REVIEW

Updated Evaluation of Agalsidase Alfa Enzyme Replacement Therapy for Patients with Fabry Disease: Insights from Real-World Data

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Abstract: The clinical use of agalsidase alfa as enzyme replacement therapy (ERT) for Fabry disease (FD) has spread since 2001, and a large body of evidence of its effectiveness has been collected. This review presents the clinical and laboratory results achieved with agalsidase alfa, which has been published in the literature. Agalsidase alfa infusion slows down or stops the progression of renal damage, expressed by reduction or stabilization of the annual decline of the glomerular filtration rate; yearly decrease of glomerular filtration rate (slope) sometimes is reduced until its stabilization. ERT prevents or reduces the occurrence of hypertrophic cardiomyopathy or slows the increase over time if it is already present. Moreover, regarding neurological manifestations, ERT improves neuropathic pain and quality of life, and recent data indicated that it may also prevent the burden of cerebrovascular disease. In addition to ERT's clinical benefits, crucial topics like the most appropriate time to start therapy and the role of anti-drug antibodies (ADA) are analyzed. Treatment with agalsidase alfa in patients with FD substantially improves their outcomes and enhances their quality of life in patients with FD.

Keywords: Fabry disease, agalsidase alfa, enzyme replacement therapy, clinical outcome in Fabry treated patients

Introduction

Fabry disease (FD) is a genetically X-linked inherited disease due to mutations of the GLA gene encoding for the enzyme α-galactosidase A. Its deficiency determines a progressive deposition of glycosphingolipids such as globotriaosylceramide (Gb3) and its derivate globotriaosylsphingosine (Lyso-Gb3) within the lysosomes with subsequent cellular functional derangements. The disorder is a multisystemic disease that, without treatment, progressively affects the heart, the kidney and the brain, leading to severe complications, including early death. Fabry is a systemic disease; however, the involvement of the kidney, heart, and nervous system leads to the main clinical outcomes.[1]

Clinically, we describe the patients according to their gender and type of mutation. Classical mutation has very low or no serum enzyme activity. It is associated in males with severe clinical features and reduced life expectancies due to kidney, heart, or nervous system involvement. The disease appears less severe later in life in females with classical mutation. The nonclassical mutation, called late-onset phenotype, causes very variable clinical features from minimal to severe illness. Often, the involvement is limited to a single organ (cardiac-variant, for example).[2]

Enzyme replacement therapy (ERT) has been available for more than twenty years, and it has undoubtedly changed the outcome of the disease. Other therapeutic choices have been available recently, such as a chaperone and the modified enzyme (pegylated), and clinical gene therapy clinical trials are currently being performed. However, the experience with these options is more limited and beyond the aims of this review.[3]

Two enzymes are available for therapy, requiring an intravenous infusion every other week. An enzyme of human cell-line origin, agalsidase alfa, is given at 0.2 mg/kg/body weight. The second is agalsidase beta, which originates from

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Chinese hamster ovary cells and is given 1 mg/kg/body weight. The agalsidase alfa has not been approved by the US Food and Drugs Administration but is available in other countries.[4] This review analyses or summarizes the published studies with agalsidase alfa and adds the authors' real-life experience with this ERT. It must be underlined that studies that support the efficacy of agalsidase beta in FD were also published.

ERT in FD aims to prevent or significantly slow down organ involvement by Gb3 deposition. ERT with agalsidase alfa has been available for human therapy since 2001. A registry called Fabry Outcome Survey (FOS) was used to collect data from FD patients worldwide (4500 patients, 26 Countries, 142 sites). It was the primary source for monitoring and disseminating the clinical experiences on the effectiveness of agalsidase alfa.[5,6]

Methods

We searched the websites PubMed, Scopus, and Web of Science for published articles from January 2001 to December 2023 using the words Fabry enzyme replacement therapy [All Fields] and agalsidase alfa enzyme replacement therapy [All Fields]. All original English papers, including case reports and reviews, were considered. All articles that reported outcomes data on patients with Fabry disease treated with agalsidase alfa were eligible for inclusion. As a result, the analysis included reports from randomized clinical trials (RCTs), non-randomized clinical trials, open-label clinical trials, prospective observational studies, retrospective cohort studies, retrospective database studies, registry studies, case series, and case reports. The study information recorded included design, patient population, percentage of male and female participants, total number of patients, number of patients lost to follow-up, ERT dosage, any dose changes or drug switches, patient age at ERT initiation or dose/ERT switch, duration of treatment, disease severity, concomitant medications and α-galactosidase activity. The extracted outcome/endpoint data included plasma and urinary (lyso-)GL-3/Gb$_3$ cardiac echocardiographic, magnetic resonance imaging (MRI) and electrocardiogram measures; glomerular filtration rate (GFR); proteinuria/albuminuria and serum creatinine levels; pain scales, gastrointestinal outcomes, quality of life Data on clinical outcomes were recorded, and outcome measures at baseline, and endpoint were extracted for all treatment outcomes.[7]

The searches were performed in June 2023.

Indications and Issues of ERT

In real-world practice, one of the critical decisions when facing a patient is the timing for starting ERT.

The appropriate timing to initiate therapy was investigated in many consensus conferences or reviews published in the literature. The European Fabry consensus group suggested that ERT should be started as soon as there are early clinical signs of organ involvement in both classical and nonclassical patients.[8] Other groups suggested starting ERT in asymptomatic males with the classical form at the age of 16 years and in females and late-onset patients in the presence of early signs of organ involvement.[9] In addition, Germain et al suggested starting therapy in asymptomatic young classical boys at the age of 7 years with a family history of disease severity in males, undetectable AGAL-A activity in peripheral blood leukocytes and plasma lysoGb$_3$ over 20 nmol/L.[10,11]

On the other hand, some factors limiting therapy may represent barriers. These include complicated venous access, mild or unclear symptoms of the FD, interference with the patient's daily life every other week, and the cost of the treatment.[12]

However, there is a widespread agreement among the authors that the best results are achievable when ERT is started early. In a retrospective analysis of 560 patients subdivided according to age and treated with agalsidase alfa, the annual changes of left ventricular mass LVM) and the glomerular filtration rate (GFR) were attenuated in the group who started ERT early (<18 years).[13] Hughes et al demonstrated that early treatment can prevent renal and cardiac damage in adults with FD. Better results were obtained if ERT was started within two years from the onset of the symptoms. In the same cohort of patients, the results were less impressive if ERT was prescribed within two years from diagnosis; the time elapsed from the onset of symptoms to diagnosis reduced the effectiveness of ERT.[14]

Based on available publications[9–11] and our real-life experience, we agree to start ERT in all classical males, asymptomatic, as early as possible to prevent the inevitable progression of organ involvement. In these cases, the dosage of lyso-Gb3, a biomarker of FD, can be helpful: high levels suggest a classical and more severe disease.[15] Starting ERT with agalsidase alfa is associated with a significant reduction of Lyso-Gb3, which remains stable at a lower level over

time. The clinical meaning of this reduction in the outcome is still unclear.[16] Classical females and patients with late-onset phenotypes must be checked every six months or annually, and ERT must be started as soon as signs or symptoms develop.

