

Update on role of agalsidase alfa in management of Fabry disease

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Abstract: Fabry disease (FD) is an X-linked lysosomal storage disorder that affects both men and women. The manifestations of this heterogeneous disease are multisystemic and progressive. Prior to the development of enzyme replacement therapy, the management and treatment for Fabry disease was largely nonspecific and supportive. Because enzyme replacement therapy became commercially available in 2001, a variety of clinical benefits in Fabry patients have been consistently reported, including improved renal pathology and cardiac function, and reduced severity of neuropathic pain and improved pain-related quality of life. This update focuses on published data on the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa, and gives a brief overview on some of the outstanding management issues in the treatment of this complex disease.

Keywords: enzyme replacement therapy, Fabry disease, agalsidase alfa

Introduction

Anderson–Fabry disease (FD; OMIM 301500) is a metabolic storage disorder resulting from deficient activity of the lysosomal hydrolase, α -galactosidase A (α -gal A).¹ In individuals with defective α -gal A, the lipid substrate globotriaosylceramide (Gb3) accumulates in lysosomes throughout the body, resulting in progressive multiple-organ pathology.¹ Early signs and symptoms characteristic of the enzymatic defect include recurrent episodes of acroparesthesia and neuropathic pain crises, angiokeratomas, hearing loss and tinnitus, hypohidrosis, and corneal lesions.² With accumulating Gb3 deposits in lysosomes and increasing age, premature mortality usually occurs due to renal, cardiac, and/or cerebral complications.³ Fabry disease is a rare X-linked genetic trait affecting primarily males in all ethnic groups. Affected hemizygous males who have no or minimal α -gal A activity exhibit the classic phenotype, with clinical manifestations presenting in childhood or adolescence.⁴ Most heterozygous females are affected, although α -gal A activity level and the onset and rate of disease progression is more variable than for hemizygous males.^{5,6} In both heterozygous females and hemizygous males, lifespan is typically reduced by approximately 15–20 years.^{3,5} Classical Fabry disease, first described independently in 1898 by Fabry in Germany⁷ and by Anderson in England,⁸ is a rare disorder, with an estimated incidence of 1 per 117,000 live births.^{4,9} The clinical spectrum of classic Fabry disease has expanded in the past 15 years due to the discovery of milder phenotypes with residual α -gal A activity, resulting in later-onset cardiac and renal manifestations.^{4,10–13} A recent Italian newborn screening study for Fabry disease determined the α -gal A activity in dried blood spots of 37,104 consecutive newborn males.⁴ In this population, Spada et al reported the

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incidence of α -gal A deficiency to be 15–20 times higher than previous estimates.⁴ Moreover, the higher incidence found by newborn screening of later-onset phenotypes compared with classic phenotypes (11:1 ratio of later-onset versus classic phenotypes, respectively) suggests Fabry disease is currently underrecognized.⁴ Similarly, a newborn screening study by Hwu et al screened 90,288 male Taiwanese newborns and reported a high incidence of approximately one in 1250 with Fabry disease mutations, 86% of which were mutations found in later-onset cardiac phenotype patients.¹⁴

Due to its rarity, the broad number and severity of symptoms, and the heterogeneous phenotypic expressions, diagnosis is often challenging, particularly for heterozygous females and later-onset phenotypes.⁴ Future newborn screening for Fabry disease, as well as screening of high-risk populations, such as male kidney recipients, could be implemented into existing screening programs to aid early diagnosis.¹⁵

Overall, clinical studies in adult Fabry patients suggest that early initiation of enzyme replacement therapy may be able to alleviate symptoms and slow disease progression. Enzyme replacement therapy appears to normalize Gb3 levels in various organs, with numerous reported symptomatic benefits.^{16–19} The Mainz Severity Score Index, which provides an overall measure of disease severity, shows a marked reduction of Fabry disease severity following at least 1 year of enzyme replacement therapy ($P < 0.001$).¹⁷ Fabry disease is a progressive disorder, so enzyme replacement therapy intervention in childhood has the potential to provide greater long-term benefits, such as reducing or eliminating major organ damage in later life.^{2,20,21} More recent studies evaluating long-term (up to 4 years of follow-up) enzyme replacement therapy in children with Fabry disease demonstrate that agalsidase alfa is well tolerated, with efficacy profiles consistent with those reported in adults.^{2,20,22} However, long-term follow-up studies are required to confirm that initiation of enzyme replacement therapy for Fabry disease during childhood can prevent the irreversible, life-threatening organ damage that can occur during adulthood.

Availability of enzyme replacement therapy

Two distinct recombinant protein replacement drugs are approved for use in Europe for the treatment of Fabry patients, ie, agalsidase alfa (Replagal[®]; Shire Human Genetic Therapies, Dublin, Ireland) and agalsidase beta (Fabrazyme[®]; Genzyme Corporation, Cambridge, MA). Studies have shown that the two recombinant enzymes exhibit identical biochemical properties and are comparable with respect to amino acid

composition, specific activity, stability, and uptake by cultured fibroblasts, with only minor differences in glycosylation composition and mannose-6-phosphate receptor-mediated cellular uptake.^{23–25} Both agalsidase alfa and agalsidase beta contain recombinant human α -gal A, but they are produced differently and are approved for administration at different doses (administered as an intravenous infusion every other week at 0.2 mg/kg for agalsidase alfa over 40 minutes²⁶ or 1.0 mg/kg for agalsidase beta over 1.5–4.5 hours).^{18,27} As with other recombinant therapies, human α -gal A treatment is expensive, and at the registered dose, the annual cost of both drugs is equal at approximately €210,000 per 70 kg patient.²⁸ Agalsidase alfa is produced using cultured human skin fibroblasts with an activated promoter of the α -gal A gene, and agalsidase beta is produced by classical transduction of Chinese hamster ovary cells with human α -gal A cDNA.^{29,30}

In June 2009, Genzyme reported viral contamination in the manufacturing process of Fabrazyme, which has led to a continuous global shortage of agalsidase beta.³¹ Updated treatment recommendations advising reduced dosing regimens have consequently been published by the European Medicines Agency for adult male patients currently receiving Fabrazyme.^{31,32} Switching to agalsidase alfa (Replagal) has also been initiated for some Fabry patients, with careful monitoring. Agalsidase alfa is licensed in Europe, as well as in Canada, Japan, New Zealand, and several countries in South America.³³ It is currently an investigational product in the US. The impact of a Fabrazyme shortage and switching to Replagal with respect to the clinical outcome is currently unknown, and hence will not be discussed further. However, clinicians treating patients with Fabry disease continue to be in discussion with the European Medicines Agency to ensure all individual patients receive the best possible treatment option based on their clinical need.

Pharmacology of agalsidase alfa

Few studies have evaluated the pharmacokinetics and pharmacodynamics of agalsidase alfa.²⁹ A single intravenous dose of agalsidase alfa 0.2 mg/kg has been shown to exhibit a biphasic serum distribution and elimination profile from the circulation in both adults and children.^{21,29,34} The pharmacokinetic properties of agalsidase alfa are essentially unaffected by the dose of the enzyme, and were not significantly different between male and female patients.²⁹ Elimination half-lives were 108 ± 17 minutes in males compared with 89 ± 28 minutes in females, and volume of distribution was approximately 17% body weight in both

genders.²⁹ Clearance normalized for body weight was 2.66 and 2.10 mL/min/kg for males and females, respectively.²⁹ A short plasma half-life, <1% of the maximal plasma concentration of agalsidase alfa, detectable 8 hours after dosing, has also been reported.^{29,35,36} The intracellular half-life of agalsidase alfa is reported to be 24–48 hours.¹⁹

Following six months of agalsidase alfa treatment, 12 of 28 male patients showed altered pharmacokinetics, including an apparent increase in clearance. These changes were associated with the development of low titer antibodies to agalsidase alfa, but no clinically significant effects on safety or efficacy were observed in the patients studied.²⁹ In children aged 7–18 years, agalsidase alfa 0.2 mg/kg is cleared faster from the circulation than in adult patients with Fabry disease ($P < 0.0001$).^{21,29}

Clinical efficacy in Fabry disease

The evidence of clinical efficacy of agalsidase alfa in Fabry disease has been reported in 5 randomized clinical trials, 13 open-label studies, and 11 reports from the Fabry Outcome Survey. The Fabry Outcome Survey is one of the most comprehensive global observational database on patients with Fabry disease. Initiated and sponsored by Shire Human Genetic Therapies in 2001, the Fabry Outcome Survey aims to increase our understanding of the nature of Fabry disease and to improve the clinical management of all Fabry patients, including women and children, receiving enzyme replacement therapy with agalsidase alfa. As of September 2010, the Fabry Outcome Survey contains data on 1933 patients from 22 countries (Shire Human Genetic Therapies, data on file), and the inclusion criteria have been previously described.³⁷

Table 1 summarizes these studies according to their primary endpoints. Plasma and urinary Gb3 levels, renal endpoints (including glomerular filtration rate), and cardiac and neurological endpoints were most commonly studied. The most recent and relevant studies are discussed relating to clinical outcome in this section.

