

SUPPORTIVE CARE IN ADULTS WITH FABRY DISEASE: LOW-COST INTERVENTIONS FOR HIGH-VALUE ACHIEVEMENTS

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ABSTRACT: Anderson-Fabry disease (or Fabry disease [FD]) is an X-linked lysosomal storage disorder that can lead to neuropathic pain, reduced physical activity, and other debilitating symptoms, besides major organ involvement, such as kidneys, heart, and central nervous system, with possible premature death. Despite specific treatments, such as enzyme replacement therapy or migalastat, adult patients may still experience clinically relevant symptoms and events. Supportive treatments are recommended, but their use is associated with disease-specific challenges. Unfortunately, few specific studies on supportive care in FD are available. Some supportive treatments, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, may contribute to slow disease progression. Recently, SGLT2 inhibitors have shown outstanding results in reducing morbidity and mortality in chronic kidney disease and heart failure; however, specific studies on FD are not yet available. A range of other supportive therapies may be useful in patients with FD to counteract additional mechanisms, besides substrate accumulation, in the pathogenetic course of the disease or simply to manage symptoms. In this review, we discuss the state-of-the-art of supportive care in FD, which requires a multidisciplinary approach that can significantly boost therapeutic potential and patient-centered care.

KEYWORDS: Fabry Disease, Supportive Care, Lysosomal storage disorder.

INTRODUCTION

Anderson-Fabry disease (or Fabry disease [FD] [OMIM 301500]) is a pan-ethnic, X-linked, lysosomal storage disorder characterized by deficient α -galactosidase A activity¹ due to pathogenic mutations in the *GLA* gene². Deficient α -galactosidase A activity is associated with the progressive accumulation of globotriaosylceramide (Gb3) and its deacylated form, globotriaosylsphingosine (LysoGb3), within lysosomes of various cells such as podocytes, cardiomyocytes, and vascular endothelial cells. The prevalence of FD is higher than previously expected; at least in some newborn screening programs, it is around 1:8000³. More than

1,000 GLA variants have been reported and classified as pathogenic, benign without clinical relevance, or of unclear significance⁴. Mutations leading to absent or near absent α -galactosidase A activity, such as nonsense variants, some missense variants, and premature stop codons, are usually associated with classic early-onset FD². The classic phenotype is characterized in males by acroparesthesia in the hands and feet, abdominal pain, hypohidrosis, heat and exercise intolerance, angiokeratoma, and cornea verticillata starting in childhood^{2,5}. The disease progresses to multisystemic involvement with major complications, such as progressive chronic kidney disease (CKD), hypertrophic cardiomyopathy, arrhythmias, heart failure (HF), and stroke occurring in young adults^{2,6}. Heterozygous females are often less affected than males but have a poorly predictable disease course due to random X-inactivation (lyonization) and variable residual enzyme activity in various cells and tissues^{7,8}. In the late-onset phenotype, clinical manifestations usually start in adulthood, mainly involving the heart and kidney. Specific treatments, i.e., enzyme replacement therapy (ERT) and chaperone therapy (migalastat), can prevent or delay FD clinical manifestations⁹⁻¹¹. Despite these interventions, patients may still experience clinically relevant symptoms and events⁹ due to multiple pathogenic mechanisms, including inflammation, oxidative stress, and endoplasmic reticulum stress with unfolded protein response¹²⁻¹⁴. Several supportive treatments can be used in FD to counteract these additional mechanisms in the pathogenetic course of the disease.

This review aims to guide clinicians toward the rational use of supportive treatments in FD by describing current drugs and strategies to reduce disease progression, alleviate symptoms, and improve patient-centered care.

Figure 1 summarizes supportive care in adults with FD discussed below.

METHODS AND SIGNIFICANCE

A large volume of literature is available for FD and its specific treatment, while poor and often fragmentary literature is available for supportive treatments. For example, some useful information about supportive treatments in FD are available in the baseline description of patients in clinical studies regarding natural history of FD¹⁵ and ERT¹⁶, but these would have been cut by a systematic database search using keywords like “Fabry disease” and “supportive treatment” or “supportive” or “adjunctive”. For this reason, a narrative review combining authors’ knowledge and literature search for single supportive drug or approach (e.g. PubMed search for “Fabry” and “ACE inhibitors”) was performed to provide comprehensive background, clinical significance and need for future research.