Another practical problem is that ERT infusions can be associated with reactions such as malaise, rigour, fever, tachycardia, hypertension or hypotension. These reactions are more frequent during the initial infusions and tend to reduce in the subsequent infusions. Antipyretic medication and a reduced infusion rate are enough to improve infusion-related reactions and enable the infusion. With agalsidase alfa, these reactions are infrequent; they are present in <20% of the infusions.[17] In our real-life experience, the infusion reactions with alfa are mild and do not usually preclude the treatment.

The development of anti-drug antibodies (ADA) is an event that can occur with ERT in 50–88% of patients, mainly in male classical patients, and it is associated with a higher prevalence of infusion reactions.[18–20] The mechanism of these reactions is traceable to circulating enzyme-antibody complexes phagocytized by white blood cells in the peripheral circle.[20]

The presence of neutralizing antibodies is connected with reduced efficacy of ERT, higher levels of serum lyso-Gb3, and more severe clinical symptoms.[21] The positivity for ADA has always crossed between the two enzymes: the ADA react both for alfa and beta enzymes. However, the prevalence of ADA in patients treated with agalsidase alfa is lower than in patients treated with beta.[22] It was suggested that an ADA test should be done annually, especially in patients with progressive disease. It has been recommended that higher enzyme doses could overcome the ADA effects, and immuno-suppressive therapy reduces enzyme inhibition in transplant patients.[23,24] There are no controlled studies to evaluate whether an increased dose of the enzyme or immunosuppressive therapy is beneficial in patients with FD and ADA.

Agalsidase Alfa Data on Cardiomyopathy

Cardiac involvement in Fabry disease is frequent, either in the classical form with systemic involvement or in the late onset "cardiac variant", with clinical manifestation confined to the heart, and significantly affects patients' prognosis and quality of life. Indeed, the leading cause of death in Fabry patients is cardiac-related, with sudden cardiac death being a primary concern.[25] Risk factors associated with sudden cardiac death are age, male gender, left ventricular hypertrophy, late gadolinium enhancement on cardiac resonance imaging, and non-sustained ventricular tachycardia.

Histopathology Findings of Fabry Cardiomyopathy

From a pathologic point of view, in the heart, glycosphingolipids deposition in all cellular types causes progressive left ventricular hypertrophy (LVH) that mimics hypertrophic cardiomyopathy's morphological and clinical picture, with dyspnea on exertion, palpitations, and angina as the typical symptoms. Indeed, angina in Fabry disease is also caused by the involvement of intramural vessels, with severe narrowing and microvascular ischemia, often causing increased troponin and repolarization abnormalities on ECG. Moreover, the involvement of the conduction system leads to arrhythmias and conduction disturbances. It is well recognized that GB3 accumulation per se cannot justify the cardiomyocyte damage and dysfunction observed in Fabry cardiomyopathy. Our group demonstrated, based on endomyocardial biopsy of FD patients, that the increased stiffness of cardiomyocytes, as well as the reduced contractile force, is related to contractile and structural protein abnormalities and that inflammation, oxidative stress and apoptosis contribute to progressive cardiac disease, with increased fibrosis and reduced response to ERT.[26–28] These observations were confirmed in subsequent studies, underlying the importance of understanding the mechanisms of Fabry cardiomyopathy at structural level.[29]

Efficacy of Agalsidase Alfa in Fabry Cardiomyopathy

Many studies have aimed to evaluate the impact of agalsidase alfa treatment on Fabry cardiomyopathy and compare it with the natural history of the disease.

Most reports (Table 1) analyzed the results of agalsidase alfa treatment based on the decreased or stabilization in either left ventricular mass (LVM) index or in left ventricular maximal thickness (LVMWT) or as conventionally assessed by standard echocardiography[30] or by cardiac magnetic resonance (CMR).[31,32] In addition, some studies reported the efficacy of ERT on cardiac symptoms (dyspnoea, palpitation, angina) and the risk of cardiovascular events.

A few years after the introduction of agalsidase alfa, its short-term efficacy on cardiac outcomes was assessed in a randomized, double-blind, placebo-controlled clinical trial[33] including 15 adult male patients. LVM at CMR, QRS duration

Table 1 Fabry Outcome Survey: Main Studies Reporting Data on the Effectiveness of Agalsidase Alfa Replacement Therapy on Fabry Cardiomyopathy

Author	Type of Study	Duration	Population	Cardiac Outcome
Hughes D et al[33]	Randomised, double-blind, placebo-controlled study	6 months	15 male patients	LVMI at CMR was significantly reduced following 6 months of treatment with agalsidase alfa compared with placebo
Beck M et al[17]	FOS retrospective study	2 years	314 patients (203 males, 111 females)	Decrease in LVH and LVMI, particularly in those patients with the greatest degree of hypertrophy and mainly in the first year of treatment
Mehta A, et al[34]	FOS retrospective study	5 years	181 adults (126 males, 55 females)	In patients with baseline LVH, treatment resulted in a sustained reduction in LVMI after 5 years, and in patients without LVH, LVMI remained stable
Beck M et al[35]	FOS retrospective analysis	5 years	164 (71 males, 93 females) patients treated vs 166 untreated cohorts	Sustained reduction in LVMI in treated patients with baseline LVH and stable LVMI in treated patients without baseline hypertrophy
Hughes DA et al[36]	FOS retrospective study	4 years	78 females aged >18 years compared with 172 males	Significant decrease in LVM index in women after 4 years of treatment with agalsidase alfa, while decreased slightly but not significantly from baseline in men.
Kampmann C et al[37]	Single center retrospective study	10 years	45 adult patients (21 men, 24 women)	No patients without LVH developed it, and no patients with LVH at treatment initiation showed a decline in LVM
Ramaswami U et al[38]	FOS retrospective analysis	10 years	69 patients, 34 men and 35 females	In patients with LVH at baseline, mean LVM index/year slightly increased over 10 years in females and males. Without LVH at baseline, mean LVM index/year was stable in females and males over 10 years.
Feriozzi et al Clin Ther.[39]	FOS retrospective study	10 years	560 patients (269 males; 291 females)	Patients with increased LVMI demonstrated a higher probability of cardiac and renal events.
Hughes et al[14]	FOS retrospective study	10 years	Prompt vs delayed treatment in patients with Fabry disease	Prompt agalsidase alfa initiation was associated with significant reduction in risk of cardiac events versus delayed treatment.

Abbreviations: LVMI, Left ventricular mass index; CMR, cardiac magnetic resonance; LVH, left ventricular hypertrophy.

and Gb3 levels in cardiac tissue, urine sediment and plasma were measured at baseline and after 6 months. Ten out of 15 patients fulfilled the baseline criterion of LVM above 225 g, which is the upper 95% confidence limit for LVM by CMR. LVM was significantly reduced following 6 months of treatment with agalsidase alfa compared with placebo (p = 0.041). A mean 20% reduction in myocardial Gb3 content was also shown compared to a 10% increase in patients receiving placebo (p = 0.42). For the clinicians, this was a critical study, demonstrating, even if in a small group of patients, the reduction in cardiac hypertrophy in association with a decrease of intramyocardial Gb3 content, and raised great hopes about the possibility of reversing cardiac hypertrophy with agalsidase alfa even in the advanced phase of the disease.