Effects on renal function

Renal dysfunction is a major complication of Fabry disease, and end-stage renal disease is most common in affected males before the fourth decade.^{3,38,39} A smaller number of heterozygous females also have a poor renal prognosis.⁵ Gb3 gradually accumulates in lysosomes in renal cells, leading to microvascular dysfunction, occlusion, and ischemia, with subsequent development of tubular atrophy, segmental and global sclerosis, and interstitial fibrosis.^{38–41} Overall, long-term enzyme replacement therapy with agalsidase alfa shows

stabilization of kidney function in patients with early stages of chronic kidney disease at baseline and slowing of progression of renal function compared with historical control subjects, even in male and female patients with advanced chronic kidney disease.^{26,42–44}

Agalsidase alfa 0.2 mg/kg every other week was initially evaluated in a randomized, double-blind, placebo-controlled clinical trial of 26 adult males with Fabry disease.²⁶ Inulin clearance and creatinine clearance were used to measure glomerular filtration rate at baseline and at week 24.²⁶ Following an initial six months of treatment with agalsidase alfa, creatinine clearance increased slightly compared with placebo, from 92.7 ± 6.2 mL/min/1.73 m² at baseline to 94.8 ± 7.7 mL/min/1.73 m² ($P = 0.02$).²⁶ Similar results were observed for glomerular filtration rate estimated by inulin clearance, although the results were not statistically significant.²⁶ During a long-term, open-label extension of this study, glomerular filtration rate was estimated using the four-variable Modification of Diet in Renal Disease method using serial measurements of serum creatinine.^{42,45} The mean (\pm standard deviation) estimated glomerular filtration rate of patients with Stage I disease (mean baseline estimated glomerular filtration rate 108.7 ± 14.1 mL/min/1.73 m², $n = 12$) or Stage II disease (mean baseline estimated glomerular filtration rate 78.6 ± 8.2 mL/min/1.73 m², $n = 8$) remained relatively stable after 4 years of treatment (mean estimated glomerular filtration rate 101.5 ± 12.4 mL/min/1.73 m² and 67.1 ± 17.0 mL/min/1.73 m², for patients with baseline Stage I and II disease, respectively).⁴² During this study, a subgroup of patients ($n = 4$) with more severe kidney dysfunction (mean baseline estimated glomerular filtration rate 47.1 ± 9.4 mL/min/1.73 m²) showed a decrease to 25.1 ± 16.4 mL/min/1.73 m², $P = 0.098$) following 48 months of enzyme replacement therapy; representing an average rate of decline of approximately 5.2 mL/min/1.73 m². None of the patients with Stage III disease at baseline progressed to end-stage renal failure during this study. More recently, Schiffmann et al demonstrated that after switching to a weekly infusion of agalsidase alfa 0.2 mg/kg despite 2–4 years of conventional treatment of agalsidase alfa 0.2 mg/kg every 2 weeks, 9 of 11 patients (82%) showed either an improvement in estimated glomerular filtration rate ($n = 3$) or a slowing in the rate of estimated glomerular filtration rate decline ($n = 6$); estimated glomerular filtration rate was calculated using the four-variable Modification of Diet in Renal Disease formula.⁴⁶ During the 24-month follow-up period on weekly dosing, the mean rate of change in estimated glomerular filtration rate was observed to slow

Table 1 Independent studies of enzyme replacement therapy with agalsidase alfa in patients with Fabry disease

Study	Study type	Duration ^a	N and gender; mean age	Primary efficacy endpoint	Primary efficacy results
Randomized controlled trials					
Schiffmann et al ²⁶	RCT, double-blind, placebo-controlled	6 months (12 doses)	26 (14 agalsidase alfa, 12 placebo) all male; mean age 34 years	Neuropathic pain	BPI score reduced from 6.2 (0.46) to 4.3 (0.73); $P = 0.02$
Moore et al ⁸²	RCT, double-blind, placebo-controlled	6 months	36 all male (26 agalsidase alfa, 10 placebo); mean age 33.7 ± 8 years	Cerebral blood flow	Abnormal resting cerebral blood flow induced by visual stimulation and acetazolamide decreased significantly following ERT; prolonged recovery of cerebral vasculature also decreased significantly following ERT
Hajjioff et al ⁷⁰	RCT, double-blind, placebo-controlled	6 months	15 all male (7 agalsidase alfa, 8 placebo); aged 25–49 years	Hearing loss	High frequency SNHL deteriorated over the first 6 months in both placebo and agalsidase alfa groups by a median of 6.8 dB ($P < 0.0001$); hearing loss subsequently improved above baseline by 1.5 dB at 18 months ($P = 0.07$); by 5 dB at 30 months ($P = 0.006$) and by 4 dB at 42 months ($P = 0.01$)
Schiffmann et al ⁷⁴	RCT, double-blind, placebo-controlled	6 months	25 all male (14 agalsidase alfa, 11 placebo)	Intraepidermal nerve fiber density	No significant difference in intraepidermal innervation density between treatment groups
Hughes et al ⁸⁸	RCT, double-blind, placebo-controlled	6 months	15 (7 agalsidase alfa, 8 placebo) all male	Myocardial Gb3 content	Left ventricular mass was reduced compared with placebo ($P = 0.041$); mean 20% reduction in myocardial Gb3 compared with a mean 10% increase in patients receiving placebo (0.42)
Open-label studies					
Kampmann et al ⁸⁹	Open-label	18 months	4 (3 female, 1 male)	LVMi	Significant reduction in LVMi ($F = 13.67$; $P = 0.002$) and mean ventricular wall thickness ($F = 8.81$; $P < 0.01$)
Hajjioff et al ⁶⁹	Open-label extension	2 years	15 all male (8 placebo); aged 25–49 years	Hearing loss	Hearing loss improved above baseline by 2.1 dB at 18 month ($P = 0.02$) and by 4.9 dB at 30 months ($P = 0.004$)
Schiffmann et al ⁶⁵	Open-label extension	3 year follow-up	26 all male	Neuropathic pain, sweat function	Overall, 12–18 months ERT reduced pain interference scores of 1.2 ± 0.48 ($P = 0.012$); sweat function improved 24–72 hours post-agalsidase alfa infusion ($0.57 \pm 0.71 \mu\text{L}/\text{mm}^2$) and normalized in 4 anhidrotic patients
Baehner et al ⁸⁴	Open-label	Up to 55 weeks	15 all females	Plasma and urinary Gb3, LVMi	Increased clearance of plasma and urinary Gb3 at 13, 27, and 41 weeks; mean urine sediment Gb3 levels decreased progressively from baseline to 13, 27, and 41 weeks, with a significant decrease from baseline to week 13 ($P = 0.03$); decrease in plasma Gb3 was also observed in this study, with a significant change from baseline ($P = 0.029$) and % change from baseline ($P < 0.001$) at week 13. LVMi reduction from baseline at 27 weeks ($P = 0.003$) and 41 weeks ($P = 0.039$), and a reduction in QRS duration at 27 weeks ($P = 0.007$); other changes included significant improvement in QoL, and no deterioration in renal function
Dehout et al ⁶⁷	Open-label, no controls	Up to 1 year	11 (9 males and 2 females); mean age 36.2 ± 3 years	Abdominal pain and diarrhea	Severity and frequency (both $P < 0.02$) of abdominal pain decreased following 6 months of ERT