FABRY NEPHROPATHY

CKD is a common and major manifestation of FD. The pathophysiology is characterized by Gb3 accumulation in various kidney cells (including podocytes, endothelial, mesangial, and tubular epithelial cells) and podocyte injury, such as foot process effacement, which can be detected early in childhood, even before microalbuminuria¹⁷. Early initiation of ERT reduces histopathological alterations of Fabry nephropathy and slows the decline in estimated glomerular filtration rate (eGFR)¹⁸⁻²¹. It is known that proteinuria and arterial hypertension are major risk factors for Fabry nephropathy^{15,22} and that proteinuria does not respond to ERT alone^{23,24}. Given their well-recognized benefits in reducing proteinuria, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are recommended in Fabry nephropathy to target albuminuria level <30 mg/g creatinine if the baseline 30–300 mg/g or <300 mg/g if the baseline >300 mg/g (roughly equivalent to proteinuria >500 mg/g)²⁵.

Unfortunately, we do not know the natural history of Fabry nephropathy “to the best of supportive treatment”, since milestone studies on the natural history of Fabry nephropathy have largely observed patients during the years when ACEIs and ARBs were not routinely used. Schiffmann et al¹⁵ observed 447 patients with untreated FD, predominantly classic phenotype ($\geq 95\%$), with a mean age of 41 years, evaluating data from registries between 1963 and 2001. The eGFR slope in males with baseline eGFR ≥ 60 mL/min/1.73 m² or <60 mL/min/1.73 m² was -3.0 mL/min/1.73 m² and -6.8 mL/min/1.73 m²/year, respectively. The eGFR slope in females with baseline eGFR ≥ 60 mL/min/1.73 m² or <60 mL/min/1.73 m² was -0.9 mL/min/1.73 m² and -2.1 mL/min/1.73 m²/year, respectively. When considering only the group with the highest potential efficacy of antiproteinuric treatment, i.e., males with eGFR <60 mL/min