The first FOS database study on the effects of ERT on the heart was reported by Beck in 314 patients receiving treatment with agalsidase alfa (188 for at least 12 months and 92 for at least 24 months).[17] Left ventricular maximal wall thickness (MWT) and LVM indexed to height (gm^{-2}) were assessed by serial echocardiography, considering MWT > 11 mm and LVM > 50 g m^{-2} as cut-off values. The study demonstrated a decrease in MWT and height-adjusted LVM, particularly in those patients with the most significant degree of hypertrophy, with the most striking changes after 1 year of treatment and a much smaller impact during the second year of ERT.

These results were confirmed by a subsequent study that showed the efficacy of a five-year course of treatment[34] in 181 adults (126 men) from the FOS. In this study, in patients with baseline cardiac hypertrophy, treatment resulted in a sustained reduction in LVM index after 5 years (from 71.4 [SD 22.5] g/m2.7 to 64.1 [18.7] g/m2.7, p=0.0111) and a significant increase in midwall fractional shortening (MFS) from 14.3% to 16.0% after 3 years (p=0.02). In patients without baseline hypertrophy, the LVM index and MFS remained stable. Overall, stabilization occurred in about 80% of patients at 5 years, 72% with baseline LVH and 92% without baseline LVH. Consistent with the previous FOS analysis, LVM index reduction occurred mainly in the first year of treatment, with stabilization during long-term follow-up.

The sustained benefits of agalsidase alfa during 5 years of treatment were confirmed in a study by Beck et al,[35] in which, for the first time, patients treated with agalsidase alfa were compared with similar untreated individuals from previous published studies.[40] The cardiac parameter analyzed was the annualized slopes in LVM index, calculated from the echocardiogram. The LVM idex rate of change estimates was derived, and for LVM index analyses, LVMI values <5 g/m2.[7] or >1000 g/m2.[7] were excluded in patients treated with agalsidase alfa had a negligible annualized rate of change in the LVMI that progressed in untreated patients. The mean rate of LVM index change was 0.33 g/m²/y in treated males and 0.48 in treated females, compared with LVM index increasing at a rate of 4.07 in untreated males and 2.31 in untreated females. In males and females with LVH at baseline, the differences in the rate of change between the ERT and untreated cohorts suggest a treatment effect. Moreover, morbidity and mortality occurred later in treated patients, with first events and deaths occurring at older ages compared with the untreated group.

Agalsidase Alfa in Fabry Females

Few studies specifically evaluated the efficacy of agalsidase alfa in females. The timing of ERT initiation and the effectiveness of agalsidase alfa treatment, specifically on Fabry females, was assessed in a cohort of 78 women treated for 4 years and compared with 172 men in a retrospective study using FOS data.[36] The left ventricular mass (LVM) index was determined by standard echocardiography and adjusted for height using the Devereux formula. Left ventricular hypertrophy (LVH) was predefined as an LVM index higher than the upper standard limit (men, ≥51 g/m;2.[7] women, ≥48 g/m).2.[7] During treatment, there was a significant decrease in LVM index in women from a mean of 48.2± 17.0 g/m2.7 at baseline to 43.7±14.3 g/m2.[7] after 4 years of treatment with agalsidase alfa, while mean LVM index had decreased slightly but not significantly from baseline in men. The reduction was significant in women with LVH at baseline. In women with normal LVM at baseline, no significant change in the LVM index indicates a lack of disease progression.

Long-Term Agalsidase Alfa Follow-Up Studies on Fabry Cardiomyopathy

Studies on long-term follow-up of patients with Fabry cardiomyopathy on ERT are also available. Kampmann et al[37] reported a 10-year follow-up of agalsidase alfa treatment in a single-centre study on 45 adult patients (21 men, 24 women). At the start of therapy, 71% of men and 67% of women presented LVM index ≥50 g/m.2.[7] After 10 years of ERT, the LVM index was not significantly changed in men and women with a baseline LVM index <50 g/m;2.[7] however, in males with baseline values ≥50 g/m,2.[7] the LVM index was significantly reduced. A marked improvement was noticeable in these patients after just 1 year, similar to the findings of short-term follow-up studies. A similar improvement after 1 year was observed in females with LVH and sustained for 3 years. However, after 10 years, the mean LVM index was not significantly different from the baseline. In addition, agalsidase alfa treatment stabilized ejection fraction heart rate and improved heart failure symptoms (NYHA class) by at least 1 class.

FOS data confirmed these observations, reporting ten years of follow-up data[41] and three-time point cardiac data were available for 69 patients, 34 males and 35 females. LVH was defined as LVMI >48 g/m2.7 in females and LVMI >50 g/m2.7 in males, calculated using the Devereux formula from measurements obtained by echocardiography. LVMI slopes over 10 years were analyzed considering sex and baseline LVH status. Baseline LVH was present in 52.9% of females and 40.0% of males. In patients without LVH at baseline, cardiac mass remained stable in females and males throughout the 10-year treatment period. Among those with LVH at baseline, the mean LVM index had slight, insignificant positive slopes for both females and males throughout the 10-year treatment periods.

Effect of Agalsidase Alfa on Cardiac Symptoms

More recent studies focused on the risk of cardiovascular events in patients who received agalsidase alfa treatment. Cardiovascular events included myocardial infarction, the occurrence of LVH (in patients without LVH at baseline, ie LVMI < 50 g/m2.[7] in males; <48 g/ m2.[7] in females), heart failure, arrhythmia, conduction abnormalities, and cardiac surgery. The effects of baseline LVH on cardiovascular outcomes were evaluated for a follow-up period of up to 10 years.[38] Among the 560 patients (269 males; 291 females) with available LVM index data, 55% had increased LVMI, and 45% had standard LVMI index at baseline. The risk of a cardiovascular event was higher in the subgroup with increased LVMI versus the standard LVM index at baseline. Moreover, the presence of LVH at ERT start was associated with

a higher risk of renal events, underlining the pathogenic correlations between chronic kidney disease and myocardial disease.

Similarly, a retrospective analysis of prompt versus delayed initiation of agalsidase alfa in the FOS, defined as <24 months from symptoms onset or diagnosis and ≥24 months from symptoms onset or diagnosis, showed that prompt initiation of ERT significantly reduced the probability of cardiovascular events including heart failure, arrhythmia, cardiac surgery, conduction abnormality, LVH, and myocardial infarction.[39]

Finally, a long-term analysis using deconstructed composite events showed that cardiac events occurred at younger ages than renal or cerebrovascular events and that male patients were more likely than female patients to experience cardiac events at a younger age of.[35] In summary, agalsidase alfa has long-term benefits for FD cardiomyopathy regardless of gender and the severity of cardiac symptoms before treatment. In patients with cardiac hypertrophy at the beginning of treatment, agalsidase alfa can stabilize cardiomyopathy with no or slight increase in the LVMI index. In contrast, in patients with normal LVMI, the treatment prevents the increase in LVM index. In both cases, agalsidase alfa treatment modifies the natural history of the disease. It should be started as soon as possible to obtain better cardiac results, even in female patients, according to available expert recommendations.[8] Indeed, data on the efficacy of early treatment on Fabry cardiomyopathy are the most important findings, as we know that FD is a progressive disease, with a natural history always marked by an increase in left ventricular wall thickness.[42]

