Fabry disease: a review of current management strategies

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Abstract

Fabry disease is an X-linked inherited condition due to the absence or reduction of α-galactosidase activity in lysosomes, that results in accumulation of globotriaosylceramide (Gb₃) and related neutral glycosphingolipids. Manifestations of Fabry disease include serious and progressive impairment of renal and cardiac function. In addition, patients experience pain, gastrointestinal disturbance, transient ischaemic attacks and strokes. Additional effects on the skin, eyes, ears, lungs and bones are often seen. The first symptoms of classic Fabry disease usually appear in childhood. Despite being X-linked, females can suffer the same severity of symptoms as males, and life expectancy is reduced in both females and males. Enzyme replacement therapy (ERT) can slow or even stabilize the progression of the disease. The rarity of the classic form of Fabry disease, however, means that there is a need to improve the knowledge and understanding that the majority of physicians have concerning Fabry disease, in order to avoid misdiagnosis and/or delayed diagnosis. This review aims to raise awareness of the signs and symptoms of Fabry disease; to provide a general diagnostic algorithm and to give an overview of the effects of ERT and concomitant treatments. We highlight a need to develop comprehensive international guidelines to optimize ERT and adjunctive therapy in patients with Fabry disease, including females and children.
Introduction

Lysosomes are involved in a myriad of cellular processes, and inborn errors of metabolism that affect the production of lysosomal enzymes produce a wide variety of symptoms and significantly reduce life expectancy. Over 40 lysosomal storage diseases (LSDs) have been identified, with a collective prevalence of approximately 1 in 7700 live births. LSDs are traditionally classified according to the specific accumulated enzyme substrate. All LSDs are inherited in an autosomal recessive manner except for Fabry disease, Hunter syndrome and Danon disease, which are X-linked disorders.

The second most common LSD after Gaucher disease is Fabry disease, with a worldwide prevalence of approximately 1 in 40 000 to 1 in 117 000 live births for the classic form of the disease. Wide variations in the prevalence of Fabry disease have been reported in different countries, and with increasing awareness and screening, it is likely that the actual prevalence may be higher than previously recorded, particularly when late-onset phenotypes are taken into account.

Fabry disease results from mutations in the GLA gene that encodes the lysosomal enzyme α-galactosidase A. A functionally relevant reduction of enzyme activity results in the accumulation of globotriaosylceramide (Gb₃) within lysosomes (Figure 1). A wide variety of progressive clinical symptoms are seen in patients with Fabry disease and many of these are seen first in early childhood (Table 1). These symptoms include burning sensations, particularly in the hands and feet (acroparaesthesia), gastrointestinal problems, angiokeratomas and temperature intolerance. Signs and symptoms that tend to develop later in adolescence and early adulthood are associated with end-organ failure and premature death. These include proteinuria and
glomerulosclerosis, cardiac hypertrophy and arrhythmia, other cardiovascular disease, and stroke.\textsuperscript{7,8}

More than 400 mutations have been identified in the \textit{GLA} gene (mainly missense mutations but also nonsense mutations and single amino acid deletions and insertions). Most of these mutations are ‘private’, having been identified only in individual families,\textsuperscript{9-13} while some others, located at CpG dinucleotides (e.g. R227X), have been found as independent mutational events.

Although Fabry disease is X-linked, obligate heterozygous females are usually affected by the disease, but exhibit symptoms that are more variable than those in men. The symptoms also tend to occur later in life.\textsuperscript{14-23} The biological basis for the manifestations seen in Fabry disease in females is not fully understood. However, it is thought to be due to random X inactivation – or Lyonization\textsuperscript{24} – whereby some cells of the body express the normal \textit{GLA} allele, whereas others express the mutated allele.\textsuperscript{25} The extent to which skewed X inactivation underlies the manifestations is unclear.\textsuperscript{19,26,27} The mean age at onset of the signs and symptoms of Fabry disease has been reported between 3–10 years in males and 6–15 years in females.\textsuperscript{28-30} The later manifestations of Fabry disease (such as renal impairment, cerebrovascular disease and cardiomyopathy) result in a reduced life expectancy, to approximately 50 years in men\textsuperscript{31} and 70 years in women.\textsuperscript{28} Furthermore, quality of life is reduced in both male\textsuperscript{32,33} and female\textsuperscript{22,34} patients, not only due to end-organ failure, but also to a range of other symptoms, including gastrointestinal (GI) problems, pain, acroparaesthesia, depression\textsuperscript{35} and temperature intolerance.
Since its introduction in 2001, ERT has been shown to be effective in alleviating many of the signs and symptoms of the disease and to slow or even reverse disease progression.\textsuperscript{36-47} Recommendations and guidelines for ERT in patients with Fabry disease have been published previously (2003\textsuperscript{48} and 2006\textsuperscript{49}) and national guidelines exist in some countries (e.g. in the UK\textsuperscript{50} and France\textsuperscript{51}). These guidelines, however, require updating, particularly when considering indications for commencing treatment in females and children. For example, a comparison of the percentage of females and males included in a registry of patients with Fabry disease has shown that 82\% of males have been given ERT compared with just 34\% of females; importantly, this difference was not justified based on the extent of major organ involvement.\textsuperscript{23}

This article is based both on the published literature and the authors’ combined clinical experience of the beneficial effects of ERT in managing patients with Fabry disease. Importantly, it also describes ‘real-world’ data collected via disease registries.

**Methodology**

In October 2008 a panel of experts with extensive clinical experience of Fabry disease met to discuss current management and treatment issues and to formulate recommendations. Panellists were chosen on the basis of specialty expertise (genetics, paediatrics, nephrology, cardiology, dermatology and neurology), with representation from throughout Europe.