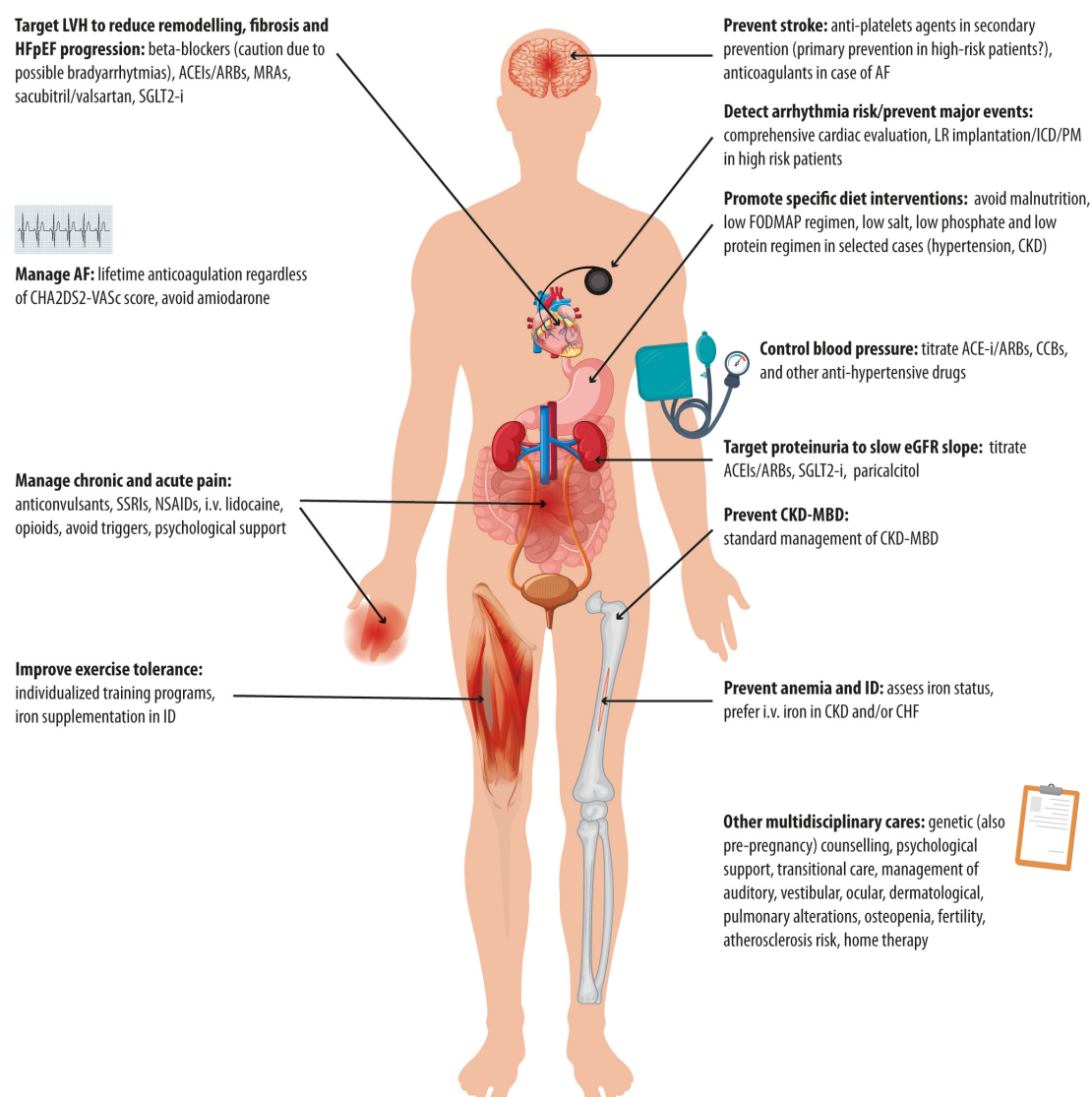


Figure 1. The wide potential of pharmacological and non-pharmacological supportive care in Fabry disease.

Abbreviations - LVH = left ventricular hypertrophy; HFpEF = heart failure with preserved ejection fraction; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; MRAs = mineralocorticoid receptor antagonists; SGLT2-i = sodium-glucose co-transporter 2 inhibitors; AF = atrial fibrillation; CKD = chronic kidney disease; ID = iron deficiency; LR = loop recorder; ICD = implantable cardioverter defibrillator; PM = pacemaker; FODMAPs = fermentable oligosaccharides, disaccharides, monosaccharides and polyols; CCBs = calcium channel blockers; CKD-MBD = chronic kidney disease-mineral and bone disorder; CHF = chronic heart failure. The figure was created with Biorender.

and mean proteinuria values of 2.6 ± 2.3 g/day, ACEIs were used in only 41% of cases. This percentage dropped to 22% in women with $eGFR < 60$ mL/min and was even lower in males and females with baseline $eGFR \geq 60$ mL/min. The study of Wanner et al²² had similar limitations, although it was conducted over an observation period from 2001 to 2009. The authors analyzed 462 patients with FD with mean ages of 34 and 39 years for males and females, respectively. ACEIs and ARBs were used in only a minority of males (23% and 17% in the faster and slower progression groups, respectively) and females (22% and 17% in the faster and slower progression groups, respectively).

In addition, antiproteinuric agents have been underused in clinical trials regarding FD-specific treatments. A recent meta-analysis evaluated the effect of agalsidase beta on $eGFR$ decline in classic patients with FD, showing a median $eGFR$ reduction of 2.46 mL/min/ 1.73 m²/year slower in treated than

in untreated patients¹⁶. Remarkably, ACEIs/ARBs were used in only 18% of treated patients (and 17% of untreated, with no statistically significant difference), despite proteinuria being reported in about half of them. In a Canadian study²⁶ the use of aspirin was surprisingly higher than renin-angiotensin blockade and statins (78% vs. 59% vs. 55%, respectively), analyzing supportive therapies in ERT-treated patients. Antiproteinuric agents have been used more in the most recent clinical trials. In an independent clinical trial comparing agalsidase alfa and beta, ACEIs/ARBs were used in 36% and 37% of patients, respectively, with no significant differences in eGFR slopes comparing the two ERT²⁷. In the ATTRACT study of migalastat²⁸, they were used in 45.8% of enrolled patients who had a stable eGFR slope after 30 months of treatment (note that at baseline, they had substantially normal renal function and low to median proteinuria levels). In two recent phase III studies of pegunigalsidase alfa, BRIDGE²⁹, and BALANCE³⁰, ACEIs/ARBs were used in 54.5% and 55% of enrolled patients, respectively; patients who had a urinary protein to creatinine ratio >0.5 g/g and were not treated with antiproteinuric agents were excluded. The mean eGFR slope dropped from -6.36 mL/min/1.73 m²/year to -1.73 mL/min/1.73 m²/year in males 1 year after switching from agalsidase alfa to pegunigalsidase alfa in the BRIDGE study²⁹. The median baseline eGFR slope was -7.3 mL/min/1.73 m²/year with a non-inferior decline to that of agalsidase beta 2 years after switching in the BALANCE study³⁰.