Schiffmann et al ¹²	Open-label extension	Up to 4.5 years follow-up	25 all males; mean age 36.8 years	eGFR, and antibody response	eGFR remained stable in subgroups of patients with mild to moderate (GFR > 90 mL/min or 60–89 mL/min, Stage I and II, respectively) baseline CKD; the slope of decline in GFR decreased in patients with more advanced baseline CKD (GFR 30–59 mL/min, Stage III) compared with historical controls; in Stage III patients, mean eGFR fell from 47.1 ± 9.4 mL/min/1.73 m ² to 24.8 ± 14.5 mL/min/1.73 m ² ($P = 0.098$) after 48 months of treatment (mean rate of decline approximately 5.2 mL/min/1.73 m ² /year; 56% of patients showed an IgG antibody response to agalsidase alfa. Increased clearance of Gb3, particularly in boys; initial beneficial response of cardiac autonomic innervation, microalbuminuria decreased in 3 of 4 children with baseline microalbuminuria
Ries et al ²²	Open-label, multicenter	6 months	24 children (19 boys and 5 girls); mean ages 11.5 and 13.5 years (boys and girls, respectively)	Plasma Gb3	Mean baseline fasting plasma Gb3 was above normal (7.91 ± 0.71 nmol/mL) in boys and normal (2.54 ± 0.25 nmol/mL) in girls; above normal mean baseline fasting plasma Gb3 in boys was significantly reduced by agalsidase alfa therapy ($P < 0.001$) whereas normal mean baseline fasting plasma Gb3 levels in girls did not change; mean eGFR, cardiac structure and function were normal and unchanged throughout
Ries et al ²¹	Open-label, multicenter	25 weeks	24 children (19 boys, 5 girls); mean age 11.8 years	Plasma Gb3	Baseline mean plasma Gb3 (9.12 ± 2.61 nmol/min) was significantly reduced by 50% in all 5 dosing groups; this reduction was independent of dose or dose frequency
Clarke et al ³⁶	Open-label, multiple dosing	10 week	18, all male	Plasma Gb3	During 24 month follow-up period after switching from EOW to weekly infusions, the mean rate of change in GFR was observed to slow from -8.0 ± 0.8 mL/min/1.73 m ² /yr to -3.3 ± 4.7 mL/min/1.73 m ² /yr ($P = 0.01$ versus EOW)
Schiffmann et al ¹⁶	Open-label, weekly dosing of 0.2 mg/kg agalsidase alfa	24 months	41, all male	eGFR	Above normal mean baseline plasma Gb3 in boys were reduced to within normal levels after 12–23 weeks of agalsidase alfa therapy, whereas normal mean baseline plasma Gb3 levels in girls declined slightly; BPI and pain-related QoL scores decreased in most patients; increases in sweat volumes were recorded in most measured patients during the period of treatment
Ramaswami et al ²	Open-label, multicenter	23 weeks	13 children (9 boys, 4 girls), median age 11 years (range 3.5–18 years)	Plasma and urinary Gb3, pain, and sweating	Mainz severity score was reduced after 1 year ($P < 0.001$) and continually improved over 4 years; BPI was reduced after 1 year ($P = 0.001$) and was sustained through 4 years; mean LVMJ decreased from baseline after 1 year ($P < 0.001$) and remained reduced through 4 years; overall, mean eGFR remained constant during study (from 91.0 ± 31.2 mL/min/1.73 m ² at baseline to 91.0 ± 25.6 mL/min/1.73 m ² after 4 years of ERT)
Whybra et al ⁶	Open-label	4 years	36 all female; mean age 47 years	Pain, eGFR	

(Continued)

Table 1 (Continued)

Study	Study type	Duration ^a	N and gender; mean age	Primary efficacy endpoint	Primary efficacy results
Schiffmann et al ²⁰	Open-label extension	4 years (6 months, plus up to 3.5 years)	17 (16 boys and 1 girl); age range 7.3–18.4 years	Plasma and urinary Gb3	Mean urine sediment Gb3 levels were reduced to normal levels ($P < 0.05$ compared with baseline during 1.5 to 4 years); BPI scores decreased significantly ($P < 0.001$); LVM indexed to height and eGFR remained stable throughout
West et al ⁴⁷	Pooled analysis (3 prospective RCT and their open-label extension studies)	Up to 4.5 years (mean 2.0 ± 1.0 year)	108 males; mean age 34 years	Mean rate of change in GFR	Mean rate of change in GFR for entire study population was -4.8 ± 10.6 mL/min per $1.73 \text{ m}^2/\text{yr}$ ($P = 0.0003$; when 8 patients with hyperfiltration were removed from analysis, the mean rate of change of GFR was -2.9 ± 8.7 mL/min per $1.73 \text{ m}^2/\text{yr}$ ($P = 0.002$))
Fabry Outcome Survey studies					
Beck et al ⁴⁸	Fabry Outcome Survey	Up to 2 years	545; 314 of whom were receiving treatment	Multiple	Stabilization of renal function following 1–2 years of ERT treatment in patients with mild to moderate renal dysfunction (GFR between 60 and 90 mL/min/ 1.73 m^2 and between 30 and 60 mL/min/ 1.73 m^2 , Stages II and III, respectively) baseline renal dysfunction; reduction in LVH from baseline; improved pain scores and quality of life were also reported
Hajioff et al ⁷¹	Fabry Outcome Survey	1 year	26	Changes in hearing thresholds	In patients with mild or moderate hearing loss at baseline, hearing thresholds improved significantly by 4–7 dB at most frequencies ($P < 0.05$); no significant change was observed for patients with normal hearing or severe hearing loss at baseline
Hoffmann et al ⁶⁴	Fabry Outcome Survey	2 years	545 (264 female and 281 male)	Pain	Statistically significant reduction in pain ($P < 0.05$), mean health-related QoL utility score was improved and maintained after 2 years ($P < 0.05$)
Schwartz et al ⁴⁹	Fabry Outcome Survey	up to 4.7 years	201 (70 female and 131 male); aged 20–60 years	eGFR	Renal function declined significantly ($P < 0.05$) in the year prior to treatment; renal function decline was halted after 1 year of treatment and sustained for up to 2 years
Hoffmann et al ⁶³	Fabry Outcome Survey	3 years	752 (393 female, 359 male); 58% of patients treated with agalsidase alfa	Pain	Significant reduction in pain after 3 years of ERT ($P < 0.05$)
Hoffmann et al ⁶⁸	Fabry Outcome Survey	2 years	342	GI symptoms	Reduced prevalence of abdominal pain, with a statistically significant decrease in male patients and in children after 1 year of ERT
Feriozzi et al ⁴³	Fabry Outcome Survey	3 years	165 (115 male and 50 female)	eGFR	In males, eGFR declined with Stage I/II renal disease (from 115 ± 22.2 to 98.3 ± 27.3 and from 76.5 ± 8.1 to 66.3 ± 21.6 mL/min/ 1.73 m^2 , respectively; both $P < 0.01$), and was stable in Stage III (from 49.1 ± 6.6 to 42.8 ± 19.9 mL/min/ 1.73 m^2); In females, eGFR was stable in stages I and III renal disease (from 103.2 ± 10.4 to 96.4 ± 17.8 and from 49.5 ± 8.3 to 46.3 ± 13.8 mL/min/ 1.73 m^2 , respectively, $P = 0.46$ and 0.28 , respectively) but declined in Stage II (from 72.5 ± 8.3 to 67.3 ± 13.6 mL/min/ 1.73 m^2 ; $P = 0.01$)

Cybulka et al ⁵⁰	Fabry Outcome Survey	2 years	36 (34 male and 2 female); mean age at transplantation: 37.6 ± 10.9 years	eGFR	During 2 years of ERT, there was a slight decrease in eGFR (from baseline eGFR 59.2 mL/min/1.73 m ² versus 51.1 mL/min/1.73 m ² at 2 years)
Kampmann et al ⁶¹	Fabry Outcome Survey, pooled analysis, retrospective study	3 years	45 (34 male, 11 female); mean age 39.8 years, 93% white	LVM	Data from 45 adult patients who had received ±36 months of ERT with agalsidase alfa were analyzed; of the 14 patients with baseline LVH, LVM decreased significantly after 1 year ($P = 0.008$) in 9 patients and after 3 years ($P = 0.037$) in 10 patients; of the 31 patients without baseline LVH, LVM significantly increased after 1 year ($P = 0.002$) and there was no significant change from baseline in 10 patients after 3 years. Sustained reduction in LVM in patients with baseline cardiac hypertrophy ($P = 0.011$), BPI, and QoL improved significantly ($P = 0.0023$ and $P = 0.0483$, respectively)
Mehta et al ⁴⁴	Fabry Outcome Survey	5 years	181 (55 female and 126 male); mean age 41.9 ± 14.5 years	Multiple	

Note: *Agalsidase alfa dose at 0.2 mg/kg every other week unless otherwise stated.

