	77	2.68	(0.97)	2.91	(2.55)	0.23	(2.42)	0.400
Year1	70	2.77	(0.97)	3.01	(2.29)	0.24	(2.18)	0.355
Year2	72	2.63	(0.98)	2.85	(2.64)	0.22	(2.47)	0.447
Year3	54	2.70	(0.98)	2.98	(2.67)	0.28	(2.67)	0.449
Year4	41	2.56	(1.07)	2.63	(2.37)	0.07	(2.35)	0.843
Year5	20	2.55	(1.10)	2.65	(2.21)	0.10	(2.17)	0.839
Year6	9	3.22	(1.09)	3.22	(2.82)	0.00	(2.65)	1.000
Year7	4	2.75	(1.50)	4.00	(3.37)	1.25	(2.63)	0.412
Patients with moderate pain at baseline (BPI score of worst pain: 5–6)								
Year0.5	27	5.48	(0.51)	4.15	(3.16)	−1.33	(3.17)	0.038*
Year1	22	5.55	(0.51)	3.64	(3.00)	−1.91	(3.12)	0.009*
Year2	21	5.62	(0.50)	3.90	(3.13)	−1.71	(3.21)	0.024*
Year3	17	5.47	(0.51)	3.88	(2.67)	−1.59	(2.94)	0.041*
Year4	8	5.63	(0.52)	3.63	(2.72)	−2.00	(3.16)	0.117
Year5	3	5.33	(0.58)	4.67	(2.52)	−0.67	(3.06)	0.742
Year6	1	5.00		10.00		5.00		
Patients with severe pain at baseline (BPI score of worst pain: 7–10)								
Year0.5	41	7.80	(0.78)	5.37	(2.83)	−2.44	(2.67)	0.000*
Year1	39	7.79	(0.86)	5.36	(2.75)	−2.44	(2.75)	0.000*
Year2	32	7.81	(0.90)	4.88	(2.62)	−2.94	(2.60)	0.000*
Year3	28	7.89	(0.96)	5.50	(2.98)	−2.39	(2.86)	0.000*
Year4	15	7.87	(0.92)	3.87	(2.83)	−4.00	(3.12)	0.000*
Year5	5	8.00	(1.22)	4.40	(3.21)	−3.60	(2.70)	0.041*
Year6	1	8.00		1.00		−7.00		
Year7	1	8.00		1.00		−7.00		

Mean (SD, where applicable).
* $p < .05$ vs baseline (paired *t*-test).