On the other hand, the progression of FD cardiomyopathy is accompanied by the establishment of secondary mechanisms of cardiac damage (ie oxidative stress, inflammation, apoptosis, fibrosis)[26,27] that cannot be reversed by ERT alone and that can be determinants to the progression of the disease and the reduced efficacy of ERT. In particular, the severity of fibrosis, as detected d by late gadolinium enhancement at CMR, has been related to the long-term response to ERT (Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: evidence for a better outcome with early treatment).[43]

In addition, cardiac downregulation of ERT receptors (mannose-6-phosphate receptors), which is more pronounced in advanced disease, can contribute to ERT resistance in the advanced phases of the disease.[44]

Comparison with Agalsidase Beta and Migalastat

Similar to the results obtained with agalsidase alfa treatment, long-term studies with agalsidase beta reported favourable cardiac outcomes. Study[45] investigated the long-term consequences of 52 of 58 patients with classic Fabry disease from the Phase 3 clinical trial of agalsidase beta using aggregate data from the trial and extension study and the Fabry Registry. Severe clinical events, such as myocardial infarction, congestive heart failure, major cardiac procedures (ie, implantation of a balloon pump, cardioverter-defibrillator or first pacemaker, or bypass surgery), stroke and death were assessed together with structural parameters, as left ventricular posterior wall thickness (LVPWT) and interventricular septum thickness (IVST). Overall, mean LPWT and IVST did not significantly increase during the 10-year treatment interval, suggesting stabilization over time. In patients aged <40 years receiving agalsidase beta, LPWT and IVST remained stable. In contrast, in patients aged >40 years at first infusion, LPWT and IVST significantly progressed from baseline to last follow-up. In addition, agalsidase beta treatment was associated with a significant 61% relative risk reduction of cardiac life-threatening events and death.

There is not evidence of the superiority of one ERT over the other. As for the chaperone treatment with Migalastat, it was shown in clinical trials and open-label extension studies that it was associated with a significant decrease in LVMI.[46]

However, no long-term follow-up studies are available, and the treatment has the limitation of being possible only for patients with known mutations.

Supportive Therapies for Fabry Cardiomyopathy

In addition to FD-specific therapies, conventional therapies are necessary to manage cardiovascular manifestations of FD. Updated expert recommendations have been provided in a recent consensus document.[47]

In particular, drugs affecting AV node conduction (beta-blockers, verapamil, disopyramide) should be used cautiously because the disease also affects the conduction tissue. At the same time, amiodarone should be limited to the management of poorly tolerated acute episodes of arrhythmia, as chronic therapy may induce phospholipidosis and potentially reduce the effect of ERT.

Agalsidase Alfa Data on the Nephropathy

Since 2001, the effectiveness of ERT has been a critical focus of clinical studies, and many papers have been published demonstrating that agalsidase alfa slows down or stops the progression of renal damage.[5,13,34–37,41] These studies assessed the effectiveness of ERT as a marker for the yearly reduction of the estimated glomerular filtration rate (eGFR) over time, namely slope (mL/min/year). (Table 2)

Data regarding the long-term effectiveness of agalsidase alfa on the progression of nephropathy collected on FOS during the first 10 years were published in 2015. To evaluate the effects of ERT, the results observed in the cohort of patients in FOS were compared with clinical and laboratory data in a cohort of untreated patients (before the availability of ERT) and published in the literature.[35] The investigation was carried out by subdividing the patients according to

Table 2 Fabry Outcome Survey: Main Studies Reporting Data on the Effectiveness of Agalsidase Alfa Replacement Therapy on Fabry Nephropathy

Author	Type of Study	Duration	Population	Renal Outcome
Dehout F et al[48]	FOS retrospective analysis	1 year	234 patients	Significant increase in eGFR in patients with mild decrease in eGFR at baseline; eGFR maintained in patients with moderate eGFR at baseline
Beck M et al[17]	FOS retrospective study	2 years	314 patients (203 males, 111 females)	Renal function stabilized in male and female patients with mild or moderate renal disease at baseline.
Schwarting A et al[49]	FOS retrospective study	2 years	201 patients aged 20–60 years; 20 patients with chronic kidney disease CKD stages II or III at baseline	Independent inverse association between serum creatinine and time on ERT; significant decline in renal function before ERT; after 1 and 2 years of ERT, decline in eGFR was stabilized
Mehta A et al[34]	FOS retrospective study	5 years	181 adults (126 males, 55 females)	Improved or stabilized renal function or decelerated decline in renal function
West M et al[50]	Three prospective, randomized, placebo-controlled trials, open-label	2 years	108 male patients aged ≥18 years	Agalsidase alfa improved or stabilized renal function in male patients. Mean estimated annual decline in GFR slowed vs placebo;
Whybra C et al[51]	Prospective, single-centre, open-label	4 years	36 adult female ERT-naïve patients	Stability or improvement in kidney function in >90% of female patients
Feriozzi S et al[52]	FOS retrospective study	>3 years	115 adult males, 55 adult females	Agalsidase alfa combined with ACE inhibitors/ARB may effectively slow the deterioration in renal function in Fabry nephropathy.
Hughes DA et al[36]	FOS retrospective study	4 years	250 patients (172 males, 78 females) aged >18 years	A decline of eGFR 1.5 mL/min/year for females and –2,1 mL/min/year for males -
Ramaswami U et al[53]	FOS retrospective study	4,2 years	8 children (7 boys, 1 girl; all symptomatic)	Renal function remained within normal limits over the observation period.
Ramaswami U et al[54]	FOS retrospective study	2 years	98 children (64 boys, 34 girls) aged <18 years	No significant changes in eGFR over 12 months or 24 months; proteinuria remained stable

(*Continued*)

Table 2 (Continued).

Author	Type of Study	Duration	Population	Renal Outcome
Feriozzi S et al[55]	FOS retrospective study	>5 years	208 patients (134 males, 74 females) aged >18 years	Rate of Fabry nephropathy progression stabilized in women; mild-to-moderate decline of renal function in men. The role of hypertension and proteinuria was highlighted.
Kampmann C et al[37]	FOS retrospective analysis, prospectively collected data	10 years	45 adult patients (21 males, 24 females)	eGFR values did not change significantly over 10 years. Renal function was maintained after 10 years of treatment.
Beck M et al[35]	FOS retrospective analysis	5 years	740 patients (treated vs untreated cohorts)	Slowed progression of renal impairment in males with poor renal function at baseline; slower decline in renal function regardless of baseline eGFR, gender and baseline urinary protein level
Goker-Alpan et al[56]	Open-label	2 years	14 children (5 boys, 9 girls)	Disease progression may be slowed when ERT is started before major organ dysfunction. Safety is confirmed
Beck M et al[57]	FOS retrospective study	ExtensionPrevious paper (+3 years)[35]	Children/adults (n=677)	The median age of the first renal event is 78.4 years in males (not evaluable in females). The probability of not having a renal event among female patients was relatively high, even at advanced ages.
Ramaswami U et al[38]	FOS retrospective data	10 years	152 patients 62 females, 90 males aged >18 years	With baseline eGFR ≥60 mL/min/1.73 m^2, the rate of eGFR change over 10 years was relatively stable in females and slightly declined in males. With baseline eGFR <60 mL/min/1.73 m^2, the rate of eGFR change was stable in females and slightly decreased in males.
Feriozzi et al[39]	FOS retrospective study	15 years	Patients who received ERT had available data for eGFR at ERT initiation	Patients with left ventricular hypertrophy demonstrated a higher probability of renal events. Patients with reduced renal function also show a higher likelihood of renal events.
Parini R et al[13]	FOS retrospective study	3 cohorts:age <18: 6.3±4.3 age >18<30: 8.6±4.9 age >30: 7.9±4.9 years	Males with childhood symptom onset who started agalsidase alfa at ≤18 years of age, >18 and ≤30 years of age, and >30 years of age	Initiating ERT in childhood before the manifestation of severe symptoms may attenuate progress.
Hughes et al[14]	FOS retrospective study	15 years	Prompt vs delayed treatment in patients with Fabry disease (agalsidase alfa initiated less or more than 24 months)	Prompt agalsidase alfa initiation was associated with:Significant reduction in risk of renal events versus delayed treatment; Fewer renal events in patients aged ≤20 years

(*Continued*)

Table 2 (Continued).