Abbreviations: eGFR, estimated glomerular filtration rate; Gb3, globotriaosylceramide; LVM, left ventricular mass; LVMI, left ventricular mass index; GI, gastrointestinal; RCT, randomized controlled trial; BPI, brief pain inventory scores; QoL, quality of life; SNHL, sensorineural hearing loss; ERT, enzyme replacement therapy; CKD, chronic kidney disease; EOW, every other week; LVH, left ventricular hypertrophy.

to -3.3 ± 4.7 mL/min/year ($P = 0.01$ versus every other week). Notably only two patients failed to improve their estimated glomerular filtration rate.⁴⁶

In a pooled analysis of three randomized, placebo-controlled trials and their open-label extension studies involving male patients, the annual rate of decline in estimated glomerular filtration rate was 7.0 mL/min/1.73 m² for 6 months of placebo treatment and 2.9 mL/min/1.73 m² for 12–54 months of agalsidase alfa treatment, suggesting that agalsidase alfa treatment may slow the natural rate of glomerular filtration rate decline in male Fabry patients.⁴⁷

Several studies from the analysis of patients in the Fabry Outcome Survey have reported that treatment with agalsidase alfa stabilizes estimated glomerular filtration rate in both male and female Fabry patients.^{43,44,48–50} Following 3 years of treatment, the overall change in estimated glomerular filtration rate for a large number of patients ($n = 165$, including 115 males and 50 females) receiving agalsidase alfa was -1.68 mL/min/1.73 m²/year for patients with baseline proteinuria <0.50 g/24 hours ($n = 40$) and -3.98 mL/min/1.73 m²/year for patients with baseline proteinuria >0.50 g/24 hours ($n = 14$).⁴³ The most recent report from the Fabry Outcome Survey describes the observations in patients who have been treated with agalsidase alfa for 5 years. The mean annual decline in estimated glomerular filtration rate was 2.46 mL/min/1.73 m² ($n = 150$, males and females).

The efficacy of agalsidase beta replacement therapy on measures of kidney function was evaluated in two randomized controlled trials and in open-label studies.^{51–54} Creatinine clearance and estimated glomerular filtration rate remained stable after more than 3 years of treatment with agalsidase beta.^{51,54} Consistent with the results for agalsidase alfa, renal disease progression was observed for some patients receiving agalsidase beta who had more advanced disease at baseline.^{51,54}

These results suggest that disease progression is related to disease severity in Fabry patients, thus early treatment could potentially provide greater benefit because there seems to be a point of no return, when the enzyme replacement therapy response is significantly reduced and renal failure is most probably irreversible.¹⁶

Effects on cardiac manifestations

Before the development of enzyme replacement therapy, cardiac involvement was the most common cause of premature mortality in Fabry disease.^{55,56} Cardiac hypertrophy, arrhythmia, valvular insufficiency, and cardiac conduction

abnormalities are common cardiac manifestations in Fabry disease.^{12,55,57} A small number of studies and observational data have provided evidence showing that 0.6–4.0 years of treatment with agalsidase alfa results in a progressive decrease in interventricular septal thickness and a reduction or stabilization of left ventricular mass index.^{48,58–60}

The effects of agalsidase alfa on cardiac structure and function were assessed in a randomized, double-blind, placebo-controlled study. In this study by Hughes et al, myocardial Gb3 content and reduction in left ventricular mass, as measured by magnetic resonance imaging, was assessed in 15 adult male Fabry patients following 6 months of enzyme replacement therapy with agalsidase alfa. Ten of the 15 patients enrolled had left ventricular hypertrophy at baseline, as measured by magnetic resonance imaging. Left ventricular mass increased in the placebo group by 21.8 g and decreased in the enzyme replacement therapy group by 11.5 g ($P = 0.041$). This equated to a mean increase in left ventricular mass index for the placebo group of 12 g/m² compared with a decrease in the treated group of 6.4 g/m² ($P = 0.02$ versus placebo).⁵⁸ Consistently, there was also a reduction in myocardial Gb3 content, albeit not statistically significant.⁵⁸ These results were confirmed in the corresponding 2-year open-label extension study. In addition, left ventricular posterior and septal wall thickness was significantly decreased, suggesting remodeling had occurred. Throughout the 2-year extension trial, significant reductions in plasma Gb3 were maintained, reflecting increased metabolism of Gb3 deposits and a possible reduction in its pathogenic tissue storage.⁵⁸ Echocardiographic data evaluation revealed a reduction in mean ventricular wall thickness ($P < 0.05$) and height-adjusted left ventricular mass (LVM/h) following 1–2 years for agalsidase alfa treatment in a large cohort of Fabry Outcome Survey patients with enlarged hearts at baseline.⁴⁸ In a case study of four patients (three female heterozygotes and one male hemizygote), 18 months of agalsidase alfa treatment resulted in a significant continuous reduction in left ventricular mass indexed to body surface area ($F = 13.67$; $P = 0.002$) and mean ventricular wall thickness ($F = 8.81$; $P < 0.01$).⁵⁹ More recently, Kampmann et al assessed the effectiveness of agalsidase alfa on LVM/h in male and female Fabry patients with and without baseline left ventricular hypertrophy.⁶¹ After 12 months of treatment in Fabry patients with left ventricular hypertrophy at baseline ($n = 14$), LVM/h decreased significantly by 9.2 ± 7.9 g/m^{2.7} ($n = 9$; $P = 0.008$). After 3 years of treatment in this subgroup, LVM/h decreased significantly by 5.1 ± 7.5 g/m^{2.7} ($n = 10$; $P = 0.037$), suggesting that enzyme replacement therapy was associated with a

significant reduction in LVM/h in patients with baseline left ventricular hypertrophy.⁶¹ After 12 months of treatment, in Fabry patients without baseline left ventricular hypertrophy ($n = 31$), LVM/h increased significantly by 3.6 ± 5.7 g/m^{2.7} ($n = 28$; $P = 0.002$). After 3 years of treatment in this subgroup, the increase in LVM/h was not significantly different from baseline in 10 patients (2.1 ± 7.9 g/m^{2.7}) suggesting stabilization of LVM/h in patients without baseline left ventricular hypertrophy. Long-term (up to 5 years) treatment with agalsidase alfa in Fabry patients has been reported from the Fabry Outcome Survey observational database.⁴⁴ In this population of males and females, stabilization or improvement in left ventricular mass index was seen in 71.9% (23/32) patients with baseline left ventricular hypertrophy, and in 92% (23/25) patients without baseline left ventricular hypertrophy.⁴⁴ In the group of 25 patients without baseline left ventricular hypertrophy, agalsidase alfa treatment resulted in small, statistically insignificant decreases in mean left ventricular mass index at years 1, 2 and 3, and a small, statistically insignificant increase in mean left ventricular mass index after 5 years.⁴⁴ Notably, a significant improvement in ventricular function (midwall fractional shortening) was observed after years 1, 2, and 3 for patients with baseline left ventricular hypertrophy, and after 1 and 2 years in patients with normal baseline left ventricular mass index. Overall, midwall fractional shortening stabilized or improved in 62.1% (18/32) of subjects with baseline left ventricular hypertrophy, and in 95.2% (20/25) of subjects without baseline left ventricular hypertrophy.⁴⁴

Interestingly, a recent study by Kampmann et al evaluated whether signs of cardiac manifestations were present in a population of 20 pediatric patients with Fabry disease (aged ≤ 18 years).⁶² Mean baseline LVM/h was 45 ± 2.3 g/m^{2.7} and 47 ± 3.4 g/m^{2.7} in boys ($n = 8$) and girls ($n = 12$), respectively. All patients had LVM/h^{2.7} greater than the 75th percentile compared to healthy controls.⁶² Following a mean follow-up of 26 months, 85.7% (12/14) patients showed a mean increase of 7.5 ± 3.2 g/m^{2.7} in LVM/h. Analyses of heart rate variability revealed that male but not female Fabry patients had significantly reduced heart rate variability, suggesting a reduction in parasympathetic stimulation of the heart ($P < 0.05$).⁶² The authors of this study concluded that progressive cardiac involvement is common in pediatric Fabry patients.⁶²

Effects on pain and quality of life

Acute neuropathic pain is a common early symptom of Fabry disease and occurs in about 80% of patients.^{37,63} Other neurological manifestations may include abnormal gut motility and pain, which have a negative impact on quality

of life.^{63,64} Small fiber neuropathy is a cause of neuropathic pain.^{5,65} Acroparesthesia and hypohidrosis can also adversely affect quality of life.^{65,66}

The effect of agalsidase alfa 0.2 mg/kg every other week on neuropathic pain was initially evaluated in a randomized, double-blind, placebo-controlled clinical trial of 26 adult males with Fabry disease.²⁶ Following an initial six months of treatment with agalsidase alfa, mean (\pm standard error) Brief Pain Inventory severity scores, reported as a primary endpoint, declined from 6.2 ± 0.46 to 4.3 ± 0.73 , compared with no significant change in the placebo group ($P = 0.02$).²⁶ Pain-related quality of life was also reduced for patients treated with agalsidase alfa versus placebo ($P = 0.05$).²⁶ Four of 11 patients treated with agalsidase alfa who were taking neuropathic pain medications at baseline discontinued these medications after 1–8 weeks compared with none of the patients ($n = 11$) taking neuropathic pain medications and receiving placebo ($P = 0.03$).²⁶ Patients in the placebo group experienced a similar decline in Brief Pain Inventory severity scores 6 months after receiving agalsidase alfa treatment in the open-label extension study.⁶⁵ No further reductions in pain scores were thereafter reported.