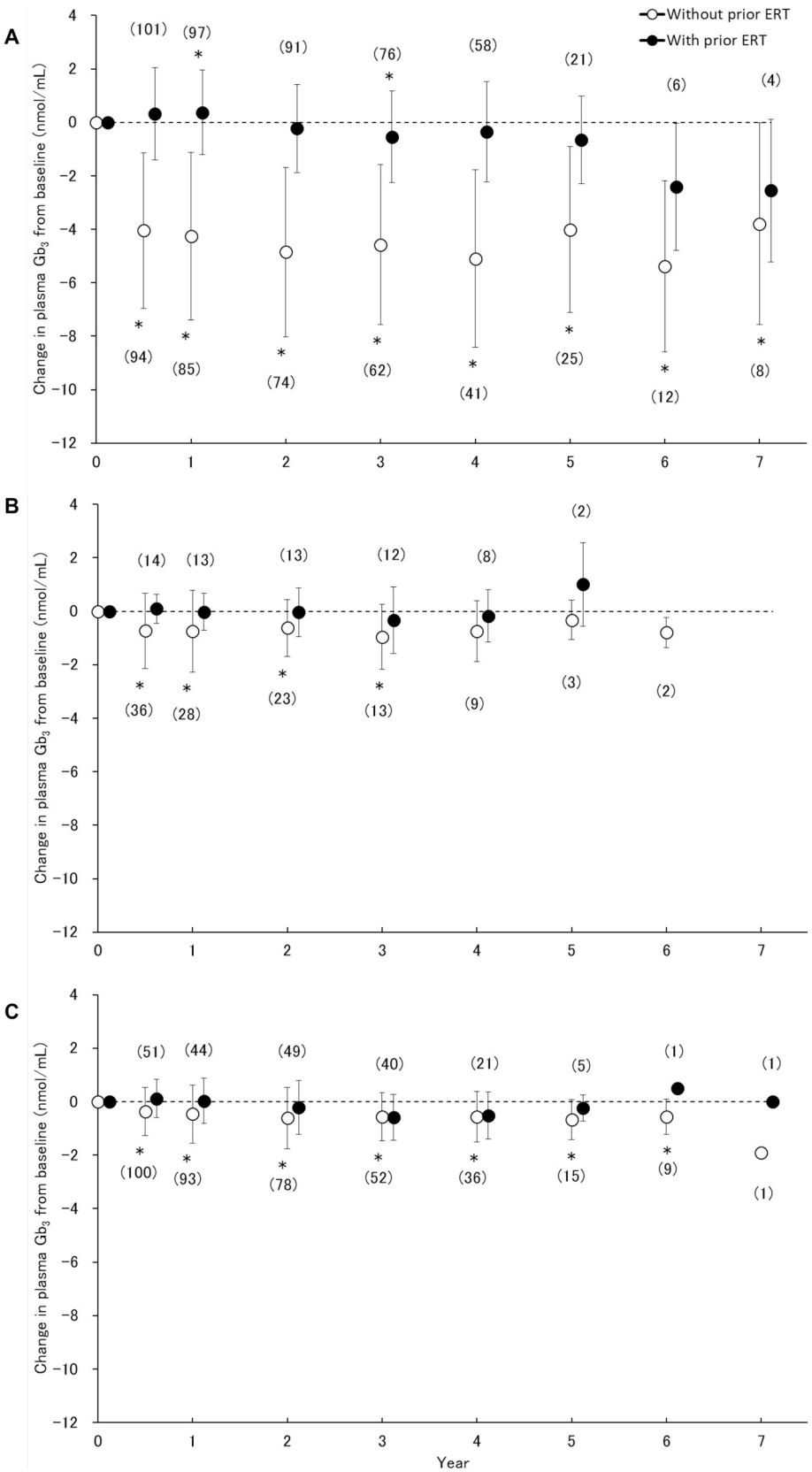

Fig. 3. Change in mean plasma Gb_3 during treatment with agalsidase alfa. (A) Change in mean plasma Gb_3 in males with classical Fabry disease. (B) Change in mean plasma Gb_3 in males with non-typical Fabry disease. (C) Change in mean plasma Gb_3 in females with Fabry disease. Data are shown as mean ± SD (where applicable). Patient numbers are shown in parentheses. Horizontal lines represent baseline. *$p < .05$ vs baseline at each point (paired *t*-test).