Author	Type of Study	Duration	Population	Renal Outcome
Cybulla et al[58]	FOS retrospective study	>5 years	153 male patients, aged>16 years	Patients with classic Fabry disease had similar rates of eGFR decline irrespective of baseline proteinuria. Baseline proteinuria significantly impacted the rate of eGFR decline overall.

gender and eGFR at baseline. With an eGFR>60 mL/min/1.73 m² at baseline, the treated males had a slope of −1,68 vs −3 mL/min/y in untreated, and the females had a slope of −0.4 in treated vs −0.9 mL/min/y in untreated. In the group with eGFR <60 mL/min/1.73 m² at baseline, the slopes were −4,7 vs −6,9 mL/min/y for males treated vs untreated and −0,3 vs −2,1 mL/min/y in females respectively treated or not.

The demonstration of a diffuse reduction of the yearly slope of eGFR undoubtedly confirmed the effectiveness of ERT with alfa in slowing down or stopping the natural course of the disease. However, we have also considered that the data were collected in different "eras". In previous years, Fabry patients' clinical attention was not as thorough as in the ERT age. At the same time, in this FOS study and other papers, it was evident that renal progression in Fabry nephropathy is affected by other drivers, such as proteinuria and arterial hypertension, as in all nephropathies. In two retrospective papers, the value of proteinuria and the presence of arterial hypertension were highlighted as markers of a faster progression of nephropathy.[52,55] In patients treated >5 years, we reported that those with 24/proteinuria at baseline <500 mg had a reduced slope of eGFR compared with patients with proteinuria between 500 mg and 1g, and even more in patients with >1g proteinuria. The negative effect of proteinuria on the progression of renal damage is based mainly on the capacity of proteinuria to induce the epithelial–mesenchymal transformation of tubular epithelium. This transformation determines the release of pro-inflammatory and pro-fibrotic cytokines in the renal tissue with the development of fibrosis.[59]

Similar slope reductions were observed for arterial hypertension. The presence of arterial hypertension negatively affected Fabry nephropathy. Indeed, hypertensive patients had a lower baseline eGFR and a higher annual slope value than non-hypertensive patients. The high blood pressure value can determine increased intraglomerular pressure with changes in glomerular structures.

These observations should bring our attention back to the supportive therapy of Fabry nephropathy. This therapy aims to reduce the non-immunological progression of renal damage. In particular, early and appropriate treatment with drugs interfering with the renin-angiotensin system is advisable to reduce proteinuria and arterial hypertension. Furthermore, other drugs, such as sodium-glucose cotransporter-2 inhibitors (SGLT2), anti-endothelin molecules, and mineralocorticoid receptor inhibitors, are attracting the attention of nephrologists to contrast the progression of renal damage. Still, their role in treating Fabry nephropathy has not yet been clarified, and a multicenter observational prospective cohort study will evaluate the effect of the SGLT2 dapagliflozin.[60]

Recently, Ramaswami et al analyzed retrospective data from a cohort of 152 patients (90 males), stratifying the patients according to the value of eGFR >60 or <60 mL/min/1.73m². After 10 years of ERT, the slope reduction was limited in males and arrested in females at −1.99 and −0.55 mL/min/y, respectively.[38]

The paediatric population (64 boys and 34 girls) has been separately analyzed in FOS. The renal function remained stable over the follow-up, and notably, there was a particular interest in safety and infusion reactions.[54] In patients with overt renal failure eGFR <60 mL/min/1.73m², the males had a mild annual slope of − 2.79 mL/min/y, while the females' eGFR remained stable at −0.14 mL/min/y. There were 55 infusion reactions in 23 children (21 males) without significant effects on the treatment, indicating continued safety of long-term ERT. The efficacy of agalsidase alfa in the paediatric population has been confirmed in other recent studies, such as by Goker-Alpan et al. She described the clinical experience of 14 children in ERT and reported stabilization of renal function without any side effects using agalsidase alfa.[56]

A peculiar issue in FD is the contemporary presence of renal and cardiac involvement called cardio-renal syndrome type 5 (see paragraph). The synergic interaction between the heart and the kidney has been extensively investigated.[39,61] The risk for synergic cardiovascular events was assessed in 560 patients with available data. The subgroup with a low eGFR at baseline (< 90 mL/min/1.73 m^2) had a significantly higher risk for a cardiovascular event (HR = 1.33; 95% CI, 1.04–1.70; P = 0.021) or a renal event (HR = 5.88; 95% CI, 2.73–12.68; P < 0.001) compared with patients with a normal eGFR at baseline (>90 mL/min/1.73 m^2). An early start of agalsidase alfa therapy may attenuate both organ damage and improve the outcome. We can suppose that the early start of ERT likely prevents the deposition of a massive quantity of Gb3, reducing the activation of pathogenetic inflammatory pathways resulting in tissue damage.[62] These mechanisms may become subsequently independent from Gb3 deposition, and a late clearance of Gb3 is less effective.[63]

A recent study has investigated the role of the type of mutation (classical or nonclassical) associated with proteinuria on the effectiveness of agalsidase alfa therapy in Fabry nephropathy.[58] In the whole population, 193 male patients treated with agalsidase alfa for more than 5 years, the higher values of proteinuria (>500 mg/24h) were associated with lower baseline eGFR (89 mL (min/1.73m2) and a faster decline of renal function (−3,6 mL/min/y) when compared with low proteinuria (<500 mg) with baseline eGFR 106 mL/min/1.73m2 and a slope −1,6 mL/min/y. A genetic analysis was carried out to investigate the role of the type of mutation on the progression of renal damage in treated patients. The mutation analysis was available in 86 patients. The final result showed that those with low proteinuria and nonclassical phenotype had the slowest value of annual slope −1.1 mL/min/y. The classical patients had a similar decline irrespective of baseline proteinuria (−1.98 and −2.08 mL/min/1.73 m^2 for the low proteinuria and high proteinuria groups, respectively. Unfortunately, only one patient had a nonclassical mutation and higher proteinuria, limiting the comparisons between groups. This evidence should be confirmed in a broader population, but it indicates a significant role of the type of mutation in the progression of renal damage. Moreover, treatment with agalsidase alfa was associated with the same progression of renal disease in classical vs nonclassical mutation. This paper suggests that all the therapeutic results should also be assessed considering the type of mutation, not only for the whole cohort of patients in the study.