During an initial day-long meeting, key issues were identified and preliminary recommendations discussed. An independent coordinator conducted searches of the
National Library of Medicine’s PubMed database, including a global search of the recent literature on Fabry disease (past 10 years) and specific searches of the entire database, addressing all issues encompassed in this review. A draft document was then prepared, which was reviewed during a second day-long meeting (March 2009). This draft was then revised and finalized by the panel. Finally, a third meeting was convened (October 2009) to prepare the manuscript for journal submission. Support for the expert panel process (travel, conference facilities, and an independent coordinator) was obtained from Shire HGT, which had no formative role in the literature review, the formulation of recommendations, or the drafting and revising of the manuscript.

Other reviews in this field have been published, but this paper also includes valuable ‘real-world’ registry data, rather than a purely systematic review of clinical trials.

**Diagnosis and screening**

**Diagnosis**

Diagnosis of Fabry disease is often delayed by at least 3 years, and often by more than 20 years, after the onset of signs and symptoms. The reasons for this delay include the condition’s rarity (and corresponding lack of awareness among clinicians) and the diversity and non-specificity of presenting symptoms. The initial presentation may be to a general practitioner/family doctor, dermatologist, ophthalmologist, paediatrician, geneticist, neurologist, cardiologist or nephrologist. A general diagnostic algorithm with appropriate investigations according to organ system involvement is shown in Figure 2.

If clinical examination raises a suspicion of Fabry disease, biochemical and/or genetic confirmation is needed. Assay of the α-galactosidase A activity in leukocytes or dried
blood spots will usually confirm the diagnosis in males. Plasma or urinary Gb$_3$ has also been used in the biochemical diagnosis of Fabry disease, but in females the level of Gb$_3$ is generally lower than in males, and is not elevated in some patients with particular mutations in the GLA gene (e.g., those with the N215S mutation).

In female heterozygotes, $\alpha$-galactosidase activity is often within the normal range. Diagnostic confirmation should therefore be made by genetic analysis in suspected cases. Recent data from the Belgian Fabry study in 1000 patients with stroke over 2 years, have shown that four female patients, heterozygous for known mutations in the GLA gene, were diagnosed with Fabry disease. This supports the need for direct sequencing in females instead of other screening strategies.

Increasingly, patients are also being diagnosed via pedigree analysis after diagnosis of another family member (Figure 2).

**Screening**

A confirmed diagnosis of Fabry disease provides the opportunity to replace the deficient enzyme and thereby slow or stabilize organ function. In addition, diagnosis of Fabry disease in an individual should lead to the screening of other family members and the provision of appropriate genetic counselling. Screening of patients with idiopathic renal, cardiovascular and cerebrovascular disease will also identify patients with Fabry disease who could benefit from ERT.

Previously undiagnosed Fabry disease has been detected in 0.25–1% of males undergoing haemodialysis. Fabry disease should also be considered in unexplained
end-stage renal disease in women, and has been detected by screening female haemodialysis patients.\(^{61-64}\) It was also recently suggested that screening kidney transplant patients for Fabry disease may be effective.\(^{64}\) Screening of at-risk groups is often conducted by measuring plasma \(\alpha\)-galactosidase A activity, but this can fail to detect cases of Fabry disease,\(^{65}\) particularly in females.\(^{66}\)

In males with left ventricular hypertrophy (LVH) or hypertrophic cardiomyopathy, 1–4% have been shown to have previously undiagnosed Fabry disease.\(^{67-69}\) Screening of female patients with hypertrophic cardiomyopathy has also detected a prevalence of Fabry disease of 1\%.\(^{69}\)

The prevalence of Fabry disease in patients with acute cryptogenic stroke was reported in approximately 5% of males and 2.4% of females aged 18–55 years (1.2% of all young stroke patients).\(^{70}\) Other studies, notably one from Belgium,\(^{71,72}\) and another from the USA,\(^{73}\) are underway. To investigate further the prevalence of Fabry disease in stroke patients, a large international screening study for Fabry disease (SIFAP – Stroke In Young Fabry Patients) has been initiated in an unselected cohort of approximately 5000 young stroke patients (aged 18–55 years) in 46 centres in Europe. Enrollment has been successfully completed (January 2010) and the first results should be available in autumn 2010.

Screening for Fabry disease has also been performed in other patient groups, such as those with unexplained atherosclerosis or cornea verticillata.\(^{74,75}\) Any screening requires a reliable and cost-effective method. Measurement of the accumulated substrate, \(G_{b3}\), in the urine has been proposed,\(^{76,77}\) but the reliability of \(G_{b3}\) as a biomarker of Fabry
disease, particularly in females, is unclear.\textsuperscript{56,78} Measurement of enzyme levels and assessment of mutational status using blood spots are increasingly utilized.\textsuperscript{79-84} A recent study from Taiwan screened nearly 172 000 newborns and identified a high frequency of Fabry disease among males (1 in 1250).\textsuperscript{82} Similarly, measuring the enzyme in urine samples by enzyme-linked immunosorbent assay (ELISA) shows promise,\textsuperscript{85} although such diagnostic methods are only reliable in males.

A newborn screening programme in Northern Italy from July 2003 until June 2005 has shown that such screening may identify a much higher incidence of Fabry disease than previously suggested.\textsuperscript{6} The ratio of classic phenotypes (characterized by little if any $\alpha$-galactosidase A activity) to late-onset phenotypes (in which residual enzyme activity is retained) was 1:11 suggesting that many detected cases would be late-onset variants of Fabry disease,\textsuperscript{6} and therefore based on current information, new born screening for Fabry disease is not justified in the authors views.