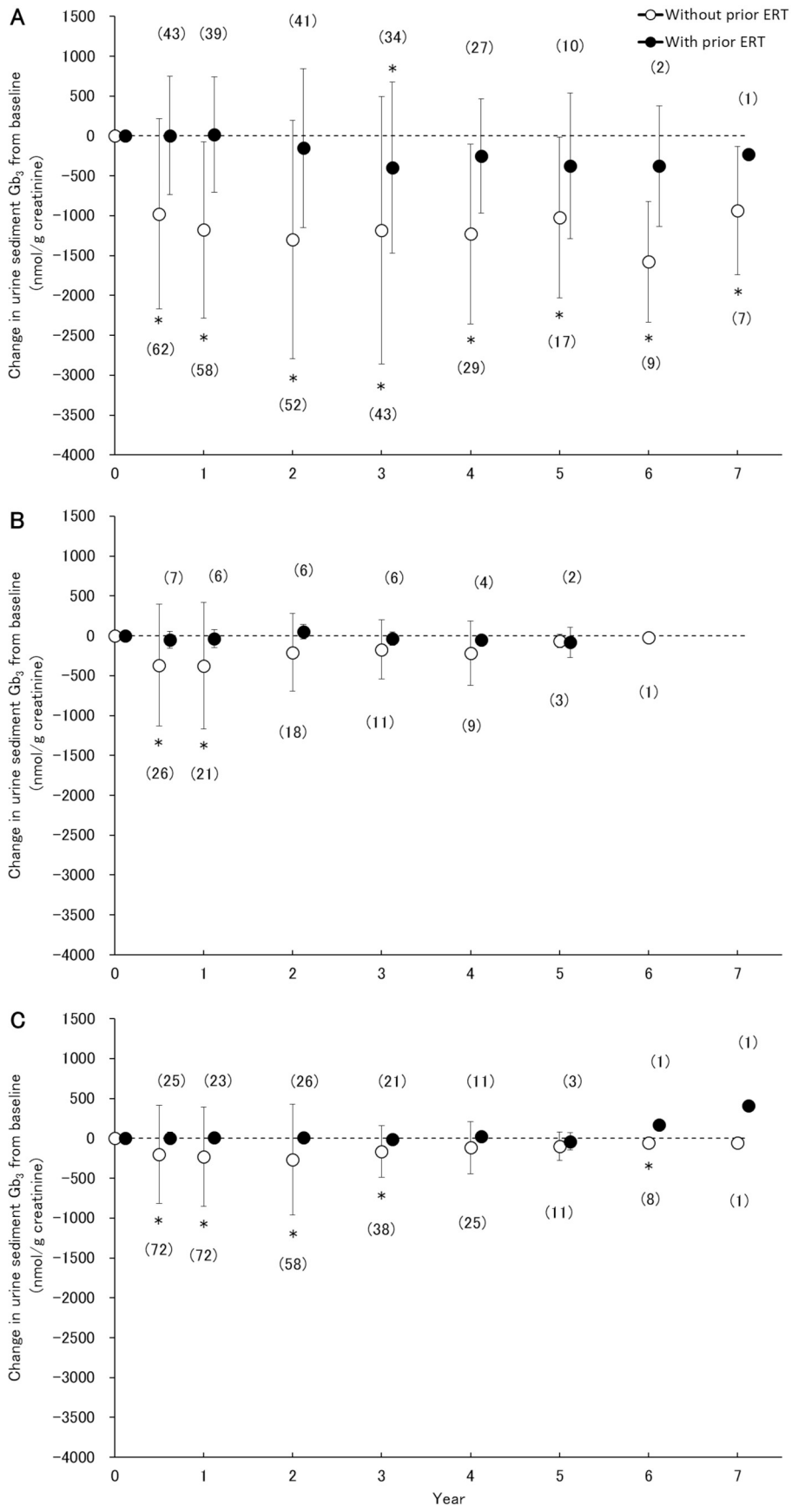

Fig. 4. Change in mean urine sediment Gb_3 during treatment with agalsidase alfa. (A) Change in mean urine sediment Gb_3 in males with classical Fabry disease. (B) Change in mean urine sediment Gb_3 in males with non-typical Fabry disease. (C) Change in mean urine sediment Gb_3 in females with Fabry disease. Data are shown as mean ± SD (where applicable). Patient numbers are shown in parentheses. Horizontal lines represent baseline. *p < .05 vs baseline at each point (paired *t*-test).

Table 4
Change in mean proteinuria during treatment with agalsidase alfa.

	n	Mean baseline proteinuria		Mean proteinuria at each year		Mean change in proteinuria from baseline		p value
		(mg/day)		(mg/day)		(mg/day)		
Males								
Year0.5	109	661	(1052)	689	(1129)	28	(592)	0.625
Year1	98	656	(1043)	612	(883)	−44	(483)	0.367
Year2	91	631	(1034)	693	(954)	62	(632)	0.354
Year3	75	631	(1079)	692	(1141)	60	(551)	0.348
Year4	53	457	(533)	701	(945)	244	(567)	0.003*
Year5	24	503	(582)	976	(1189)	473	(787)	0.007*
Year6	6	572	(450)	1308	(1334)	737	(1042)	0.144
Year7	5	672	(762)	1009	(1115)	337	(477)	0.189
Females								
Year0.5	90	281	(544)	314	(567)	33	(403)	0.445
Year1	89	249	(527)	306	(583)	58	(387)	0.162
Year2	78	267	(559)	292	(509)	25	(337)	0.511
Year3	56	279	(630)	291	(471)	12	(348)	0.795
Year4	35	225	(407)	323	(513)	98	(398)	0.153
Year5	14	127	(125)	308	(460)	181	(418)	0.129
Year6	9	103	(94)	224	(298)	121	(222)	0.141
Year7	2	135	(177)	96	(121)	−39	(56)	0.504

Mean (SD, where applicable).
* $p < .05$ vs baseline (paired *t*-test).

with hypertension.

3.4.4. Cardiac evaluations

The QRS duration measured via electrocardiography was evaluated to assess the heart conduction system. The QRS duration was significantly prolonged from baseline to last visit in the males (from 121.9 to 127.0 ms, mean of 3.1 years treatment, n = 114, p = .038) and females (from 104.2 to 108.5 ms, mean of 2.9 years treatment, n = 98, p = .040).

The LVMI measured via echocardiography was evaluated to assess hypertrophic cardiomyopathy. The changes in the mean LVMI during agalsidase alfa treatment are shown in Table 7. Significant increases were observed at 4 years of treatment in the classical Fabry disease males and significant decreases were observed at 1 year of treatment in the non-typical Fabry disease males. No significant changes were observed at all other points. In the patients with hypertension, no significant changes were observed in the LVMI from baseline to last visit (from 72.1 to 73.9 $g/m^{2.7}$, mean of 3.0 years treatment, n = 26, p = .608) but in the patients without hypertension, the LVMI significantly increased from baseline to last visit (from 64.9 to 69.1 $g/m^{2.7}$, mean of 2.9 years treatment, n = 112, p = .021).