Several reports from the Fabry Outcome Survey indicate that agalsidase alfa has a beneficial effect on pain and quality of life.^{44,48,63,64} Recent reports from the Fabry Outcome Survey show that after 5 years of agalsidase alfa treatment, mean average pain was reduced from baseline.⁴⁴ Reductions were significant at 2, 3, and 5 years ($P = 0.0015$, $P = 0.0128$, and $P = 0.023$, respectively). Brief Pain Inventory severity scores also decreased, with significant reductions at 2 and 5 years ($P = 0.0076$ and $P = 0.0137$, respectively).⁴⁴ Clinically significant reductions (defined as improvement of >1 point on the Brief Pain Inventory) were observed for “average pain” ($n = 32$; 60.4% patients) and “worst pain” ($n = 26$; 53.1% patients).⁴⁴ The EuroQoL questionnaire used to assess quality of life in the Fabry Outcome Survey revealed significant improvements compared with baseline following 1, 2, and 5 years of enzyme replacement therapy ($P = 0.0247$, $P = 0.0026$, $P = 0.0483$, respectively), suggesting that agalsidase alfa may improve quality of life in both male and female Fabry patients.⁴⁴

Agalsidase alfa has been reported to provide relief of gastrointestinal symptoms, such as abdominal pain and diarrhea.^{67,68} Dehout et al reported a decrease in frequency and severity of abdominal pain and diarrhea following 6 months of agalsidase alfa treatment.⁶⁷ Following 1 year of agalsidase alfa treatment in both Fabry adults and children, the prevalence of abdominal pain, present in more than 50%

of patients ($n = 178$) prior to enzyme replacement therapy, was significantly reduced in adults and children.⁶⁸

Effects on other organs/systems

Ear, nose and throat

Progressive hearing impairment is a common manifestation in Fabry disease.^{69,70} Agalsidase alfa treatment for 6 months compared with placebo was reported to reverse hearing deterioration for 15 male Fabry patients in a randomized, double-blind study.⁷⁰ In an open-label extension of this study, hearing loss slightly improved above baseline by 5 dB after 30 months of agalsidase alfa treatment ($P = 0.004$).⁶⁹

Similarly, Fabry Outcome Survey data ($n = 26$) show improvements of similar magnitude (1 and 7 dB) following agalsidase alfa treatment over 12 months in Fabry patients with moderately abnormal hearing thresholds at baseline.⁷¹ Hajioff et al conclude that agalsidase alfa treatment can stabilize and possibly improve hearing for Fabry patients who have not progressed to severe hearing loss.⁷¹ Clinical evidence is lacking to support any definitive conclusions that enzyme replacement therapy has any effect on hearing loss.

Central nervous system

Central nervous system manifestations of Fabry disease consist of cerebrovascular disease, including large vessel ectasia, large-vessel occlusive disease, and small vessel occlusive disease.⁷²

A 3-year, open-label extension study reported that agalsidase alfa significantly improved thermal sensation, especially in the foot, as well as improved sweat function.⁶⁵ A significant improvement in sympathetic skin responses in seven male patients during 2 years of agalsidase alfa has also been reported.⁷³ Nerve fiber regeneration has not yet been observed.⁷⁴

Data from the Fabry Outcome Survey have demonstrated that cerebrovascular disease often coexists with advanced renal or cardiac disease.⁷⁵ A recent prospective study of cryptogenic stroke in young adults ($n = 721$), using an α -gal A enzyme-screening assay, suggested that up to 1.2% of patients with stroke aged between 18–55 years might have Fabry disease.⁷⁶ However, the prevalence of unrecognized Fabry disease among young patients with ischemic strokes is unknown.^{76–78} The significant prevalence rate discrepancies reported in these studies (first ischemic stroke, prevalence range 0–2.17) is most probably due to differences in study populations, as outlined in the Wozniak et al study.⁷⁷ Atypical variants of Fabry disease with late-onset cerebrovascular disease have been observed in a Belgian cohort of young patients with

cerebrovascular disease, but the clinical relevance of this remains unclear at present.⁷⁹ Cerebrovascular complications of stroke and transient ischemic attacks have been reported in 5%–27% of heterozygous Fabry females.^{5,37,80} One study has shown a higher prevalence of ischemic stroke and transient ischemic attacks in female Fabry patients compared with men (27% versus 12% for females and males, respectively).³⁷

Changes in cerebral blood flow velocities have been published for Fabry patients treated with agalsidase alfa.^{72,81,82} Moore et al reported a significant decrease in cerebral hypoperfusion versus placebo following 6 months of treatment with agalsidase alfa in a randomized controlled trial of 26 male Fabry patients.^{72,82} No impact on the incidence of stroke was reported.^{72,82} In the open-label extension study, Moore et al demonstrated a reduction in elevated cerebral blood flow velocities after 18 months of agalsidase alfa therapy.⁸¹ The relationship between increased risk of stroke in Fabry disease and elevated regional cerebral blood flow remains unclear.⁷²

Effects in women

In contrast with the long-held assumption that women with Fabry disease are rarely symptomatic, the majority of females who are heterozygous for disease causing mutations in the α -gal A gene report clinical features of Fabry disease.^{5,6,83} In one study, severe manifestations of disease were reported. For example, 77% of women reported neurological involvement, 59% cardiac involvement, and 40% renal involvement.⁸³ Results from the Fabry Outcome Survey database and the baseline demographic data within it have been published recently, demonstrating that enzyme replacement therapy should not be restricted to hemizygous men, but should also be considered for heterozygous females and children.³⁷ In 165 patients with Fabry neuropathy (including 50 female patients), Feriozzi et al demonstrated that enzyme replacement therapy with agalsidase alfa for 3 years might slow the decline in renal function in both male and females.⁴³ In women, the mean estimated glomerular filtration rate decline was 1.20 ± 3.28 mL/min/1.73 m²/year, with a mean reduction in estimated glomerular filtration rate over 3 years of 5.0 mL/min/1.73 m² ($P < 0.001$).⁴³

A single-center, open-label study of agalsidase alfa performed in 15 adult women with Fabry disease. In this clinical study by Baehner et al, female patients received enzyme replacement therapy for up to 55 weeks. Overall, agalsidase alfa in heterozygous females was demonstrated to regress left ventricular hypertrophy, improve quality of life, stabilize renal function, and reduce blood and urine

glycolipid levels.⁸⁴ Similarly, this study confirmed previous reports in male Fabry patients pertaining to the safety and pharmacokinetics of agalsidase alfa.⁸⁴ A significant decrease in left ventricular mass index from baseline was observed at 27 weeks ($P = 0.003$) and 41 weeks ($P = 0.039$), and a significant reduction in QRS interval was observed at week 27 ($P = 0.007$).⁸⁴ Significant improvements in physical and general health subscales and the physical component score of the Short Form-36 questionnaire were also reported after 6 months of agalsidase alfa treatment.⁸⁴ Evaluation of these 15 women continued in a 4-year, open-label extension study to evaluate the long-term response of females with Fabry disease to agalsidase alfa treatment. A total of 40 female patients were evaluated. Overall, in this long-term evaluation of the effects of enzyme replacement therapy on kidney function in women with Fabry disease, agalsidase alfa appeared to stabilize or improve estimated glomerular filtration rate in this cohort.⁶ Patients with Stage I and III chronic kidney disease remained mostly stable during the treatment period, only one of nine Stage I chronic kidney disease patients progressed to Stage II chronic kidney disease, and none of the Stage III chronic kidney disease patients ($n = 3$) showed disease progression.⁶ The subgroup of patients ($n = 20$) with moderately reduced kidney function at baseline (Stage II) showed a significant increase in estimated glomerular filtration rate after 1 year of treatment, which remained improved during 4 years of treatment.⁶ Six women who initiated angiotensin-converting enzyme inhibitors or angiotensin receptor blockers during the study demonstrated stable estimated glomerular filtration rate thereafter.⁶