Given the heterogeneity of patients enrolled and the variable use of supportive treatments, often at unknown dosages in clinical trials, it is difficult to establish the impact of antiproteinuric agents on the eGFR slope. However, a great therapeutic potential of a carefully-titrated antiproteinuric therapy was elegantly demonstrated by Tahir et al³¹ in 11 patients with Fabry nephropathy, also treated with agalsidase beta. Sustained reductions in proteinuria with stabilization of eGFR were achieved in six patients with Fabry-related CKD stage III or IV. Median proteinuria decreased from 1.24 g/24 h to 0.21 g/24 h, and the average progression rate of eGFR was -0.23±1.12 mL/min per 1.73 m² per year with 30 months of follow-up. Additionally, Warnock et al³² demonstrated the effectiveness of combined treatment with agalsidase beta and antiproteinuric therapy in reducing eGFR slope. In their study, patients who achieved a urinary protein to creatinine ratio <0.5 g/g or a ≥50% reduction in their baseline ratio had significantly better eGFR slopes than patients who did not achieve the goals (-3.6 mL/min/1.73 m²/year vs. -7.0 mL/min/1.73 m²/year, respectively).

Considering the above data globally, ACEIs and ARBs appear to be crucial, as well as ERT, in slowing the course of Fabry nephropathy. In selected patients with moderate-severe CKD and proteinuria, they can slow eGFR decline even more than ERT at a significantly lower cost. Their optimal titration is sometimes challenging because of hypotensive effects (which may be instead beneficial in hypertensive patients) and the risk of hyperkalemia and acute kidney injury. However, these factors are unlikely to justify such underutilization in clinical studies, which probably reflects the poor sensitivity of clinicians in past years.

Some authors have also highlighted the potential benefits of other antiproteinuric agents in Fabry nephropathy, such as paricalcitol³³, a drug licensed for the prevention and treatment of secondary hyperparathyroidism in moderate-severe CKD or end-stage renal disease, and amiloride³⁴, a potassium-sparing diuretic.

Given their outstanding effects in reducing morbidity and mortality in CKD and HF, sodium-glucose cotransporter-2 (SGLT2) inhibitors are major candidates for implementing the supportive treatment of FD. These drugs, initially introduced as hypoglycemic agents, act by inhibiting the sodium-glucose cotransporter channels in the S1 tract of the proximal tubule, which are responsible for most filtered glucose reabsorption. Empagliflozin and dapagliflozin reduced the risk of progression of kidney disease and cardiovascular death compared with placebo in a wide range of patients with CKD, independently of type 2 diabetes mellitus and history of HF³⁵⁻³⁷. Their nephroprotective effect is probably exerted through multiple mechanisms, including restoring glomerular tubular feedback, which protects against glomerular hyperfiltration damage. Reduction of glucose and sodium reabsorption in the proximal tubule leads to increased sodium transport at the macula densa, increased adenosine release, vasoconstriction of the afferent arteriole, and reduced intraglomerular pressure³⁸. These effects may be additional to those exerted by ACEIs and ARBs, which act on the efferent arteriole, causing vasodilation. Other beneficial effects of SGLT2 inhibitors include reduced blood pressure, uric acid, oxidative stress, pro-inflammatory mediators, and increased hemoglobin^{39,40}, which are potential Fabry nephropathy therapeutic benefits that are not fully addressed by ERT. A temporary initial decline in eGFR is expected in patients starting these drugs, not precluding long-term kidney protection. A multicenter study of the effects of dapagliflozin on albuminuria and eGFR decline in patients with FD is ongoing and will hopefully provide relevant data⁴¹.

Other multifactorial conservative approaches are required to manage CKD, including dietary modifications, vitamin D supplementation, erythropoiesis improvement, electrolytes, and acid-base correction. Dietary restriction of salt and protein is a fundamental component of CKD management, aimed at reducing the complications of CKD and mitigating the progression of renal dysfunction. Indeed, a low-sodium diet helps control hypertension and fluid retention, while protein restriction reduces uremic toxins production and improves the control of hyperphosphatemia and metabolic acidosis. However, protein restriction should be individualized based on CKD stages, the presence of proteinuria, and nutritional status⁴².