The E/A wave ratio and ejection fraction measured via echocardiography were evaluated to assess diastolic and systolic function. No significant changes were observed in the E/A wave ratio from baseline to last visit in the males (from 1.38 to 1.30, mean of 2.9 years treatment, n = 69, p = .145) and females (from 1.28 to 1.21, mean of 2.7 years treatment, n = 57, p = .288). The ejection fraction significantly decreased from baseline to last visit in the males (from 60.3 to 57.6, mean of 3.1 years treatment, n = 94, p = .011) and females (from 63.6 to 60.0, mean of 2.7 years treatment, n = 75, p = .003). No significant changes were observed in the ejection fraction measured via cardiac magnetic resonance imaging from baseline to last visit in the males (from 57.2 to 58.3, mean of 2.5 years treatment, n = 6, p = .829), but significant increases were observed in the females (from 67.1 to 69.9, mean of 3.5 years treatment, n = 4, p = .006), although the amount of data was small.

3.4.5. Mortality

Kaplan-Meier survival analyses (mortality) in the treated patients in this survey are shown in Fig. 5. Twenty-five male patients and 6 female patients died during the study period. The median age at death in the male patients was 77 years. The causes of death were cardiac disease (12 males and 5 females), renal disease (1 male), stroke (1 male and 1 female), others including septic shock, gastrointestinal haemorrhage,

Table 5
Change in mean eGFR during treatment with agalsidase alfa.

	n	Mean baseline eGFR		Mean eGFR at each year		Mean change in eGFR from baseline		p value	Mean yearly change in eGFR
		(mL/min/1.73 m^2)		(mL/min/1.73 m^2)		(mL/min/1.73 m^2)			(mL/min/1.73 m^2)
Males (Classic phenotype)									
Year0.5	121	92.7	(34.6)	93.2	(35.4)	0.5	(11.1)	0.619	1.00
Year1	113	92.5	(34.7)	91.5	(36.5)	−1.0	(10.2)	0.289	−1.03
Year2	101	94.7	(32.8)	91.1	(35.9)	−3.6	(11.1)	0.002*	−1.79
Year3	85	93.8	(32.1)	87.5	(39.2)	−6.3	(16.8)	0.001*	−2.09
Year4	60	96.9	(28.1)	88.8	(33.8)	−8.1	(15.3)	0.000*	−2.04
Year5	26	94.1	(29.1)	81.6	(34.8)	−12.5	(15.4)	0.000*	−2.50
Year6	4	76.4	(27.9)	59.1	(43.3)	−17.3	(16.3)	0.124	−2.88
Year7	4	100.9	(6.9)	97.9	(29.5)	−3.1	(24.0)	0.814	−0.44
Males (Non-typical variant)									
Year0.5	37	65.5	(25.1)	64.9	(26.5)	−0.6	(9.7)	0.718	−1.17
Year1	31	66.5	(25.2)	65.3	(27.0)	−1.2	(11.2)	0.544	−1.24
Year2	28	70.2	(24.0)	66.7	(26.8)	−3.5	(10.9)	0.103	−1.73
Year3	19	72.2	(24.5)	66.1	(29.3)	−6.1	(11.2)	0.028*	−2.04
Year4	14	73.5	(20.5)	67.6	(23.1)	−5.9	(10.6)	0.057	−1.47
Year5	5	70.8	(14.6)	66.0	(24.9)	−4.7	(12.6)	0.447	−0.95
Year6	2	80.0	(10.9)	70.8	(9.2)	−9.2	(1.7)	0.084	−1.54
Females									
Year0.5	142	79.5	(26.3)	78.6	(26.0)	−0.9	(11.0)	0.328	−1.81
Year1	130	79.6	(25.5)	78.0	(24.3)	−1.6	(9.6)	0.059	−1.61
Year2	121	79.4	(24.8)	76.6	(25.1)	−2.9	(11.7)	0.008*	−1.44
Year3	89	78.4	(24.4)	75.3	(24.3)	−3.1	(12.2)	0.020*	−1.02
Year4	58	76.4	(25.6)	72.0	(25.2)	−4.4	(14.8)	0.028*	−1.10
Year5	24	85.7	(29.6)	76.2	(22.0)	−9.4	(16.2)	0.009*	−1.89
Year6	10	91.4	(30.7)	79.7	(26.2)	−11.7	(13.2)	0.021*	−1.95
Year7	2	102.0	(3.1)	83.5	(0.1)	−18.5	(3.2)	0.078	−2.64

Mean (SD, where applicable).
* $p < .05$ vs baseline (paired *t*-test).