\section*{Signs and symptoms of Fabry disease}

Fabry disease has progressive effects on multiple organ systems, including the kidney, heart and brain (Table 1). Here, we summarize the main signs and symptoms of Fabry disease that occur in men, women and children.

\subsection*{Renal dysfunction}

Renal involvement is reported in approximately 50\% of patients with Fabry disease – proteinuria is the most frequent renal symptom.\textsuperscript{16,39} Although renal disease is more common in patients aged 30 years or more,\textsuperscript{16,21} it is also reported in children and adolescents with Fabry disease,\textsuperscript{29,86} where mild albuminuria may be the first sign of
progressive renal disease. Proteinuria has been reported in boys at 10.3 years of age and girls at 8.1 years of age.\textsuperscript{29} Biopsy studies have shown that glomerular and vascular changes are present before progression to overt proteinuria. Renal biopsy may therefore be a useful tool for the early detection of renal disease.\textsuperscript{87}

A recent retrospective natural history study of patients with Fabry disease has shown that baseline proteinuria, reduced baseline estimated glomerular filtration rate (eGFR) and male gender are associated with more rapid progression of nephropathy.\textsuperscript{88}

An analysis of the causes of death reported for 181 affected relatives and 42 patients (699 males and 754 females) enrolled in FOS (the Fabry Outcome Survey) indicates that the importance of renal disease as a cause of death appears to be decreasing, while the importance of cardiac disease is increasing, probably reflecting improvements in the management of renal disease in these patients.\textsuperscript{89} Similar findings have been observed in an analysis of patients in the Fabry Registry, where cardiovascular disease was also the most common cause of death.\textsuperscript{90}

**Cardiac abnormalities**

All cardiac structures, including the myocardium (Figure 3), conduction system and valves may be affected in patients with Fabry disease.\textsuperscript{16,91,92} Angina pectoris is frequently reported in both men and women. Coronary artery disease and myocardial infarction also occur\textsuperscript{31} and are probably related to coronary microvascular dysfunction.

Arrhythmia is common in patients with Fabry disease, and its frequency increases with age in both genders.\textsuperscript{93} Permanent and paroxysmal atrial fibrillation and intermittent
ventricular tachycardia are the most common cardiac manifestations of the disease. LVH is detected in approximately 50% of patients and is more frequent and has an earlier age of onset in males than in females. LVH is generally symmetrical, although asymmetric septal hypertrophy has been described. LVH appears to be positively correlated with the frequency of arrhythmia, valvular disease (mitral and aortic) and other cardiac signs and symptoms, including an increased intima-media thickness of the common carotid artery. Aortic root dilatation is highly prevalent in male patients affected with Fabry disease (DP Germain, unpublished data) (Figure 4).

Cardiac symptoms can be detected in some children with Fabry disease. Both male and female paediatric patients can be affected by more serious effects on the heart and kidneys. For example, in a study of 20 paediatric patients with Fabry disease, it was found that all patients had a left ventricular mass indexed to height above the 75th percentile of normal controls. There was also a reduction in heart rate variability, reflecting a reduction in parasympathetic cardiac stimulation.

**Cerebrovascular manifestations**

Transient ischaemic attack (TIA) and stroke are frequently observed in Fabry disease. Onset is earlier in males than females, and TIAs have even been reported in paediatric patients with Fabry disease. Recurrence is common and, once detected, the prognosis is poor. Renal and cardiac disease can co-exist with cerebrovascular disease and may predispose patients with Fabry disease to neurological disability and stroke, however, recent data show that most patients (70.9% of males and 76.9% of females) had not experienced renal or cardiac disease before their first stroke. In addition, 50% of males and 38.3% of females had their first stroke before being diagnosed with Fabry disease. The ‘pulvinar sign’ is a characteristic MRI manifestation
of Fabry disease\(^{101}\) (Figure 5). Rarely, subclinical white matter lesions have been reported in children with AFD and it is therefore important to elicit a family history of early stroke or TIAS.

**Gastrointestinal symptoms**

Overall, approximately 50% of patients with Fabry disease reported GI symptoms.\(^{4,6}\) Abdominal pain (often after eating) and diarrhoea are the most frequent manifestations, but other GI symptoms include constipation, nausea and vomiting.\(^{4,6}\) Although some reports have suggested that GI symptoms may be more frequent and have an earlier onset in males,\(^{16,102}\) a recent analysis of a large cohort of patients showed that females are more likely to report GI symptoms than males.\(^{4,6}\)

The median age of onset of many GI symptoms is before the age of 15 years.\(^{4,6}\) GI symptoms (primarily altered bowel habits and abdominal pain) are present in approximately 60% of children under the age of 10 years.\(^{29}\) However, another recent report states that gastrointestinal symptoms were present in only 18% of children.\(^{86}\)

**Dermatological signs**

Angiokeratomas are a hallmark of Fabry disease (but are not specific for Fabry disease)\(^{103-106}\) – 66% of males and 36% of females have angiokeratomas\(^{106}\) (Figure 6). Diffuse angiokeratomas are typically located on the lower trunk. A thorough physical examination is important to be sure to detect them, and the commonest areas involved are the underwear and genital region, the palms, around the mouth and lips and the umbilicus. Other frequent symptoms are hypohidrosis, telangiectasia and lymphoedema, and although all are more frequent in males with Fabry disease, there is
still a high prevalence of these symptoms in females.\textsuperscript{106} Facial dysmorphism, with a characteristic coarsening of the facial features, is increasingly recognized\textsuperscript{107,108} (Figure 7).