Vitamin D deficiency is common in CKD and FD, contributing to the onset of bone mineral disorders and cardiovascular disorders. To maintain adequate serum levels of 25-hydroxyvitamin D and reduce the risk of secondary hyperparathyroidism and renal osteodystrophy, supplementation with inactive and active vitamin D analogues or receptor activators is often necessary⁴³.

In advanced stages of CKD, when conservative management is no longer sufficient, renal replacement therapies such as dialysis or kidney transplantation may be considered⁴⁴. To date, although few data are available for patients with FD undergoing dialysis, ERT is considered safe and potentially effective in reducing cardiac and cerebrovascular complications⁴⁵. Theoretically, ERT is not cleared by high- and low-flux hemodialysis filters⁴⁶. However, more prospective data from larger studies are necessary. Kidney transplantation offers the most effective long-term treatment for patients with end-stage renal disease affected from FD, with the same patient and graft survival rate observed in other transplanted patients for different nephropathies⁴⁷⁻⁴⁹. Early promising evidence from case reports and a series of combined kidney and liver transplants appeared to normalize plasma alpha-galactosidase levels, representing an effective ERT. Nevertheless, recent data have shown no cross-correction of the enzymatic defect between cells in patients with FD undergoing kidney transplantation⁵⁰⁻⁵⁴. In kidney transplant recipients, ERT is safe and protective for patient and graft survival. It should not be discontinued, as it effectively controls the extra-renal complications of FD. Importantly, high-dose immunosuppression reduces the anti-ERT antibody level without improving the long-term outcomes. Furthermore, glycosphingolipid accumulation recurrence in the transplanted kidney has been reported in retrospective studies but did not affect the clinical outcomes^{48,49,55}.

A summary of the main supportive treatments and strategies in Fabry nephropathy is reported in Table 1.

FABRY CARDIOMYOPATHY

Fabry cardiomyopathy is another common and major manifestation of FD, occurring in 40–60% of patients, representing the leading cause of death⁵⁶. The mechanical effect of Gb3 and LysoGb3 accumulation in myocytes, intramyocardial vessels, and conduction tissue explains only a small part of the complex pathophysiology. Substrate accumulation triggers secondary processes of lysosomal dysfunction, i.e., mitochondrial dysfunction with impaired energy production, sarcomere, Golgi and endoplasmic reticulum dysfunction, and ion channel and autophagy alterations, which in turn impair myocyte function⁵⁷. Furthermore, these cellular alterations promote inflammation, which also appears to be triggered by T cells and NK cells through Toll-like receptor 4-dependent mechanisms, leading to myocyte hypertrophy and fibrosis⁵⁶. All these mechanisms lead to left ventricular hypertrophy (LVH), diastolic dysfunction, myocardial ischemia, and fibrosis. Given that specific treatments are less effective the longer the delay in their initiation, early diagnosis and treatment are critical. ERT has been shown to be effective in delaying LVH progression and reducing cardiovascular events in the early stages of the disease^{24,58,59}. Fewer data are available about migalastat: although clinical trials have shown a significant reduction in the left ventricular mass index, subsequent real-world data have also shown a heterogeneous clinical response depending on genetic variants^{60,61}. In patients with Fabry cardiomyopathy, supportive treatments are required to target secondary pathophysiological events triggered by substrate accumulation, such as myocyte remodeling, fibrosis, and arrhythmias. As in the general population, assessment of cardiovascular risk factors, e.g., hypertension, dyslipidemia, diabetes, overweight, and smoking, and their prevention and/or treatment are central management goals⁶². It has been shown that subjects with FD have an increased likelihood of cardiovascular events (7.8 in men and 4.5 in women)⁶³. The prevalence of hypertension is highly variable in clinical trials, ranging from 28.4% to 56% of patients with FD, with a higher prevalence in those with CKD⁶⁴. High blood pressure variability throughout the day has been described, probably favored by autonomic dysfunction⁶⁵. Therefore, 24-hour blood pressure measurements may better detect patients with hypertension⁶⁶, enabling them to initiate medications to reduce their cardiovascular and renal progression and cerebrovascular disease.

Table 1. Supportive treatments in Fabry nephropathy.