Proteinuria has been reported in approximately 41% of women enrolled in the Fabry Outcome Survey, compared with 54% of men, although women with Fabry disease rarely develop end-stage renal failure.⁴⁸ Following 4 years of treatment with agalsidase alfa, proteinuria was significantly reduced to a mean of 339 ± 230 mg/24 hours in 11 patients (35%) with proteinuria ≥ 300 mg/24 hours at baseline (mean 858 ± 751 mg/24 hours, $P < 0.01$).⁶ Brief Pain Inventory severity scores were reduced from 4.6 ± 2.9 at baseline to 3.3 ± 2.9 after 12 months ($P = 0.001$) and remained significantly reduced during the 4-year study.⁶ Left ventricular hypertrophy (defined as left ventricular mass ≥ 48 g/m^{2.7}) was present in 69% of females (25 of 36 patients) at baseline.⁶ LVM/h was significantly reduced after 12 months of agalsidase alfa treatment in these 25 females with baseline left ventricular hypertrophy. Of these 25 patients, 13 (52%) experienced decreases in LVM/h $> 20\%$, seven (28%) demonstrated decreases in LVM/h of 10%–20%, and two (8%)

demonstrated decreases between 7.2 and 3.5%. After 4 years of treatment, seven of 25 patients with baseline left ventricular hypertrophy were classified as having normal LVM/h.⁶ Only one of the subgroup of 11 females with normal baseline LVM/h (47.7 g/m^{2.7}) was reclassified as having left ventricular hypertrophy at study completion (50.3 g/m^{2.7}).⁶ Based on the results from the Fabry Outcome Survey, Whybra et al suggest that women with any signs or symptoms of Fabry disease should be considered for enzyme replacement therapy.⁶

Effects in children

Observations from pediatric studies are consistent with the safety and efficacy profiles reported for agalsidase alfa in adults.^{2,20,22,115} Efficacy and safety results of an initial 23-week, multicenter, open-label Fabry Outcome Survey trial in nine boys and four girls have been reported.² The median age at treatment initiation was 11 years, and agalsidase alfa 0.2 mg/kg was administered as a 40-minute infusion every 2 weeks. Only one male patient developed IgG antibodies during treatment.² In this study, agalsidase alfa was well tolerated, and infusion-associated reactions were mild and resolved without sequelae.² At baseline, all boys had increased plasma Gb3 levels, whereas plasma Gb3 concentrations were all within the normal range for girls.² After 12 and 23 weeks of treatment, plasma Gb3 levels decreased to near normal levels in boys and declined slightly in girls. For all boys, the mean urinary Gb3:sphingomyelin ratio decreased from 4.6 at baseline to 2.5 after 23 weeks of treatment.² In girls, the mean urinary Gb3:sphingomyelin ratio decreased from 0.7 at baseline to 0.3 at week 23.² The study also demonstrated reduced Brief Pain Inventory scores for “pain at its worst” from a mean baseline score of 2.8 to 1.5 at week 23, and “pain on average” from a mean baseline score of 2.2 to 0.9 at week 23.² Pain-related quality of life scores, including interference of pain on general activity, mood, walking ability, normal work, relationships, and enjoyment of life also decreased, and eight patients reported no pain interference in any quality of life categories at study end.² Increased sweat volumes were recorded after 23 weeks of treatment with agalsidase alfa.² Six of 10 patients who experienced acroparesthesia at baseline reported an improvement after 23 weeks of agalsidase alfa treatment.²

Similar clinical benefits have been documented in a second open-label study, which assessed the efficacy and safety of agalsidase alfa treatment for six months in 24 children with a mean age of 11.8 years.²² Overall,

renal function remained normal following six months of enzyme replacement therapy (mean baseline estimated glomerular filtration rate = 121 ± 5.0 mL/min/1.73 m² and mean estimated glomerular filtration rate after 26 weeks = 116 ± 3.9 mL/min/1.73 m²).²² Mean plasma Gb3 was significantly reduced among the 19 boys with elevated baseline fasting plasma Gb3 ($P < 0.001$).²² In contrast, plasma Gb3 levels did not change among the five girls with normal baseline plasma Gb3 concentrations.²² Cardiac structure and function were normal and did not change during the study.²² In both boys and girls, mean LVM/h showed a nonsignificant decrease after 25 weeks of treatment.²² Of note, three children with high-normal LVM/h at baseline (>40 g/m^{2.7}, two girls and one boy) demonstrated a 15% mean decrease in LVM/h after 25 weeks of enzyme replacement therapy.²² Heart rate variability, which was decreased in boys compared with girls at baseline, improved significantly in boys.²² In addition, 55% of patients who were receiving anticonvulsive medication for neuropathic pain were able to decrease or cease their consumption.²²

Long-term extension data of the latter study have been recently published.²⁰ Schiffmann et al demonstrated that agalsidase alfa treatment for 4 years was well tolerated in children.²⁰ Twenty-four children (19 boys and five girls), 10 of whom were treated for 4 years, showed significant reductions in pain scores, as well as sustained and improved heart rate variability in boys, estimated glomerular filtration rate, and LVM/h, which remained stable throughout the 4-year study period.²⁰ Overall, >93% of adverse events were reported as mild or moderate in severity for the 24 patients, and <10% were deemed by the study investigators to be possibly related (6.5%) or probably related (3.4%) to study treatment.²⁰ Only one male patient tested positive for IgG antibodies during this study.²⁰

Ramaswami et al have recently evaluated the safety of enzyme replacement therapy with agalsidase alfa in young children enrolled in the Fabry Outcome Survey.⁸⁵ This retrospective chart review identified eight children (mean age 5.0 ± 1.6 years) in the Fabry Outcome Survey who began treatment with agalsidase alfa 0.2 mg/kg intravenously every other week when younger than 7 years. Vital signs and adverse events were monitored throughout the study period. Glomerular filtration rate was estimated, and LVM/h (2.7) was assessed using echocardiography. Patients received 1.2–6.7 years of treatment (mean 4.2 years). Infusion reactions occurred in three patients and were of mild or moderate severity. IgG antibodies to agalsidase alfa were found in one patient who experienced two mild and

one moderate infusion reactions. Mean glomerular filtration rate was within the normal range at baseline and remained normal. Left ventricular mass index was above the 75th percentile for age-matched children in five of six patients evaluated at baseline. Only two patients exceeded this threshold at their last assessment. This study further emphasizes the importance of early diagnosis and follow-up of children with Fabry disease.⁸⁵ The burden of Fabry disease in children is mostly due to neurological manifestations.³⁴ Despite the small number of pediatric patient studies, Fabry Outcome Survey results to date reveal an overall improvement in pain, with either improvement or no change from baseline in most patients.³⁴ Infusion-associated reactions in pediatric Fabry Outcome Survey patients were generally mild and similar to those reported in adults.³⁴

Early diagnosis is paramount, because renal pathology has been described even in young children (age range 7–18 years) who may have not yet developed overt proteinuria or decline in glomerular filtration rate; overt proteinuria has been reported in children as young as 10 years of age.^{86–88} Tøndel et al performed kidney biopsies in nine children, including two boys receiving enzyme replacement therapy.⁸⁶ Notably, accumulation of Gb3 was found in nearly 7/9 (80%) of the young patients as well as glomerular, interstitial, or vascular lesions, even prior to the development of clinical renal functional impairment.⁸⁶ However, 7/9 patients also had early onset microalbuminuria, thus emphasizing the importance of regular and early renal follow-up.⁸⁶ Other pediatric studies have highlighted the importance of accurate diagnosis and careful monitoring for Fabry disease, because specific symptoms have been associated with greater disease severity and poorer prognosis.^{89,90} For example, retinal vascular tortuosity has been recognized as a predictive factor of a more severe illness in Fabry children.^{89,91} Allen et al investigated the correlation with Fabry genotype and systemic disease severity in children with ophthalmic manifestations.⁸⁹ Overall, ophthalmic manifestations were found in 76% of children predicted to have complete loss-of-function α -Gal A mutations ($P=0.003$) and in only one patient with a genotype predicted to give some residual α -Gal A function.⁸⁹ Thirteen (50%) of the 26 Fabry children were found to have corneal verticillata.⁸⁹ Seven children (27%) had evidence of retinal vascular tortuosity.⁸⁹ All seven children (four girls and three boys) had more severe systemic disease suggestive of autonomic neuropathy, such as diarrhea and syncope.⁸⁹ In another Fabry Outcome Survey study that investigated the epidemiology of hearing impairment and tinnitus in children with Fabry disease, Keilmann et al reported greater disease

severity scores, measured by signs and symptoms questionnaires, in children with tinnitus.⁹⁰

Comparator studies: agalsidase beta versus agalsidase alfa

The clinical outcomes of agalsidase beta or agalsidase alfa in Fabry disease have been measured in a number of independent studies against a variety of endpoints. Most of these studies measured subclinical parameters rather than clinical outcomes per se.⁹² Both formulations are reported to provide several clinical benefits in the treatment of Fabry disease. However, comparison of therapeutic efficacy between the two distinct products is limited, probably due to the small number of randomized controlled trials, the small number of patients enrolled in these studies, different patient inclusion criteria, disease heterogeneity, short trial durations, as well as differences in outcome parameters and infused doses.^{28,35,93,94}

To date, direct in vitro studies or studies in mice have shown no important differences between the two available enzyme preparations.^{24,25,28,35,95–98} A few recent head-to-head clinical studies of the relative efficacies of agalsidase beta compared with agalsidase alfa have been conducted.^{28,94,99,100} These trials are summarized in Table 2.