**Ocular and auditory symptoms**

Cornea verticillata is diagnostic for Fabry disease and occurs in over 70\% of males and females.\textsuperscript{109} Ophthalmological features have been reported in approximately 60\% of children with Fabry disease.\textsuperscript{29} Other ocular abnormalities, observed in fewer patients, can include vessel tortuosity and cataract, both of which have a higher prevalence in males. Tortuous vascular lesions on the retina may be associated with more severe disease.\textsuperscript{108} The presence of retinal vessel tortuosity in children has recently been associated with loss of function mutations, and may represent a severe phenotype.\textsuperscript{110}

High frequency sensorineural hearing loss is common in Fabry disease.\textsuperscript{111} Males appear to be affected earlier in life than females and, although hearing is worse in patients with Fabry disease than in the general population, clinically relevant hearing impairment only affects approximately 16\% of patients.\textsuperscript{112} Sensorineural hearing loss is less common in children than previously reported, although tinnitus appeared to correlate significantly with severity of clinical presentation in children.\textsuperscript{113}

**Neurological symptoms**

Neurological symptoms are the most frequently reported symptoms in Fabry disease (occurring in approximately 80\% of patients).\textsuperscript{16,47} Neuropathic pain has a mean age of onset of approximately 9–14 years for males and 16–20 years for females.\textsuperscript{16,47} Pain is most often felt in the hands and feet, but can occur anywhere in the body.\textsuperscript{47} As pain can
improve over time, adults in whom Fabry disease is suspected should be asked to recall their history of pain in childhood. Other early symptoms relate to autonomic dysfunction and include hypo- or anhidrosis and abnormal temperature and exercise tolerance, while other neurological symptoms can contribute to other manifestations of the disease (e.g., abnormal GI motility with pain). 49.114,115 Although hypohidrosis is a classic feature of Fabry disease, a recent report detected hyperhidrosis in 11.9% of females and 6.4% of males, and is also reported in childhood.115

The neurological symptoms of acroparaesthesia and altered temperature sensitivity are also the most frequent early symptoms in children – a study of 82 children enrolled in FOS documented one of these symptoms in approximately 80% of patients mostly under 10 years of age.29

**Depression and reduced quality of life**

Depression is a frequent and under-diagnosed problem among patients with Fabry disease. In a UK-based survey, as many as 46% of patients were found to have depression and 28% could be classified as having severe clinical depression.35 Most patients were previously undiagnosed for depression,35 highlighting the need for the correct assessment of depressive symptoms in patients with Fabry disease. The benefits of treatment on depression are currently unknown.

Depression, and many of the other symptoms listed above, can have a serious effect on quality of life in patients with Fabry disease. Reductions in quality of life have been shown using a variety of measures including the SF-36, RAND-36, EuroQoL and Fabry-specific questions.22,32–34 In women, the effect of Fabry disease on quality of life was of a similar magnitude to the effect of multiple sclerosis and rheumatoid arthritis,34 and in
men the effects were more severe than in males with severe haemophilia and were similar to a male population with AIDS.\textsuperscript{32,33}

**Other symptoms**

Cardiopulmonary impairment has been demonstrated in men and women with Fabry disease,\textsuperscript{116,117} with mild to severe airway obstruction present in 26% of women and 61% of men.\textsuperscript{117} Because of the presence of pulmonary impairment, smoking should be avoided in patients with Fabry disease.

Fabry disease may be complicated by osteopenia of the lumbar spine and femoral neck.\textsuperscript{118} With the introduction of ERT and the potential improvement in the clinical course of the disease, increased knowledge and awareness of this co-morbidity is warranted, as more patients may live to have disease-related complications.

Other symptoms that can be present in a large proportion of patients with Fabry disease include anaemia\textsuperscript{119} and fever.

**Enzyme replacement therapy**

ERT for Fabry disease became available in most of Europe in 2001 with the introduction of two products, agalsidase alfa (Replagal\textsuperscript{®}, Shire HGT Inc) and agalsidase beta (Fabrazyme\textsuperscript{®}, Genzyme Corp.), and has subsequently become available in many other countries. The advent of ERT has provided the first opportunity to address the underlying enzyme deficiency of Fabry disease.
The effective management of Fabry disease requires a multidisciplinary approach, involving specialist physicians in the disease itself, but also specialist nurses, paediatricians, ophthalmologists, nephrologists, cardiologists, neurologists, gastroenterologists, dermatologists, geneticists and genetic counsellors.

Agalsidase alfa is purified from a stably transfected human cell line and is infused at a dose of 0.2 mg/kg over a period of 40 minutes, every 2 weeks. One study has investigated the efficacy of agalsidase alfa administered weekly at 0.2 mg/kg and has indicated that weekly infusions may be beneficial in some patients.

Agalsidase beta is produced in Chinese hamster ovary cells and is infused at a dose of 1.0 mg/kg over a period of up to 4 hours, every 2 weeks. However, in selected patients it can be infused more quickly. The use of a lower maintenance dose of agalsidase beta, 0.3 mg/kg, has been evaluated and has been shown to maintain Gb₃ clearance in the short term in some, but not in all, patients. The longer-term clinical effects of this lower dose of agalsidase beta, however, have not been evaluated.

The safety and early efficacy parameters have also been demonstrated in children with Fabry disease.