Treatment/therapeutic strategy	Therapeutic target	Specific considerations/challenges in FD
ACEIs/ARBs	Reduce proteinuria (reducing indirectly nephropathy progression)	<ul style="list-style-type: none"> • Largely under-used in clinical studies regarding the natural history of Fabry nephropathy^{20,21} • Appear to slow eGFR slope if carefully titrated and combined with agalsidase beta^{31,32}
Paricalcitol and amiloride	Reduce proteinuria (reducing indirectly nephropathy progression)	Single-series studies ^{33,34}
SGLT2-i	Reduce nephropathy progression ³⁵⁻³⁷ through multiple mechanisms ³⁹⁻⁴⁰	One ongoing study in FD ⁴¹
Dietary modifications: salt and protein restriction	Blood pressure control, reduced fluid retention, and uremic toxins production, improved control of hyperphosphatemia and metabolic acidosis ⁴²	No specific studies in Fabry nephropathy
Supplementation with inactive and active vitamin D analogues or receptor activators	Reduce the risk of secondary hyperparathyroidism and renal osteodystrophy ⁴³	No specific studies in Fabry nephropathy
Anti-hypertensive drugs	Lower blood pressure	<ul style="list-style-type: none"> • Autonomic dysfunction may lead to high blood pressure variability during the day; 24-hour blood pressure measurements may better detect patients with hypertension⁶⁶ • Beta-blockers should be used with caution because of common observation of resting bradycardia and chronotropic incompetence in patients with FD⁶⁸ • Non-dihydropyridines CCB should be used with caution given the risk of atrio-ventricular conduction impairment in Fabry cardiomyopathy⁵⁶
Iron supplementation, ESAs	Anemia of CKD ¹²⁸	No specific studies in Fabry nephropathy

Abbreviations - FD = Fabry disease; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; eGFR = estimated glomerular filtration rate; SGLT2-i = sodium-glucose co-transporter 2 inhibitors; CCBs = calcium channel blockers; ID = iron deficiency; ESAs = erythropoiesis-stimulating agents; CKD = chronic kidney disease; ESRD = end-stage renal disease; ERT = enzyme replacement therapy.

HF is a consequence of myocardial hypertrophy and diastolic dysfunction. The ejection fraction (EF) is usually normal in the early-mid stages of FD but may decrease due to fibrosis and myocardial death in untreated patients with advanced disease⁵⁶. Cornerstone medications for HF and LVH include ACEIs, ARBs, mineralocorticoid receptor antagonists (MRAs), and beta-blockers⁶⁷. As described above, ACEIs and ARBs also play a crucial role in patients with Fabry nephropathy and proteinuria. MRAs should be considered in patients with HF and left ventricular systolic dysfunction⁶⁷. ACEIs, ARBs, and MRAs should be used with caution in patients with associated advanced Fabry nephropathy because of the risk of hyperkalemia or acute renal failure. Beta-blockers should also be used with caution because of the common observation of resting bradycardia and chronotropic incompetence in patients with FD⁶⁸. Loop diuretics should be considered to treat congestion symptoms in patients with HF⁶⁹. Calcium channel blockers may play an important role in patients with arterial hypertension, angina, which is a common symptom of FD, left ventricular outflow tract obstruction (LVOTO), and cerebrovascular disease⁶⁹; some caution is required regarding non-dihydropyridines, given the risk of atrioventricular conduction impairment in Fabry cardiomyopathy. In cases of symptomatic left ventricular outflow tract obstruction that cannot be managed with medications, significant pressure gradients can be treated via interventional procedures, such as septal myectomy or alcohol ablation⁷⁰. While ACEIs/ARBs, beta-blockers, MRAs, and loop diuretics are widely used in patients with FD in clinical trials, and their use is recommended²⁴, no data are available for sacubitril/valsartan and SGLT2 inhibitors in this specific population. As in Fabry nephropathy, SGLT2 inhibitors also have great potential in Fabry cardiomyopathy. In a recent meta-analysis regarding SGLT2 inhibitors in HF, a reduction in the risk of cardiovascular death, hospitalization for HF, and all-cause mortality was shown in a wide range of patients with HF, regardless of diabetes mellitus and EF⁷¹. Heart transplantation should be considered in patients with advanced symptomatic HF with severe left ventricular systolic and diastolic dysfunction despite optimal medical therapy⁶².