Vedder et al conducted an open-label prospective study comparing agalsidase alfa at its registered dose of 0.2 mg/kg every other week with an equivalent dose of agalsidase beta at 0.2 mg/kg every other week.²⁸ The primary endpoint for this study was reduction in left ventricular mass after 1 and 2 years of enzyme replacement therapy. Twenty-six of the 29 patients enrolled had baseline left ventricular hypertrophy (13/14 subjects in the agalsidase alfa group and 13/15 subjects in the agalsidase beta group). There was no difference in median cardiac mass between groups at baseline ($P=0.48$). Overall, changes in left ventricular mass ($P=0.3$) and other disease parameters did not differ between the two groups following 1–2 years of enzyme replacement therapy. A slightly increased decline in left ventricular mass observed in the agalsidase beta group (15% versus 11% after 12 months and 11% versus 5% at 24 months, for beta versus alfa, respectively) was not deemed statistically significant by the study authors.²⁸ Vedder et al also reported that α -gal A antibodies in male adults occurred in approximately one-third of treated patients, but twice as often ($P=0.005$) with agalsidase beta when dosed at 1.0 mg/kg every other week (8/10 patients) compared with agalsidase alfa at 0.2 mg/kg every other week (4/10 patients). This difference was not observed with agalsidase beta at the lower dose of 0.2 mg/kg every other week (6/10 patients).⁹⁹

Table 2 Comparison studies of enzyme replacement therapy with agalsidase alfa and agalsidase beta in patients with Fabry disease

Reference	Study type	Duration	N and gender; mean age ^{a,b}	Primary efficacy endpoint	Primary efficacy results
Vedder et al ²⁸	Open-label	24 months	34 (18 male, 16 female); 18 patients received agalsidase alfa at 0.2 mg/kg, and 16 patients received agalsidase beta at 0.2 mg/kg	Reduction in LVM	After 12 and 24 months of treatment, the authors in this study reported no significant reduction in LVM, which was not different between the two treatment groups; also, no differences in GFR, pain, and decline in Gb3 levels were found in the two groups; the occurrence of treatment failures did not differ between the two treatment groups; antibodies developed only in males (4/8 in the agalsidase alfa group and 6/8 in the agalsidase beta group)
Vedder et al ²⁹	Open-label, not prospectively designed	12 months	52 (28 males and 24 females); agalsidase alfa at 0.2 mg/kg (n = 18; 10 male, 8 female), agalsidase beta at 0.2 mg/kg (n = 13; 8 male, 5 female), or agalsidase beta at 1.0 mg/kg (n = 21; 10 male, 11 female); age range 19–73 years	Plasma and urinary Gb3, and antibody response	LVM significantly decreased in patients receiving 1 mg/kg EOW, whereas no decrease was reported in groups receiving 0.2 mg/kg EOW; 1 mg/kg dose appeared more effective in reducing plasma and urinary Gb3 in the presence of neutralizing antibodies
van Breemen et al ¹⁰⁰	Open-label	12 months	43 (22 males and 21 females); agalsidase alfa at 0.2 mg/kg (n = 14; 7 male, 7 female), agalsidase beta at 0.2 mg/kg (n = 11; 6 male, 5 female), or agalsidase beta at 1.0 mg/kg (n = 18; 9 male, 9 female); age range 18–71 years	Gb3	Prominent reductions of plasma Gb3 in Fabry males within 3 months for each treatment regimen (P = 0.0313), followed by relative stability up to 12 months of treatment; reductions or stabilization observed in all females in each treatment regimen
Sirrs et al ⁴	Canadian Fabry Disease Initiative	3 years and ongoing	244 (149 female and 95 male); mean age 41.9 ± 14.5 years	Multiple	Ongoing; published abstracts report preliminary data in the 244 enrolled patients, and show no significant differences in clinical outcomes at up to year 3 between the two forms of agalsidase treatment ^{102,103}

Notes: ^aAgalsidase alfa dose at 0.2 mg/kg every other week as stated; ^bAgalsidase beta dose at 0.2 mg/kg or 1.0 mg/kg every other week as stated.

Abbreviations: Gb3, globotriaosylceramide; GFR, glomerular filtration rate; LVM, left ventricular mass; EOW, every other week.

Consistent with other studies, none of the female patients developed antibodies.⁹⁹ However, the impact of antibody formation on long-term clinical outcome remains unclear.⁹⁹ A recent paper by Bénichou et al analyzed the potential impact of IgG antibodies to agalsidase beta on efficacy following 5 years of enzyme replacement therapy.¹⁰¹ No correlation was found between anti- α -Gal A IgG titers and the onset of clinical events or the rate of change in estimated glomerular filtration rate.¹⁰¹ A statistically significant association was observed between anti- α -Gal A IgG titers and Gb3 deposition in skin fibroblasts during treatment, suggesting impairment of Gb3 clearance in some patients with high antibody titers.¹⁰¹ Determination of the long-term impact of circulating anti- α -Gal A antibodies on clinical outcomes requires continued monitoring during treatment.¹⁰¹

In a similar cohort of patients, Van Breeman et al recently described that agalsidase alfa 0.2 mg/kg every other week, agalsidase beta 0.2 mg/kg every other week, and agalsidase beta 1.0 mg/kg every other week resulted in marked decreases in elevated plasma Gb3 in Fabry males within three months ($P = 0.0313$), after which levels stabilized.¹⁰⁰

The Canadian Fabry Disease Initiative is a large randomized controlled trial that has been initiated to provide robust multicenter national data on the natural history of the disease and on the comparative efficacy of agalsidase alfa and beta in enzyme replacement therapy-naïve Fabry patients.⁹⁴ Multiple variables are to be studied during the 10-year treatment investigation. Several published abstracts have reported preliminary data for the 244 enrolled patients, and showed no significant differences in clinical outcomes at up to year 3 between the two forms of agalsidase treatment.^{94,102,103} Future publication of this data will be particularly important to assess safety and clinical efficacy.

Safety and tolerability

The most common adverse events with agalsidase alfa are infusion-associated reactions, which occur in approximately 13.7% of treated Fabry patients in clinical trials.^{16,29,48} These adverse events are typically mild to moderate in severity, and include rigors, fever, nausea and vomiting, headache, chest pain, flushing, pruritus, rhinitis, tremor, dyspnea, somnolence, and acroparesthesia.^{6,16,48} The Fabry Outcome Survey data, based on treatment of 314 patients, described serious adverse events in 27 male and 11 female subjects, which were deemed not related to agalsidase therapy by the treating physician.⁴⁸ Most of these events were attributed to the natural progression of Fabry disease, and included strokes, transient ischemic attacks, arrhythmias, renal dysfunction,

vertigo, and sudden deafness.⁴⁸ Combined analysis of long-term clinical trials shows that IgG antibodies have been observed in approximately 24% of the male patients after 3–12 months of treatment with agalsidase alfa, but no IgE antibodies or anaphylactic reactions have been noted.²⁹ Interestingly, 7% of treated patients demonstrate immunological tolerance based on the disappearance of IgG antibodies over time.^{34,104} Antibodies to agalsidase alfa have not been shown to be associated with any clinically significant effects on safety or efficacy.²⁹ Consistent with other studies, a long-term study of the efficacy and tolerability of agalsidase alfa in 36 female Fabry patients detected no antibodies during the treatment period.⁶ In vitro studies demonstrate that IgG antibodies cross-react similarly with both agalsidase alfa and beta, resulting in neutralization of α -Gal A activity.^{34,105} Safety and tolerability with long-term agalsidase alfa treatment has been demonstrated, and no additional safety concerns have been raised in children or females. No safety concerns have been described for agalsidase alfa infusions used in the home setting.^{2,42,44}