Table 6
Change in mean eGFR during treatment with agalsidase alfa by patient characteristics.

		n	Mean baseline eGFR		Mean eGFR at last visit		Mean change in eGFR from baseline		p value	Mean yearly change in eGFR
			(mL/min/1.73 m^2)		(mL/min/1.73 m^2)		(mL/min/1.73 m^2)			(mL/min/1.73 m^2)
Baseline eGFR (mL/min/1.73 m^2)	Males									
	≥130	15	149.1	(18.6)	146.4	(38.4)	−2.7	(30.0)	0.736	−0.99
	90 to < 130	64	108.4	(11.6)	105.1	(18.8)	−3.2	(12.7)	0.047*	−0.92
	60 to < 90	51	78.5	(9.0)	71.6	(15.5)	−6.9	(15.3)	0.002*	−2.22
	30 to < 60	29	46.5	(9.3)	34.0	(17.5)	−12.5	(14.5)	0.000*	−4.45
	< 30	11	19.8	(7.3)	14.6	(6.9)	−5.2	(5.9)	0.015*	−2.76
	Females									
	≥130	6	143.2	(12.4)	125.3	(15.4)	−17.9	(26.6)	0.160	−5.13
	90 to < 130	42	102.0	(9.2)	98.1	(13.0)	−3.9	(11.8)	0.037*	−1.45
	60 to < 90	75	74.7	(8.3)	72.2	(14.2)	−2.5	(12.2)	0.078	−0.79
	30 to < 60	24	48.9	(7.1)	46.0	(12.6)	−3.0	(7.5)	0.065	−0.96
	< 30	5	18.4	(8.7)	14.1	(10.0)	−4.3	(6.1)	0.193	−2.67
Baseline proteinuria (mg/day)	Males									
	< 100	51	100.4	(34.6)	97.6	(36.9)	−2.9	(13.0)	0.124	−0.95
	100 to < 300	18	79.6	(24.5)	76.4	(27.1)	−3.1	(9.3)	0.170	−0.98
	300 to < 1000	22	72.1	(32.4)	59.8	(34.6)	−12.3	(15.4)	0.001*	−3.24
	≥1000	24	55.0	(27.8)	40.5	(24.3)	−14.5	(12.0)	0.000*	−4.52
	Females									
	< 100	64	76.9	(19.5)	73.4	(22.4)	−3.5	(11.6)	0.019*	−1.16
	100 to < 300	17	89.3	(31.4)	84.2	(31.0)	−5.1	(15.3)	0.186	−1.38
	300 to < 1000	14	70.1	(28.4)	65.2	(27.2)	−4.9	(10.3)	0.096	−2.14
	≥1000	7	62.8	(29.3)	51.0	(28.9)	−11.8	(9.0)	0.013*	−4.23
Hypertension	Males									
	Presence	23	63.3	(30.0)	51.6	(32.1)	−11.8	(10.8)	0.000*	−3.92
	Absence	147	90.4	(34.5)	85.3	(40.3)	−5.1	(16.4)	0.000*	−1.64
	Females									
	Presence	31	67.2	(28.3)	60.8	(29.4)	−6.4	(9.9)	0.001*	−1.93
	Absence	121	82.1	(24.1)	79.1	(24.1)	−2.9	(12.8)	0.013*	−0.98

Mean (SD, where applicable).
* $p < .05$ vs baseline (paired *t*-test).

etc. (7 males) and unknown (4 males). The causes of death for which a causal relationship to Replagal could not be ruled out were cardiac disease (2 males), septic shock (1 male) and unknown (1 male).

4. Discussion

This report represents extensive and long-term data for the safety and effectiveness of ERT with agalsidase alfa in Japanese practical treatment.

The initial signs and symptoms of classic phenotype Fabry disease emerge as neuropathic pain, angiokeratomas, hypohidrosis, etc., during childhood and adolescence [3]. Because these signs and symptoms are not specific to Fabry disease, the diagnosis was frequently delayed by > 20 years [3,11]. In this survey, about half of the classic phenotype Fabry patients were diagnosed at < 30 years, although it was unknown at what age the initial signs and symptoms appeared. This suggests that Fabry disease has been diagnosed at an early stage in Japan; however, even earlier diagnosis is desired for the appropriate management of this condition. ERT for Fabry disease has been administered before study participation by 40.2% of patients, and most Japanese Fabry patients had received agalsidase beta, until viral contamination during the manufacturing process of agalsidase beta led to a global shortage in June 2009 [12,13]. The percentage of patients with dialysis and renal transplantation at baseline in the males was more than in the females. This is consistent with the literature [14,15] that renal disease progression in males was faster than in females. The percentage of patients with heart pacemaker at baseline in females or classic Fabry disease males was less than that in non-typical variant Fabry disease males. The reason may be that the age of the non-typical variant Fabry disease males at baseline was higher than the others and because the severity of cardiac abnormalities increases with age in both genders in the literature [16–18]. There was no substantial difference in the frequency of specific signs and symptoms of Fabry disease at baseline from the previous literature [19–21]; however, specific data in this survey indicated a relatively high percentage of ophthalmological manifestations in the females. The reason for this phenomenon is unknown.