**Efficacy data**

**Pivotal clinical trial results**

The initial randomized controlled clinical trial of agalsidase alfa, 0.2 mg/kg, in 26 adult male patients with Fabry disease showed that 6 months of ERT significantly reduced pain and pain-related quality of life, improved renal structure (increase in the percentage
of normal glomeruli) and function (increase in creatinine clearance), improved cardiac conduction and decreased plasma Gb₃.³⁸

Similarly, in the initial randomized controlled clinical trial of agalsidase beta, 1.0 mg/kg, in 58 adult patients (56 males and 2 females), 20 weeks of ERT was effective in decreasing plasma and tissue Gb₃. There was also a reduction in pain scores at 20 weeks, although no differences between the treatment and placebo groups were seen after week 20.³⁷

In a recent independent study of all patients with Fabry disease in Canada, which compared the effects of agalsidase alfa, 0.2 mg/kg, and agalsidase beta, 1.0 mg/kg, no differences in clinical outcomes could be determined between the two forms of agalsidase (24 months of treatment).¹²⁷,¹²⁸ This study is ongoing and the 3-year results are currently under analysis and being prepared for publication.

**Data from other studies and outcome surveys**

Much of the long-term data on the efficacy and safety of ERT in Fabry disease has been obtained from open-label extension studies to the original clinical trials and from patients enrolled in post-marketing surveillance surveys. The longest evaluation of the use of agalsidase alfa comes from FOS, with 5 years of experience now showing sustained clinical improvements.¹²⁹ Agalsidase alfa significantly reduced LV mass, stabilized renal function and improved quality of life and pain.¹²⁹ In the longest published evaluation of agalsidase beta to date (an open label extension of the original 20-week randomized clinical trial to up to 54 weeks), renal function in the majority of patients remained stabilized.¹³⁰
Greater detail on the clinical data with agalsidase alfa, 0.2 mg/kg, and agalsidase beta, 1.0 mg/kg, are discussed together below.

**Overall effects of ERT**

Generally, ERT normalizes Gb₃ levels in a wide variety of organs in most patients and may be associated with symptomatic benefits. Overall measures of Fabry disease severity, such as the Mainz Severity Score Index (MSSI), have shown a general reduction in disease severity after at least 1 year of ERT.¹³¹ In 51 adults with advanced Fabry disease, ERT was shown to delay the time to first clinical event (renal, cardiac or cerebrovascular event or death) compared with placebo over a mean of 18.4 months.¹³²

**Cardiac disease**

ERT resulted in a progressive decrease in interventricular septum thickness and a decrease or stabilization of LV mass after 6–24 months.⁴⁰¹³³ Significant reductions in LV mass were observed in women after only 27 weeks on ERT.¹⁷ Furthermore, improvements in LVH and regional myocardial function were observed after 12 months of ERT.¹³⁴ Another study has indicated that the response to ERT in terms of cardiac perfusion is dependent on the degree of cardiac hypertrophy before treatment – more severe hypertrophy resulted in a poorer response.¹³⁵ However, in apparent contrast to this finding, mean ventricular wall thickness and LV mass were reduced in a large cohort of patients after 1 and 2 years of ERT, with the largest decreases observed in patients with the greatest degree of hypertrophy at baseline.³⁶ A study of 2 years of ERT showed that resting heart rate and end-systolic volume decreased and ECG parameters and ventricular mass remained stable in nine patients with Fabry disease. However, they concluded that ERT with agalsidase beta has only minimal effects on cardiovascular signs and symptoms and that conventional cardiovascular treatment is still important in
patients with Fabry disease. More recently, longer-term ERT for 3 years has been shown to have significant cardiac benefits in a group of 32 patients, resulting in a significant reduction in LV mass ($P<0.001$), an improvement in myocardial function ($P=0.045$) and a higher exercise capacity ($P=0.014$) in those patients without fibrosis.

Clearance of Gb$_3$ from cardiac interstitial capillary endothelial cells was seen after 5 months of ERT with agalsidase beta in 72% of treated patients versus 3% of patients given placebo ($P<0.001$), with the capillary endothelium remaining free of Gb$_3$ after 60 months of ERT in 6 of 8 patients who consented to end-of-study biopsy. However, Gb$_3$ clearance was not observed from the most numerous cardiac cells – cardiomyocytes – after ERT.

**Renal function**

Creatinine clearance and eGFR remained stable after 1–2 years of ERT with agalsidase alfa, and also after longer-term treatment of 30–36 months and 54 months with agalsidase beta. In the 54-month study using agalsidase beta, renal disease progressed in some patients, which seemed to be related to the severity of the disease before treatment (most had significant proteinuria and evidence of sclerotic glomeruli). Thus, the initiation of ERT before the development of significant proteinuria may be key to preventing future kidney disease in these patients, as supported by a retrospective analysis of the progression of renal disease in patients not receiving ERT.

In an analysis of pooled data from three studies of the effect of ERT on renal function in a total of 108 adult male patients with Fabry disease, it was shown that measured GFR is stabilized for up to at least 4.5 years of treatment with agalsidase alfa. In the 6-month placebo-controlled phase of the studies analysed, the mean annualized rate of
change in GFR was \(-7.0 \pm 32.9\) ml/min per 1.73 m\(^2\) in patients given placebo compared with \(-2.9 \pm 8.7\) in 85 non-hyperfiltrating patients given agalsidase alfa for 6 months. In patients with a normal or reduced GFR at baseline, there was no significant decrease in GFR during the period of treatment with agalsidase alfa. The changes in actual GFR observed in this study after treatment with agalsidase alfa, 0.2 mg/kg, were not significantly different from the changes in eGFR reported after treatment with agalsidase beta, 1.0 mg/kg.\(^{130,143}\)