Outstanding management issues

The overall goal of enzyme replacement therapy is to prevent disease in younger patients, and to potentially halt disease progression and reverse underlying pathologic abnormalities in patients with more advanced disease.^{106–108} Results from clinical trials to date have highlighted that early initiation of enzyme replacement therapy may have the potential to delay and reverse the underlying clinical outcomes, such as renal failure, in patients with Fabry disease.^{18,42} Moreover, the use of enzyme replacement therapy in children is well tolerated, decreases pain, and improves pain-related quality of life.^{2,20,22} However, long-term follow-up is necessary to ascertain whether starting treatment in childhood will prevent and/or stabilize end organ damage and increase life expectancy.³⁵

The possibility to halt or even reverse the progress of Fabry disease before irreversible damage organ occurs necessitates accurate and rapid diagnosis, monitoring, and treatment of the disease.⁸⁹ Difficulties in comparing clearance of Gb3 and monitoring the clinical efficacy of enzyme replacement therapy in treated patients are highlighted by the wide variety of methodologies utilized in the studies to date. A reliable early biomarker or predictor of disease progression for both genders would prove valuable in this regard.³⁵ The novel plasma biomarker, globotriaosylsphingosine (lyso-Gb3), is currently being studied as a potential biomarker for Fabry disease.¹⁰⁹ Studies to date report increased plasma lyso-Gb3 in male patients, which was

higher in cases of the classic phenotype, whereas plasma lyso-Gb3 was moderately increased in females, and this correlated with a decrease in α -Gal A activity.¹⁰⁹ Monitoring of microalbuminuria is currently recommended in Fabry patients, and could be readily used as a predictive indicator of early renal disease.⁸⁸ Early changes in renal morphology can occur in adults and children with normal glomerular filtration rate.^{86,110} Precise assessment of glomerular filtration rate is therefore critical for early diagnosis, monitoring and treatment of nephropathy in these patients.⁸⁸ Renal biopsy has been suggested as a potential tool to assess kidney disease severity accurately in pediatric Fabry patients, but further evaluation of this invasive procedure is warranted.^{86,88} Recent evaluation of different estimated glomerular filtration rate formulae, such as the Modification of Diet in Renal Disease method and the Schwartz formula commonly used in adult and pediatric Fabry patients, respectively, report overestimation of glomerular filtration rate, especially in the early stages of chronic kidney disease; it has been suggested that all Fabry Outcome Survey estimated glomerular filtration rate data in children be recalculated using the new abbreviated Schwartz measured glomerular filtration rate formula.^{88,111} The widely acknowledged lack of precision of estimated glomerular filtration rate measurements, particularly in pediatric patients, emphasizes the need for consensus guidelines and more accurate diagnostic tools.^{88,111}

Consensus guidelines and recommendations for enzyme replacement therapy in Fabry patients have been published but, based on more recent data including Fabry Outcome Survey analyses, require updating.^{112–114} The European Medicines Agency have also issued treatment guidelines for patients with Fabry disease following continued shortages of agalsidase beta, which include adjusted dose regimens for adult male and female patients to 0.3 mg/kg every other week, switching to and starting treatment-naïve patients on alternative treatments, such as agalsidase alfa.¹¹⁵ A similar approach had been adopted for a shortage of Cerezyme® (imiglucerase for injection; Genzyme Corporation) for the treatment of Gaucher's disease.¹¹⁵ These extraordinary shortage circumstances have required a rapid global adaptation to current management strategies from industry, funding bodies, clinicians, patient organizations, and patients themselves.¹¹⁵ Due to the rarity of Fabry disease and the small numbers of patients available to be enrolled in large-scale, placebo-controlled clinical trials, data from registries, such as the Fabry Outcome Survey, are extremely valuable to further our understanding about the effect of enzyme replacement therapy in Fabry patients. Analysis of all randomized trials,

open-label studies, and Fabry Outcome Survey data to date demonstrate clinical benefits of agalsidase alfa compared with placebo and provide further understanding of the natural history of Fabry disease, as well as the long-term safety of enzyme replacement therapy. Overall, agalsidase alfa treatment appears to be positively related to patients' health-related quality of life, ameliorating the natural course of the disease.³⁵ However, the value of enzyme replacement therapy for event-free survival, incidence and severity of comorbidities, as well as sustained improvement of patient health-related quality of life is not yet realized.³⁵

Enzyme replacement therapy is a lifelong treatment for patients with Fabry disease, and home therapy has been proven to be beneficial for patients' quality of life whilst optimizing health care resources. The benefit of a 40-minute infusion and good safety profile of agalsidase alfa in adults and children has been regarded as more convenient in a home setting.⁴² Most patients in the UK have enzyme replacement therapy at home, and home care providers have experienced specialist nurses who provide this service, liaising closely with hospital clinicians and nurses.¹¹⁶ Recent studies have shown home infusion with agalsidase alfa to be convenient, and less stressful, as well as having a positive impact on patient satisfaction and possible cost reduction.^{42,116} The quality of evidence differs vastly between the studies mentioned in this review, from randomized controlled trials that are relatively short in duration, to open-label follow-up, and to registry data, which rely on good quality retrospective data, which has its own limitations. As a result, further randomized controlled studies may be required to define the appropriate time to initiate enzyme replacement therapy, as well as the optimal treatment dose for the individual patient.³⁵ Careful and individualized treatment planning should be guided by accurate and earlier diagnosis of patients and timely assessment of organ damage. A study of two agalsidase beta dosing regimens in treatment-naïve male pediatric patients without severe symptoms will examine the efficacy and safety of two lower-dose regimens of Fabrazyme in male patients aged 5–18 years over the course of 5 years. Data from this study, described as Fabrazyme: Intervening Early at a Lower Dose (FIELD), may provide further supporting evidence for early and more flexible treatment, especially in pediatric patients and/or those with milder symptoms for Fabry disease.¹¹⁷

Preliminary data from the Canadian Fabry Disease Initiative suggest no significant differences in efficacy or safety between the two enzyme replacement therapy preparations. Owing to the recent production difficulties with agalsidase

beta, further evaluation of a balanced and factual comparison of these two drugs may be hindered.¹¹⁵ In addition, there is a lack of in vitro studies available to allow relevant comparisons.

The systemic nature of Fabry disease necessitates a multidisciplinary management approach involving, for example, cardiologists, nephrologists, pediatricians, neurologists, ear, nose and throat specialists, psychologists, and specialist nurses. Other needs of Fabry patients and their families, such as genetic counseling and family screening, and treatment options such as home-based therapy should also be made available, because these are likely to have a positive impact on quality of life.³⁴ In addition to enzyme replacement therapy, adjunctive therapies should be integrated, such as the use of appropriate analgesia for neuropathic pain, anti-hypertensives and the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for proteinuria, because these currently play an essential part in the optimal management of Fabry disease.¹⁶

Conclusion

Fabry disease is a slowly progressive disease with clinical manifestations often occurring in early childhood. Currently, in the absence of a suitable biomarker to establish the rate and severity of disease progression, monitoring patients regularly, both adults and children, for the onset of renal, cardiac, and central nervous system manifestations is essential to determine the timing of enzyme replacement therapy and adjunctive therapy. Over the past decade, the use of enzyme replacement therapy in patients with Fabry disease has significantly improved their quality of life and delays/stabilizes disease progression.

Given the cost of enzyme replacement therapy and the burden of treatment over a prolonged period of time, it is vitally important to analyze long-term follow-up data to determine the point of no return with respect to disease progression, and thus optimizing the timing for commencing enzyme replacement therapy. Consensus guidelines of when to initiate enzyme replacement therapy are limited because of the rarity of the disease and a lack of reliable controlled studies designed to confirm the appropriate timing of initiation of enzyme replacement therapy. However, based on personal clinical experience, as well as recently published literature, the author's view is that initiation of enzyme replacement therapy must be considered carefully in a selected group of children with Fabry disease who have no residual enzyme activity and/or manifest early disease-related symptoms which significantly affect their quality of life.

These patients have a very high likelihood of developing significant complications related to Fabry disease.

Allen et al also correlated early ocular manifestations with genotype and overall disease severity in children with Fabry disease.⁸⁹ Absent alfa-galactosidase A activity and genotype with loss of function mutations seem to be the best predictors of disease progression that we have in children currently, together with family history of a tendency to develop early strokes, and renal and cardiac complications. Once signs and symptoms develop, irreversible damage has probably already occurred. Regular follow-up will also enable clinicians to detect early evidence of cardiac, renal, or central nervous system disease in children, such as increase in left ventricular mass index above age-appropriate centiles, early onset of microalbuminuria, retinal vessel tortuosity, uncontrolled neuropathic pain, and recurrent fever pain crises. It is recommended that both male and female pediatric patients who remain asymptomatic in early childhood must have regular follow-up assessments at least once a year.

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