Overall, the percentage of patients with ADRs was 24.5%, and this was lower than in Japanese clinical trials (83.3%; 10/12 patients) or in non-Japanese clinical trials (63.1%; 41/65 patients) described in Replagal's Japanese package insert. However, they are difficult to compare because the sample sizes were small in the clinical trials and the collection situation of the ADRs differed between the clinical trials and post-marketing surveillance. In addition, this percentage was slightly lower than that in the ongoing Fabry Outcome survey (33.9%; 188/555 patients) [22]. In this survey, IRRs occurred in 12.6% of patients, and 69% occurred within 6 months after the initiation of treatment with agalsidase alfa. In addition, in the patients with allergy to some antigens besides agalsidase beta, the percentage of patients with IRRs was higher than in those without allergy. Although this survey suggests that almost all IRRs are manageable with appropriate treatment (for example, steroids and/or antihistamines), it may be better to pay attention to IRRs in patients with early dosing or allergy. The percentage of patients with IRRs in females was lower than in males. Because heterozygous females have alpha-galactosidase A residual activity, it may be unlikely to cause allergic reaction to agalsidase alfa purified from stably transfected human foreskin fibroblasts [23]. The treatment of Fabry disease with agalsidase alfa was well tolerated as overall assessment of safety in this survey.

In this study, IgG antibodies developed in 11.4% (16/140) of the male patients, among which developed in 14.4% (15/104) of the classical Fabry disease and in 2.8% (1/36) of the non-typical Fabry disease. From the etiology of Fabry disease phenotypes it is reasonable

Table 7
Change in mean LVM index during treatment with agalsidase alfa.

	n	Mean baseline LVM index		Mean LVM index at each year		Mean change in LVM index from baseline		p value
		($g/m^{2.7}$)		($g/m^{2.7}$)		($g/m^{2.7}$)		
Males (Classic phenotype)								
Year0.5	43	67.5	(41.3)	69.1	(45.7)	1.6	(13.6)	0.459
Year1	40	64.3	(42.1)	64.9	(40.0)	0.6	(14.3)	0.777
Year2	35	63.4	(39.1)	66.8	(42.2)	3.4	(20.0)	0.320
Year3	31	66.5	(44.0)	69.8	(42.1)	3.3	(18.5)	0.328
Year4	23	54.5	(32.0)	61.8	(38.2)	7.4	(15.7)	0.035*
Year5	8	53.9	(30.2)	68.9	(50.9)	15.0	(23.4)	0.112
Year6	4	57.8	(39.9)	81.3	(73.2)	23.5	(34.7)	0.268
Year7	2	71.0	(63.1)	122.8	(121.8)	51.7	(58.7)	0.430
Year8	1	115.7		192.1		76.4		
Males (Non-typical variant)								
Year0.5	23	80.8	(39.7)	79.4	(39.6)	−1.4	(13.9)	0.638
Year1	19	85.1	(41.0)	79.9	(35.7)	−5.3	(9.9)	0.031*
Year2	15	78.8	(36.7)	70.3	(26.7)	−8.5	(16.1)	0.060
Year3	14	73.0	(41.8)	68.8	(37.3)	−4.2	(13.8)	0.271
Year4	14	70.6	(38.4)	67.2	(33.2)	−3.4	(10.3)	0.240
Year5	5	75.6	(30.3)	75.4	(23.3)	−0.2	(14.4)	0.973
Year6	2	75.6	(47.0)	91.0	(63.5)	15.5	(16.5)	0.412
Females								
Year0.5	50	64.1	(22.3)	65.9	(22.8)	1.8	(14.5)	0.384
Year1	45	61.5	(21.2)	64.2	(25.1)	2.8	(12.7)	0.147
Year2	39	64.3	(23.1)	66.9	(25.5)	2.7	(14.0)	0.240
Year3	27	70.0	(21.7)	74.3	(27.1)	4.3	(16.4)	0.187
Year4	19	68.7	(19.1)	71.3	(30.0)	2.6	(22.7)	0.626
Year5	7	75.5	(19.4)	79.8	(34.0)	4.3	(30.8)	0.727

Mean (SD, where applicable).
* $p < .05$ vs baseline (paired *t*-test).