Treatment with agalsidase alfa for 3 years was shown to be effective in slowing the deterioration of renal function in patients with Fabry nephropathy in an analysis of ‘real-world’ clinical data from 165 adult patients (115 men and 50 women) in FOS.\(^{144}\) An analysis of patients in FOS who have received 5 years of treatment with agalsidase alfa demonstrated that the mean annual decline in eGFR was 2.46 ml/min/1.73 m\(^2\).\(^{129}\)

Even in patients with advanced renal disease or kidney transplant recipients, ERT, by addressing the underlying metabolic deficiency, may slow the progression or development of extra-renal signs and symptoms of the disease.\(^{145,146}\)

*Pain and quality of life*

In an early trial of ERT, overall pain, pain intensity and some aspects of quality of life were apparently improved after just five infusions,\(^{147}\) and subsequent larger-scale, longer-term studies show that these improvements are maintained for up to 54 months.\(^{130}\) In the largest cohort of patients assessed to date, pain severity was significantly reduced in 81 patients on ERT for 2 years and in 62 patients on ERT for 3 years, and all dimensions of pain perception were improved.\(^{47}\) As in the initial
assessments of ERT, improvements in pain were accompanied by improvements in health-related quality of life, which were maintained after 24 month of ERT.\textsuperscript{36,43}

Other effects of ERT are listed in Table 2.\textsuperscript{42,44,46,148-152}

**Effects of ERT in women**

A prospective single-centre open-label study of the effects of agalsidase alfa in 36 women treated for 4 years showed that ERT significantly ($P<0.01$) reduced the overall burden of the disease, significantly ($P=0.001$) reduced ‘pain at its worst’, as measured by the Brief Pain Inventory, and significantly reduced LV mass ($P<0.001$). Renal function remained constant during the 4 years of the study, and ERT was well tolerated.\textsuperscript{153}

**Effects of ERT in children**

Although some of the studies discussed above have included patients under 18 years of age, several studies have assessed the effects of ERT specifically in children with Fabry disease. These are particularly important as recent improved understanding of the disease burden of Fabry disease in childhood suggests a need for earlier treatment.

The prevalence of GI symptoms, including post-prandial pain, vomiting and nausea, was reduced gradually with time on ERT in an open-label survey of 16 children. Reductions were significant for pain and vomiting by 37–48 weeks.\textsuperscript{123}

In a 23-week study, ERT was shown to reduce pain scores and the use of analgesics, and to improve pain-related quality of life in children ($n = 13$; median age, 11 years).\textsuperscript{124} Other changes included an increased sweat volume and a reduction in acroparaesthesia and GI symptoms; no changes were observed in ear symptoms, heat intolerance or
cardiac measurements. Similar results were observed after 26 weeks of ERT in 24 children with a mean age of 11.8 years.

In the longest study described to date in paediatric patients, the effect of ERT with agalsidase alfa was investigated in 19 boys and 5 girls, ten of whom were treated for 4 years. Pain scores, as measured by the Brief Pain Inventory, decreased significantly during treatment, and heart rate variability improved (increased) in male paediatric patients throughout the duration of the study. Left ventricular mass and eGFR remained stable over the study period.

**Home therapy**

The burden of intravenous infusions of ERT every 2 weeks can be significant for patients. Infusion typically takes place over a duration of 40 minutes for agalsidase alfa and up to 4 hours for agalsidase beta (shorter if tolerated). Home therapy could help to manage this burden for some patients (i.e., stable patients who tolerate the infusions and have a suitable home environment). If implemented successfully, home therapy can reduce the burden on specialist Fabry disease centres. Initial reports also suggest that patients prefer home treatment and, given certain conditions, ERT can be given in the home setting in a safe and reliable manner, with a positive impact on patient satisfaction and cost reduction.

**Tolerability**

As ERT involves infusion of a protein, the most common treatment-related adverse events with ERT are infusion-related events. Infusion-associated reactions have been reported in 12–67% of patients and the most frequently reported events are rigors, fever,
altered sensation, nausea, headache, vomiting, flushing, chest pain, rhinitis, pruritis, tremor, dyspnoea, somnolence and acroparaesthesia. For agalsidase alfa an overall rate of infusion-associated reactions of 13.7% is reported. A quoted rate of infusion-associated reactions of 67% is given for patients treated with agalsidase beta in clinical trials. Most events are mild to moderate, generally start after three to five infusions and decrease in frequency with prolonged ERT. These events often result in the adjustment of infusion rate or temporary interruption of infusion, or may require preventative medications, but do not frequently result in treatment withdrawal.

In a long-term evaluation of agalsidase alfa-treated patients followed in FOS, no new safety concerns were identified in the 555 patients who fulfilled the criteria for safety analysis.

Many infusion reactions coincide with seroconversion, and IgG antibodies to the infused protein develop in 16–90% of patients receiving ERT, but it is unclear whether treatment efficacy is affected. The rate of occurrence of low titre IgG for agalsidase alfa treatment is 24%. For agalsidase beta, the majority of patients studied in clinical trials have developed IgG antibodies with treatment, typically within 3 months of the first infusion. IgE antibodies have been detected only in patients infused with agalsidase beta.

The tolerability profile for ERT in children does not appear to differ significantly from that in adults.
Supply of ERT

The supply of agalsidase beta has been reduced, since June 2009, due to production problems. This has resulted in some patients either being switched to receiving agalsidase alfa or to having a reduced dose of agalsidase beta. Patients in whom the dose or formulation of ERT has been amended will require careful monitoring in order to assess impact on safety and clinical efficacy, and the publication of the data will be particularly important.