From all these data published on the ERT with agalsidase alfa, we can conclude that agalsidase alfa slows down or stops (mostly in females) the progression of renal disease, and the treatment has to be started early. In addition, we should also treat the non-immunological factors of renal damage progression with appropriate and timely concomitant therapy.

ERT with agalsidase beta has demonstrated its effectiveness on renal involvement in FD. Germain[45] et al reported the experience from the Fabry registry after ten years of agalsidase beta treatment. The cohort of the patients was subdivided into high-risk (HRI)or low-risk renal involvement (LRI) stratified according to more or less than 1g/proteinuria 24h: patients with mild proteinuria (<1g/24h) and less sclerotic glomerular damage had a better outcome. The mean slopes for the estimated glomerular filtration rate for LRI and HRI were −1.89 mL/min/1.73 m^2/year and −6.82 mL/min/1.73 m^2/year, respectively. These results were confirmed in a recent study with the Fabry registry in patients (117 males, 59 females) who initiated treatment 30 years before ag. The eGFR slopes were −1.18 and −0.92 mL/min/1.73m2/year, respectively, for males and females. In addition, these data reaffirm the role of proteinuria in the progression of renal damage. For males with higher 24-hour proteinuria, the eGFR slope was −2.39 mL/min/1.73m^2/year compared to −1.18 mL/min/1.73m^2/year for males with low proteinuria.[64]

The oral chaperone Migalastat has significantly reduced the progression of Fabry nephropathy in patients with amenable mutations. However, clinical experience is shorter than ERT, and the drug is not indicated when the GFR is less than 30 mL/min/1,73m.2[65]

In real life, we should pay attention to early signs of renal involvement to start ERT without waiting for overt proteinuria or eGFR reduction, as recommended in an international survey that involved clinical researchers worldwide who used a modified Delphi model.[9] The presence of mild pathologic values of urinary albumin/creatinine excretion (microalbuminuria) or podocytes in the urine (podocyturia) can be red flags to start ERT. The young population should be alerted to the high value of eGFR. This marker, easily detectable, can indicate a condition of glomerular hyperfiltration (eGFR<135 mL/min/1,73m^2). Glomerular hyperfiltration can damage the glomerular structures, precede overt nephropathy, and can be corrected with ERT.[66] Moreover, an increase of serum cystatin C, a little-used marker of renal function, may indicate nephropathy early on when values of serum creatine (and then eGFR) are still in the normal range.[67]

Finally, renal transplant is the therapy of choice in uremic patients, and it has been successfully carried out in Fabry patients. Agalsidase alfa was prescribed in renal transplant patients (before or after the transplant), and the renal function remained stable, the drug was well tolerated, and there was no interference with immunosuppressive therapy.[68]

Cardio-Renal Syndrome

An acute or chronic heart or kidney dysfunction can mutually interact, determining pathological consequences on other organs. The physio-pathological consequences are described as cardiorenal syndrome. There are different subtypes of this syndrome; an acute cardiac attack can negatively affect the renal blood flow, or an acute kidney injury can determine cardiological dysfunction. The same interactions can develop in chronic kidney disease or chronic heart failure.[69] A pathology characterizing the fifth type affects both organs contemporaneously, as in diabetes. The cardio-renal in Fabry disease is included in this fifth subtype. The concomitant alteration of the heart and the kidney is due to the damage induced by Gb3 deposition and the inflammatory and pathological pathways resulting in tissue fibrosis. These activated processes play a crucial role in determining the failure of both organs. Agalsidase alfa was evaluated in a large FOS study, which included more than 500 patients.[39] The investigation assessed how cardiac or renal damage could affect the patient's outcome. The presence of a previous LVH was followed by a higher occurrence of cardiovascular or renal events than patients without LVH. The same results occurred in patients with normal renal function (eGFR>60 mL/ min/1,73m^2) who had fewer cardiac and renal events. Similarly, a German study[61] evaluated not only the effect of cardiac and renal involvement of Fabry patients on ERT, both alfa and beta agalsidase, but also their cardiac, renal, and neurological outcomes. A reduction of eGFR <75 (eGFR>60 mL/min/1,73m2) at baseline) was associated with increased risk for cardiovascular endpoints and renal and neurological outcomes.

These observations confirm the significant pathological role of the cardiorenal interactions and are indicative of the need for a prompt start of therapy to try to reduce these pathological loops.[14]

The high-sensitivity troponin T and N-terminal pro-brain natriuretic peptide (NT-proBNP) are biomarkers from the early stages of cardiomyopathy in Fabry disease[9,70,71] and can indicate heart involvement. Therefore, the cardio-renal syndrome can help in early suspicion of cardiac pathology, which should be strictly assessed with the possible concomitant nephropathy.

Agalsidase Alfa on Neurological Disease

PAIN

Pain is the hallmark of the classical form of FD. Patients describe four types of pain, mostly involving the soles of the feet and palms of the hands. Types of pain include evoked pain (characterized by allodynia or hyperalgesia), episodic pain, chronic, permanent pain, and pain crises (also known as Fabry crises), excruciating pain that can last hours or days. Pain can be triggered by stress, heat, fever, exercise, or fatigue and is usually described as a burning, stabbing, or electrifying sensation. These sensations are often combined with hypohidrosis or anhidrosis and can lead to exercise intolerance.[72,73]

The overall prevalence of any pain in patients with FD is 73.1%; pain occurs more frequently in males (81.4%) than females (65.3%), with a mean age at onset of 14.8 years in males and 19.8 years in females.[74] In the pivotal, double-blind, placebo-controlled study, Schiffmann evaluated 26 adult males with FD. Pain was assessed using the Brief Pain Inventory (BPI), which contains questions relating to pain and its interference with life, and each question is answered by circling a number between 0 and 10 to obtain a score.[22]

Significant decrements of 1.9 points in the BPI score of worst pain (P<0.2) and 1.1 points in pain-related quality of life (P=0.05) were observed only in the treated group of 14 patients while without pain medication.

A 3-year open-label extension study followed this study. In patients who crossed over from placebo to ERT (N=10), mean pain-at-its-worst significantly decreased from 6.9 to 4.5. Moreover, there was a significant reduction in the threshold for cold and warm sensations in the foot. At 3 years, sweat function improved 24–72 hours post-enzyme infusion (0.57–0.71 - l/mm2) and normalized in 4 anhidrotic patients. The authors concluded that prolonged ERT in FD leads to a modest but significant improvement in the clinical manifestations of the small-fibre neuropathy associated with this disorder.[69] No evidence of small-fibre skin reinnervation was identified.[75]

Beck et al[17] reported the effect of ERT on 315 patients included in FOS. After 1 year of treatment, there were significant improvements in walking ability, general activity, routine work and social relationships. After 2 years of treatment, there were substantial improvements in the BPI subscales "average pain" and "pain now". Changes in pain medication did not explain improvements in BPI scores. Moreover, there was a significant improvement in the EQ-5D utility score throughout the 2 years of treatment.