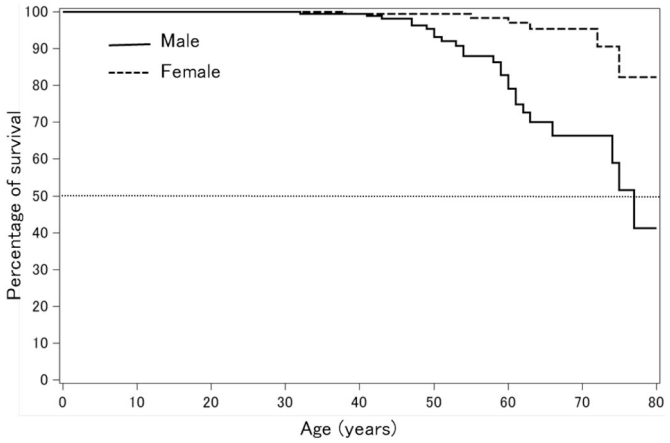

Fig. 5. Kaplan-Meier survival analyses for mortality in this survey.

that the classical Fabry disease had a higher rate of antibody positive. On the other hand, these rates were lower than in published literature [24–27]. Although this results may suggest that Japanese has a low antibody positive rate to agalsidase alfa, it is difficult to conclude as such with only this results because the result of antibodies may be different depending on the measurement method and assessment method. No IgE antibodies developed in all of the patients measured. This is consistent with the literature [28]. The percentage of patients with IRRs in the IgG antibody positive patients was higher than in the negative patients. Although not directly comparable, these results were similar to the literature [29]. Formation of IgG antibodies against agalsidase may not only affect to safety but also to effectiveness. It has been suggested that IgG antibodies in ERT for Fabry disease inhibits alpha-galactosidase A enzyme activity [25,30,31]. There are reports that IgG antibodies may affect or may not affect the reduction in plasma Gb_3 of patients [32,33]. Some data suggested that IgG antibodies affects the reduction of urine sediment Gb_3 in patients [30,32,34]. From these reports and this study, it seems that IgG antibodies may not affect the reduction of plasma Gb_3 but may affect urine sediment Gb_3.

Pain crises are a major contributor to the quality of life with Fabry disease [35]. In this study, we evaluated pain using BPI scores. The effect of agalsidase alfa on pain was confirmed in a randomized controlled trial, prospective clinical trial [36–38], and cohort studies [22,35]. In this survey, no significant changes were observed in the overall mean BPI score of worst pain from baseline to last visit. However, the BPI score of worst pain significantly decreased at some time points in patients with moderate (score 5–6) and severe (score 7–10) pain at baseline. Since analgesics were administered to 55% (162/296) of the patients with available data for BPI scores (worst pain) in this observational survey, the reduction in the BPI scores may not only be the effect of agalsidase alfa. Pain relief in Fabry disease can be expected by combining analgesics and ERT. The EQ-5D score was evaluated to investigate the quality of life in patients with Fabry disease as whole clinical outcome. Although there are reports that significant improvement in the EQ-5D score were observed in patients with one or five years of treatment with agalsidase alfa [22,39], no significant improvement was observed in this survey. Since it is implied that the EQ-5D score deteriorated with age in female patients [40] and Fabry disease is a progressive condition, maintaining the EQ-5D score is a benefit of ERT.

The major storage product in Fabry disease is Gb_3, which is elevated in most patients with this condition. Plasma or urine sediment Gb_3 is a surrogate marker for assessing the efficacy of ERT and cannot be considered as a valid biomarker [41,42]. However, the plasma Gb_3 levels were used as an endpoint in many clinical trials. The plasma Gb_3 levels decreased to approximately 50% of the value at baseline in the literature [36,42]. In this survey, the same result was observed in the classic phenotype patients without prior ERT. Meanwhile, no significant change in plasma Gb_3 was observed in the patients with prior ERT at almost all points but a significant increase was observed in the classic phenotype patients after one year of treatment and a significant decrease after 3 years of treatment. The reason for this is unknown; however, similar data are described in the literature concerning the clinical course of patients who switched from agalsidase beta to agalsidase alfa [43].