Concomitant therapies to ERT

In addition to providing ERT to treat the underlying enzyme deficiency in patients with Fabry disease, concomitant treatments may also be required, particularly when organ damage has already occurred.

Renal disease

Patients with Fabry disease who have established renal failure will require appropriate management of anaemia, renal bone disease and hypertension. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are useful as antiproteinuric agents and in the control of hypertension in patients with proteinuria. Many patients with Fabry disease and renal involvement who have not been given ERT may require dialysis or renal transplantation – transplanted kidneys remain free of Gb₃ accumulation and 5-year organ survival is as good as in patients without Fabry disease.
**Cardiovascular disease**

Conventional cardiac treatments (diuretics, ACE inhibitors, ARBs, β-blockers, implantable cardiac devices, heart transplantation etc) should be considered for patients with cardiovascular manifestations of Fabry disease. In patients with advanced congestive heart failure, heart transplantation is an option and, as in renal transplants, the intrinsic enzyme production within the graft may prevent re-occurrence of cardiac symptoms associated with Fabry disease.

**Cerebrovascular disease**

Typically, prophylactic agents (i.e., aspirin or other anti-platelet drugs) are used to minimize the risk of stroke. Hypotension and hypertension should be avoided and treated appropriately.

**GI symptoms**

Some success has been achieved by managing delayed gastric emptying and dyspepsia with metoclopramide and H2 blockers, respectively, in patients with Fabry disease.

**Angiokeratomas**

Laser methods to treat angiokeratomas may be painful and do not prevent the formation of new lesions. Topical moisturizers can be helpful in preventing skin fissures due to hypohidrosis and thus may reduce skin infection.

**Ocular and auditory problems**

Most ocular manifestations of Fabry disease do not cause impaired vision, and their symptomatic treatment is rarely necessary. Hearing loss can be managed with hearing aids.
Pain

The pain associated with Fabry disease can be managed with analgesics, but nonsteroidal anti-inflammatory drugs are generally ineffective and narcotic analgesics should be avoided where possible because of potential dependency problems. Phenytoin, carbamazepine, gabapentin, tricyclic antidepressants and topiramate have all been used to manage pain in Fabry disease.

The future

An important step in the improved management of Fabry disease in the future will be increased awareness of Fabry disease among a wide range of specialists and general physicians. The provision of specialist-specific algorithms for the diagnosis and treatment of Fabry disease, together with comprehensive international management guidelines, will be key to optimizing individual patient care.

Molecular chaperone therapy

Although ERT remains the major approach for the treatment of patients with Fabry disease and other LSDs, other therapies have been investigated. Of these, pharmacological chaperones are showing the most promise for patients with specific mutations resulting in misfolded or unstable enzymes. Pharmaceutical chaperones are small molecular ligands that can be administered orally and which bind selectively to the misfolded enzyme, promoting correct folding and delivery of the enzyme to the lysosome. In the case of Fabry disease, use of the chaperone 1-deoxygalactojirimycin hydrochloride has been shown to increase the activity of several α-galactosidase A
responsive mutants and to reduce urinary levels of Gb$_3$ in those patients who have missense mutations.\textsuperscript{170}

**Conclusions and summary**

Early diagnosis of Fabry disease is essential in order to provide appropriate and timely treatment, which is now focused on ERT. Such treatment at the licensed doses for the two available replacement enzymes (agalsidase alfa, 0.2 mg/kg; agalsidase beta, 1.0 mg/kg) has been shown to improve quality of life and to reduce progression or stabilize end-organ structure and function. To achieve these benefits for the majority of patients, awareness of Fabry disease must be increased among the many disciplines that are likely to encounter this condition in children and young adults. Awareness of the possibility of Fabry disease in different patient groups, such as those with unexplained cardiac or renal disease, may help in identifying more patients with Fabry disease (and subsequent pedigree analysis will identify others before they develop potentially irreversible organ damage). The clinical consequences of not providing ERT are clear in terms of end-organ disease and early mortality in both male and female patients.

There is also a need to collect further outcome survey data (i.e., real-world data) to complement and confirm the results from shorter controlled randomized trials. Surveys such as FOS and the Fabry registry are therefore important to increase our understanding of Fabry disease and the long-term effects of ERT. Finally, comprehensive guidelines for optimizing and standardizing the diagnosis and treatment of Fabry disease, and tailoring these to the needs of individual patients, are required.
Acknowledgements

The authors represent the Fabry Expert Group, which is an international panel of clinicians with extensive clinical experience of Fabry disease. The authors thank Shire HGT for the support given to the Fabry Expert Group. We acknowledge Dr Cate Orteu, from The Royal Free Hospital, London, for provision of Figure 7. The authors also acknowledge the editorial assistance provided by Communigen, Oxford, UK, which was funded by Shire HGT. The authors are responsible for the interpretation presented in this review. All authors have approved the final version of the manuscript and are fully responsible for its content.
References


EN.REFLIST
Table 1. Typical signs and symptoms of Fabry disease according to age.