The clinical response after 5-year treatment with agalsidase alfa in 181 adult patients enrolled in FOS was analyzed by Mehta et al.[34] Average pain, measured by BPI score, improved significantly, from 3.7 at baseline to 2.5 after 5 years (P=0.0023). Quality of life, measured by deviation scores from average Euro Qol values, improved significantly, from –0.24 at baseline to –0.17 after 5 years (P=0.0483).

Ries et al conducted a 6-month open-label study at 3 tertiary care centres with 24 children (19 boys and 5 girls) with a mean age of 11.8 (6.5–18) years. Improvement in pain assessed by either the BPI or QoL subscores with only 6 months of agalsidase alfa therapy was not statistically significant. However, 55% of patients on anticonvulsive medication for neuropathic pain could decrease or cease their consumption of these drugs.[76]

A long-term open-label study of this group of children reported significant improvement in "pain at its worst": mean pain score declined from 6.05 to 3.19 (P < 0.001). Similar reductions were seen in the BPI "average pain" score from 2.96 at baseline to 1.70 after 1 year of agalsidase alfa (P < 0.05) and remained significantly reduced throughout 4 years.[77]

In a retrospective study of 98 children included in FOS, Ramaswami et al evaluated the response of pain to agalsidase alfa in the group with at least 1 year of treatment. Baseline and 12-month data were available for 28 boys and 17 girls, and baseline and 24-month data were available for 22 boys and 17 girls. Reductions in pain prevalence and pain crises were observed in the patients showing pain attacks or chronic pain at baseline.[42]

In an open-label study, Whybra et al evaluated the response to ERT in 36 symptomatic women with FD. There was a significant improvement in pain: BPI "pain at its worst." The pain score at baseline was 4.6 ± 2.9 and declined to 3.3 ± 2.9 after 12 months (P = 0.001).[51]

Responses to treatment from 78 women who were treated for 4 years, compared with those of 172 men, were obtained from the FOS. No significant improvements in BPI scores were seen.[36]

A randomized, double-blind, placebo-controlled crossover study investigated 3 dosing intervals in 18 Fabry patients to explore whether more frequent doses were beneficial.[78] Each patient received 3 agalsidase alfa dosing schedules for four weeks (A: 0.2 mg/kg every 2 weeks, B: 0.1 mg/kg/week, C: 0.2 mg/kg/week). No significant differences were found among the schedules for the primary efficacy outcome of self-assessed health state or pain scores. A trend toward increased sweat volume on QSART testing was seen with treatment schedule C. Weekly infusions of agalsidase alfa were not better than the approved dosing schedule. A limitation, however, was that patients enrolled in the study had received ERT for some years, were relatively old (mean age 47 years) and had high health state levels and low levels of pain.

Hoffmann et al evaluated the response to patients' pain included in FOS[5.] The severity of pain at baseline and after 24 months of treatment was available in 81 adult patients (50 males, 31 females). In addition, for 62 patients (41 males, 21 females), data about the severity of pain at baseline and after 36 consecutive months of ERT were analyzed. After 24 months, all dimensions of pain perception showed improvements, and severity classification shifted toward less severe pain (P<0.05). Average changes in the visual analogue scale after 24 months using signed-rank tests also demonstrated significantly less pain in "pain at its worst" (P<0.005), "pain at its least" (P<0.005), "average pain." (P<0.0005), and "pain now" (P<0.0005). Mean changes were of similar magnitude in males and females. Data collected after 36 months of treatment with agalsidase alfa supported the 2-year results.

Vedder et al evaluated 34 FD patients treated with either agalsidase alfa or agalsidase beta at a dose of 0.2mg/kg biweekly. No significant improvement in pain scores was seen in either group. Unfortunately, patients without pain were not excluded from this analysis.[79]

Several groups reported that the results of pain scores after patients on agalsidase beta were switched to agalsidase alfa with conflicting results.

A group of 89 adult patients with FD who had received agalsidase beta (1.0 mg/kg body wt) for >1 year were nonrandomly assigned to continue this treatment regimen (regular-dose group, n=24), to receive a reduced dose of 0.3–0.5 mg/kg and a subsequent switch to 0.2 mg/kg agalsidase alfa (dose-reduction-switch group, n=28), or to directly

switch to 0.2 mg/kg agalsidase alfa (switch group, n=37) and were followed-up for 2 years. Frequencies of pain attacks and permanent pain remained stable in all three groups between baseline and 2-year follow-up.[80]

One study reported no changes in pain in 40 patients who switched from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW and were followed for 28–150 months.[81]

One publication (including 105 patients followed for 8–16 months) reported statistically significant increases in chronic pain and pain attacks after switching from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW.[82,83]

Case reports, and an uncontrolled small series of patients reported improvements in pain or acroparesthesias.[83–89]

In summary, we can conclude that the beneficial effect of Agalsidase alfa in pain improvement was documented in the short-term controlled initial study[22] and sustained throughout long-lasting prospective studies in both adults[74] and children.[77]

Similarly, registry studies identified continuous pain improvement 2 and 5 years after ERT initiation.[17,34,74] Moreover, coincident beneficial effects were reported in case reports and uncontrolled small series.[83–89]

Pain improvement is usually combined with better quality of life scores,[90] but most studies agree that it is partial, and the patients typically require the use of concomitant neuropathic pain medications.

Based on these studies and similar results with the use of agalsidase beta, there is broad consensus that ERT should be considered for symptomatic boys and girls with neuropathic pain. Moreover, asymptomatic boys may benefit from an earlier initiation of ERT based on the following criteria: presence of a pathogenic GLA variant responsible for the classic phenotype, family history of disease severity in males, undetectable AGAL-A activity in peripheral blood leukocytes and plasma lysoGb$_3$ over 20 nmol/L. There is currently no data supporting ERT initiation in asymptomatic girls.[11,91]

ERT should be considered in children with neuropathic pain even if completely controlled (not interfering with daily activities) with pain medication[8] Both Agalsidase alfa and beta are similar in regards to the benefit of pain and quality of life.[92] In our practice, we start ERT treatment in patients with FD, either male or female, who develop pain that can not be easily controlled with neuropathic pain medications, and we quantify the response using BPI. Pain is usually improved at least partially, but in our experience, concomitant medications are necessary for many patients to optimize pain control. Carbamazepine was the drug of choice for many years; more recently, pregabalin/gabapentin and duloxetine are also commonly used. Considering that depression is a frequent finding in patients with FD and is associated with chronic neuropathic pain, dual antidepressants like duloxetine or venlafaxine, in our experience, are very useful in these patients with fewer side effects than tricyclics.[92,93]

Non-steroidal anti-inflammatory drugs are not indicated to treat neuropathic pain and may lead to gastric and renal side effects. Moreover, opioids should be avoided as a chronic treatment in patients with neuropathic pain because of the risk of addiction, and cannabinoids are not effective in neuropathic pain and have a high risk of addiction and psychiatric side effects.[94,95]

Cerebrovascular Disease

The prevalence of cerebrovascular disease in FD patients identified in the FOS was 11% in males and 15% in females, a prevalence 12 times higher than that observed in a comparable non-Fabry population.[96]

In the global Fabry Registry, 6.9% of males and 4.3% of females with FD had an ischemic or hemorrhagic stroke. Furthermore, 50% of males and 38% of females developed their stroke before the diagnosis of FD was known[97] Moreover, FD has been identified as an underdiagnosed aetiology of stroke in the young.[98,99] Whether ERT is beneficial for the prevention of stroke is still a controversial topic.