Renal function was assessed by proteinuria and eGFR. It has been widely reported that ERT does not decrease proteinuria in patients with Fabry disease [44–49]. In this survey, mean proteinuria tended to increase slightly in both genders. There are reports that angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and vitamin D are effective for the reduction of proteinuria in patients with Fabry disease [50,51]. In this survey, 102 patients had these drugs administered in 217 patients with available data for proteinuria and no clear effect was observed. However, since proteinuria has been reported as a risk factor for the progression of renal disease in Fabry disease [15] and our data also suggest that with higher baseline proteinuria a faster decrease in eGFR is observed (Table 6), both in our study as well as in published literature [46,48,52,53], it may be advisable to add these drugs to ERT. In this survey, the mean yearly decreases in eGFR in the males were less than the natural history of kidney function in Fabry male patients [14,52]. These data and the difference between age at dialysis or renal transplantation of patients before and after treatment may suggest that ERT prolongs the period to end-stage renal disease for 4.1–7.2 years. Table 6 shows that the higher eGFR at baseline patients have, the slower decrease in eGFR of the patients is observed in males; however, this is unclear in females. At least in males, it may be preferable to initiate ERT while eGFR is normal and better to start ERT before eGFR becomes 60 mL/min/1.73 m^2 or less as previously recommended in the literature [32,48,52,54].

We examined the influence of hypertension on renal function in Fabry disease. Although there was no substantial difference, both male and female patients with hypertension had a faster decrease in eGFR than without hypertension as noted in the published literature [48]. Patients with Fabry disease will need to be more aware of lifestyle-related diseases that affect renal function than healthy subjects.

Cardiac manifestations in Fabry disease are important. Various symptoms such as cardiomyopathy, valvular disease, conduction system disease, coronary artery disease, and cardiac death are more frequent in female patients [17,55]. It has been reported that QRS duration as an evaluation item of conduction system disease is prolonged (> 120 ms) in some patients with Fabry disease, especially males [56]. Regarding the effect of ERT on QRS duration, there are contradictory reports of significant improvements (shortened) from a randomized controlled trial and of no significant changes from a double-blind randomized controlled trial [36,57]. QRS duration was significantly prolonged from baseline in this study. However, the value at last visit was within the normal range or slightly higher. The LVMI is well-known parameter of cardiomyopathy assessment in Fabry patients and there are many reports that the LVMI remains stable or significantly decreases with agalsidase alfa treatment [22,37,57,58]. However, the LVMI increased with age in untreated and treated patients in the registry data [17,37]. In this survey, no significant change was observed at most time point in the male and female patients; this may suggest that the LVMI in patients with Fabry disease was stabilized by agalsidase alfa.

We also examined the influence of hypertension on LVMI in Fabry disease. The LVMI significantly increased only in patients without hypertension; however, the reason why is unknown. We evaluated the E/A wave ratio and ejection fraction, although both parameters cannot distinguish patients from healthy subjects [57,59]. No significant change was observed in the E/A wave ratio, which remained stable during treatment. Although the ejection fraction measured by echocardiography significantly decreased from baseline to last visit in both males and females, based on ejection fraction data measured by echocardiography and cardiac magnetic resonance imaging that were almost in the normal range, the ejection fraction remained stable during treatment as in the present literature [57–59]. These cardiac assessments may suggest that agalsidase alfa has beneficial effect for controlling the progression of cardiac symptoms of Fabry disease. Furthermore, since there are reports that patients with myocardial fibrosis were resistant to ERT and early and long-term ERT reduced myocardial fibrosis [59–61], it is important to initiate ERT as soon as possible.

The estimated median survival time of untreated patients with Fabry disease was 50 years (males) and 70 years (females) in the literature published in 2001 [19,20], and was 60 years (males) in the literature published in 2009 [14]. The estimated median survival time of the treated patients in this survey was 77 years in males (Fig. 5) as in the present cohort study [54], and is almost same as normal male subjects in Japan. Although it is difficult for patients with Fabry disease to recognize the effect of ERT, this result is the overall benefit of agalsidase alfa.

In conclusion, this all-case observational survey indicated that agalsidase alfa 0.2 mg/kg every other week was well tolerated and controlled the progression of symptoms (especially renal and cardiac) of Fabry disease in adults. These results confirm findings from previously published studies that have analysed the safety and effectiveness of ERT. Furthermore, considering these results and the present reports, it may be preferable to administer concomitant medications as necessary and to initiate ERT before cardiac and/or renal symptoms progress. Because this was a non-interventional observational survey study, it has some limitations, including the lack of a control group, the lack of information on alpha-galactosidase A genes in patients, the possibility to estimate with fewer ADRs, and a small number of some parameters such as cardiac magnetic resonance imaging. Nevertheless this was an all-case survey study, the study population was large and there was no patient selection bias. Other limitations of this study include the lack of Lyso-Gb3 data because this survey was planned in 2006, the lack of eGFR data calculated not by CKD-EPI but by modified IDMS-MDRD for Japanese, and the lack of eGFR data for phenotypes in Table 6 because the amount of available data of non-typical Fabry disease males was very limited.

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