<table>
<thead>
<tr>
<th>Typical time at onset</th>
<th>Signs and symptoms</th>
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<tbody>
<tr>
<td>Childhood and adolescence (≤16 years)</td>
<td>• Neuropathic pain&lt;br&gt;• Ophthalmological abnormalities (cornea verticillata and tortuous retinal blood vessels)&lt;br&gt;• Hearing impairment&lt;br&gt;• Dyshidrosis (hypohidrosis and hyperhidrosis)&lt;br&gt;• Hypersensitivity to heat and cold&lt;br&gt;• Gastrointestinal disturbances and abdominal pain&lt;br&gt;• Lethargy and tiredness&lt;br&gt;• Angiokeratomas&lt;br&gt;• Onset of renal and cardiac signs, e.g. microalbuminuria, proteinuria, abnormal heart rate variability</td>
</tr>
<tr>
<td>Early adulthood (17–30 years)</td>
<td>• Extension of any of the above&lt;br&gt;• Proteinuria and progressive renal failure&lt;br&gt;• Cardiomyopathy&lt;br&gt;• Transient ischaemic attacks, strokes&lt;br&gt;• Facial dysmorphism</td>
</tr>
<tr>
<td>Later adulthood (age &gt;30 years)</td>
<td>• Worsening of any of the above&lt;br&gt;• Heart disease (e.g. left ventricular hypertrophy, angina, arrhythmia and dyspnoea)&lt;br&gt;• Stroke and transient ischaemic attacks&lt;br&gt;• Osteopenia and osteoporosis</td>
</tr>
</tbody>
</table>
### Table 2. Effects of ERT on other signs and symptoms of Fabry disease.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Enzyme</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amelioration of GI pain and diarrhoea at 6 months and 3 years of treatment</td>
<td>Agalsidase alfa</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Agalsidase beta</td>
<td>148</td>
</tr>
<tr>
<td>Improvement of acroparaesthesia at 24 months</td>
<td>Agalsidase alfa</td>
<td>152</td>
</tr>
<tr>
<td>Improvement of anhidrosis after 24 months</td>
<td>Agalsidase alfa</td>
<td>42,152</td>
</tr>
<tr>
<td>Improvement of pulmonary symptoms</td>
<td>Agalsidase beta</td>
<td>149</td>
</tr>
<tr>
<td>Improvement of hearing loss at 12 months</td>
<td>Agalsidase alfa</td>
<td>44</td>
</tr>
<tr>
<td>Significant decrease in cerebral hyperfusion versus placebo after 6 months, although no impact on incidence of stroke or TIAs</td>
<td>Agalsidase alfa</td>
<td>150</td>
</tr>
<tr>
<td>Significant improvement (reduction) in elevated cerebral blood flow velocities after 18 months</td>
<td>Agalsidase alfa</td>
<td>151</td>
</tr>
</tbody>
</table>
Figure 1. Kidney biopsy: accumulation of globotriaosylceramide within the lysosomes of glomerular podocytes.

Courtesy: Dominique P Germain, University of Versailles, France.
**Figure 2.** General algorithm for the diagnosis and assessment of patients with Fabry disease (see text for more detail). The initial point of presentation will vary depending on the first symptom. A particular specialist may therefore focus on just one aspect of the disease in the algorithm below before confirmation of the diagnosis and consideration of enzyme replacement therapy.

- **Family member with Fabry disease**
- **Symptoms suggestive of Fabry disease** (e.g. angiokeratomas, acroparesthesiae) see Table 1
- **Biochemical/genetic analysis: males**
  - Measurement of plasma or urinary GB₃ or lyso-GB₃
  - Measurement of plasma α-galactosidase A activity
  - Confirmation of Fabry disease by genetic analysis of the GALA gene
- **Genetic/biochemical analysis: females**
  - Genetic analysis of the GALA gene
  - Measurement of plasma or urinary GB₃ or lyso-GB₃

**Initial positive diagnosis of Fabry disease – referral to tertiary centre**

**Baseline valuation at tertiary centre**

**Pain/QOL**
- Structured assessment scales (e.g. BPI, VAS, SF-36)

**Neurological system**
- Brain MRI
- Temperature sensitivity tests
- Electromyography

**Eyes/ears**
- Slit–lamp examination
- Audiogram

**Renal function**
- Urine dipstick test (microalbuminuria/proteinuria)
- 24-hour urine protein
- Biopsy (only if indicated)
- Ultrasound (vascular lesions)

**Cardiography**
- ECG
- Echo
- 24-hour Holter
- Assessment of cardiac function

**GI system**
- Diarrhoea
- Constipation
- Abdominal pain

**Dermatology**
- Angiokeratomas
- Dyshidrosis
- Telangiectasia

**Enzyme replacement therapy**
**Concomitant therapy**

**Follow-up**
Figure 3. A (C below) - Left ventricular endomyocardial biopsy showing a fragment of conduction tissue (CT) in which almost the entire cell area is occupied by large vacuoles (arrows) whereas in the working myocardium only small perinuclear vacuoles are evident. B (D below) – Transmission electronmicroscopy showing the vacuoles to consist of single membrane-bound myelin bodies containing concentric lamellae suggestive of Fabry disease.91

Figure 4. Aortic root dilatation (47 mm) in a 51-year-old male patient with Fabry disease.\textsuperscript{7}

Courtesy: Olivier Dubourg and Dominique P Germain, University of Versailles, France.
**Figure 5.** A – T1 sagittal image showing a slight hyperintensity (yellow arrows) in the pulvinar area of a 46-year old male Fabry patient. B – T1 axial image showing a well-defined symmetric hyperintensity (yellow arrows) of both pulvinar nuclei of a 46-year old male Fabry patient.

Courtesy: Frederic Colas, Robert Carlier and Dominique P Germain, University of Versailles, France.
Figure 6. Typical angiokeratomas.

Courtesy: Dominique P Germain, University of Versailles, France.
Figure 7. Typical facial dysmorphism in a patient with Fabry disease. Male patient treated with ERT for 10 years, showing prominent supra orbital ridges, bushy eyebrows, peri-orbital puffiness, mild ptosis, prominent jaw line. Facial features seem to normalise to a degree in patients on ERT.