It was initially considered that ERT was ineffective in reducing the risk of stroke and did not cross the blood–brain barrier, which was one of the explanations for this assumption. Nevertheless, autopsies from FD patients on ERT treatment indicate an almost complete clearance of endothelial glycolipids but persistent marked storage in vascular smooth muscle cells associated with intimal fibrous thickening and adventitial fibrosis.[100,101] It must be stressed that these patients were severely affected by their disease, and ERT started very late, possibly at an irreversible stage of vascular damage.

More recent studies suggest that ERT has a protective effect on cerebrovascular disease. A latency of 6 months from the onset of ERT was necessary to see beneficial results in significant complications, including stroke, using agalsidase beta[102.] A recent meta-analysis included 7 cohort studies and 2 RCTs involving 7513 participants (1471 on ERT vs 6042 on native treatment). The pooled proportions analysis showed that the stroke recurrence ratio in the ERT treatment group, including both agalsidase alfa

and beta, was 8.2% [95% CI 0.038, 0.126] and in the native-treatment group, was 16% [95% CI; 0.102, 0.217] (p = 0.03)[103] Moreover, ERT may reduce both the burden of disease, as shown with agalsidase beta,[104,105] and the risk of thromboembolic events, including stroke, as demonstrated with agalsidase alfa.[106]

The neurological data of the ERT are shown in Table 3. Furthermore, the beneficial effects of agalsidase alfa include stabilizing and improving cardiomyopathy in patients with Fabry and reducing the risk of cardioembolic stroke.[1,5,33,107]

In our practice, in the presence of asymptomatic white matter lesions, we indicate antiplatelet drugs and statins and tight control of cardiovascular risk factors.

We indicate ERT in patients with transient ischemic attack or ischemic or hemorrhagic stroke. Anticoagulation therapy is reserved for patients with confirmed cardioembolic stroke.

Table 3 Main Studies Reporting Data on the Effectiveness of Agalsidase Alfa Replacement Therapy on Pain

Author	Type of Study	Duration	Population	Renal Outcome
Schiffmann R et al[22]	Randomized double-masked placebo-controlled	1 year	26 male patients	Significant reduction in pain and pain-related quality of life in the treated group
Schiffmann R et al[75]	Open-label extension study	3 years	26 male patients	On the 10 patients who crossed from placebo to ERT, there was a significant improvement in pain. In addition, warm and cold thresholds, as well as sweating improved
Beck M et al[17]	FOS retrospective study	2 years	314 patients (203 males, 111 females)	Significant improvements in walking ability, general activity, regular work and social relationships. There was also a substantial improvement in pain.
Ries et al[76]	Prospective open-label study	6 months	24 children (19 males,5 females)	No significant improvement in pain severity
Schiffmann R et al[77]	Prospective long-term open-label	3.5 years	17 children (16 males, 1 female) who completed the 6-month trial of Ries et al 2006	Significant reduction in pain severity
Whybra C et al[51]	Prospective, single-centre, open-label	4 years	36 adult female ERT-naïve patients	Significant improvement of the "pain at its worst" section of BPI
Hughes DA et al[36]	FOS retrospective study	4 years	250 patients (172 males, 78 females) aged >18 years	No significant reduction of pain in both males and females after 4 years
Ramaswami U et al[54]	FOS retrospective study	2 years	98 children (64 boys, 34 girls) aged <18 years	Reductions in pain prevalence and pain crises were observed in the patients showing pain attacks or chronic pain at baseline
Hughes DA et al[78]	Randomized double-masked placebo-controlled study	14 weeks	18 patients	Using more frequent doses of Agalsidase alfa: 0.1 mg/kg/week, 0.2 mg/kg/week. No significant differences were found in pain scores.
Vedder A. et al[79]	Prospective randomized open-label	2 years	34 adult patients who received either agalsidase alfa or beta 0.2mg/kg	No difference in pain scores between groups
Hoffmann B. et al Clin J Pain.[74]	FOS retrospective analysis	3 years	24 months: 81 adult patients (50 males, 31 females).36 months: 62 patients (41 males, 21 females)	Significant improvement in the severity of pain both at 24 and 36 months

Other Clinical Manifestations

Gastrointestinal manifestations (abdominal pain, constipation, diarrhoea) are among the most frequent and crucial factors negatively affecting Fabry patients' daily social and working lives. As specialists dedicated to FD, we should pay more attention to patients' complaints regarding gastrointestinal symptoms. Additionally, the response to ERT is usually good, so the reaction to these symptoms was proposed as an "index of effectiveness" of therapy.

A FOS study based on 342 patients treated with agalsidase alfa showed a reduced prevalence of abdominal pain and diarrhoea after 12 and 24 months. The result was also present in the paediatric subgroup: statistically significant reduction in abdominal pain (64% to 36% in children) and diarrhoea (36% to 7% in children) after 12 months.[74] For completeness in real life, it must be said that, rarely, some patients respond less well to ERT, and occasionally, the symptoms can worsen.

The cochlear-vestibular apparatus of the ear can also be affected in FD. The most common clinical event is hearing loss, which is usually slowly progressive and bilateral. Sometimes, it may present as sudden and unilateral. There are limited papers on this subject. Some years ago, in a study of 26 patients at baseline and after 12 months of agalsidase alfa, there was a stabilization or improvement in patients with low to moderate hearing defects. In severe cases, the hearing did not improve.[9,109] More recently, in a long-term study (51 months), the positive effect of ERT on auditory function was confirmed, showing a substantial stabilization of hearing ability.[110]

Other symptoms, such as hypohidrosis and pain, affect Fabry patients' quality of life (QoL). The improvement of the ability to sweat in a limited population treated with agalsidase alfa was reported by Schiffmann.[108]

Comments and Conclusions

After over 20 years, we can state that ERT's availability and early indication have been associated with improved outcomes for patients with FD. The published data demonstrate that agalsidase alfa treatment improves clinical signs, symptoms, and disease outcomes. The effectiveness of agalsidase alfa on heart involvement reduces cardiomyopathy's progression and prevents its development. The impairment of renal function is slowed down or stopped in most patients. The benefits for the neurological manifestations are more limited, but ERT improves pain and is associated with a reduced burden of cerebrovascular disease.

ERT and agalsidase alfa have, of course, some limitations, such as an incomplete capacity to diffuse into the tissue (ie blood–brain barrier) or the presence of ADA reducing their clinical effectiveness, but that does not prevent ERT from significantly improving the natural history of FD and significantly reducing cardiac, renal and neurological events in patients with early treatment.

The cardiorenal axis is a typical example: it benefits from the synergic effect of agalsidase alfa on both organs and reduces renal and cardiac events.

ERT availability has increased medical awareness regarding earlier diagnosis of FD and resulted in a more intensive evaluation and follow-up of these patients regarding adequate treatment using both ERT and concomitant medication.

Furthermore, because the ERT improves diarrhoea, gastrointestinal pain, or sweating capacity, it leads to a better quality of life in patients with FD, directly benefiting patients' daily social, working and familial lives.

We conclude that there is robust evidence to state that agalsidase alfa is a safe and effective treatment for patients with FD.

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