Arrhythmias and conduction impairment are common in FD and may be present even in the early stages of the disease due to early involvement of the conduction system and ion channels⁵⁶. At least annual follow-up with 12-lead ECG and Holter ECG is strongly recommended⁷². The simple evaluation of a 12-lead ECG is a treasure trove of information in FD, allowing staging of cardiac involvement⁷³. Arrhythmia risk assessment in FD is a complex process based on 12-lead ECG, Holter ECG, echocardiogram, and cardiac MRI combined with clinical and phenotypic evaluation. The implantation of a loop recorder has shown great potential in acquiring valuable information that traditional exams might miss. This leads to clinically relevant actions in Fabry cardiomyopathy, e.g., device implantation, anticoagulation, and change in medical therapy^{74,75}. However, the process of selecting patients who can benefit from this approach is still poorly studied. Pacemaker implantation is 25 times more common in FD than in the general population⁷⁶. In addition to bradyarrhythmia, tachydysrhythmias also occur, and their prevalence increases with myocardial fibrosis on MRI and with age⁷⁷. A systematic literature review estimated that ventricular tachycardia (VT) occurs in 15.3%, and an implantable cardioverter defibrillator (ICD) is implanted in 4.2% of patients with FD⁷⁷. ICD is recommended in secondary prevention after sudden cardiac arrest due to VT/ventricular fibrillation or in cases of sustained VT causing syncope or hemodynamic compromise if life expectancy is greater than 1 year⁵⁸. Patients with FD are eligible for ICD implantation in primary prevention in case of NYHA class II–III and left ventricular EF \leq 35%. ICD should also be considered in patients with advanced hypertrophy and fibrosis who require pacemaker implantation or present non-sustained VT. The mere presence of asymptomatic runs of non-sustained VT does not require the use of antiarrhythmic drugs⁵⁸. Atrial fibrillation (AF) is a frequent finding in Fabry cardiomyopathy. To date, no risk score has been validated to estimate the probability of cardioembolic events in the Fabry population, and conventional ones, such as CHADS2 and CHA2DS2-VASc scores, are considered to underestimate the risk. Therefore, initiation of anticoagulation is recommended in case of evidence of AF or flutter, regardless of conventional risk scores⁵⁸. In the absence of contraindications, such as renal function impairment, direct oral anticoagulants should be considered the first-line therapy⁵⁸. In AF, rhythm control has several limitations. Amiodarone should be avoided because it interferes with ERT activity and lysosomal function; its initiation has been associated with acute HF in patients with FD⁷⁸. Dronedarone, sotalol, flecainide, and propafenone are contraindicated in patients with HF⁵⁸.

A summary of the main supportive treatments and strategies in Fabry cardiomyopathy is reported in Table 2.

Table 2. Supportive treatments in Fabry cardiomyopathy.

Treatment/therapeutic strategy	Therapeutic target	Specific considerations/challenges in FD
ACEIs/ARBs, MRAs Beta-blockers	HF, LVH, LV dysfunction ⁶⁷ HF, LVH ⁶⁷ , rate control in AF	See Table 1 Caution due to the common observation of resting bradycardia and chronotropic incompetence in patients with FD ⁶⁸
Loop diuretics (e.g., <i>Furosemide</i>)	Symptomatic treatment of HF	No specific studies in Fabry cardiomyopathy
CCBs	Arterial hypertension, angina, LVOTO, cerebrovascular disease	Non-dihydropyridines CCBs should be used with caution given the risk of atrio-ventricular conduction impairment in Fabry cardiomyopathy ⁵⁶
Sacubitril/valsartan and SGLT2-i	Reduce cardiovascular disease through multiple mechanisms ⁷¹	One study is ongoing in FD regarding dapagliflozin ⁴¹
I.V. iron supplementation	Iron deficiency in CHF	It may improve skeletal and cardiac function, patient symptoms, and outcomes, but there are no specific studies on Fabry cardiomyopathy
Antiarrhythmic drugs	Rhythm control in AF	Amiodarone should be avoided because it interferes with ERT activity; usage associated with acute HF ⁷⁸
Anticoagulants	Stroke prevention in AF or flutter	Since conventional risk scores are not validated to estimate the probability of cardioembolic events in FD, anti-coagulation is usually recommended despite CHADS2 and CHA2DS2-VASc scores ⁵⁸
PM and/or ICD implantation	Prevention of serious bradyarrhythmias or tachydysrhythmias	Potential advantages of LR-implantation in capturing arrhythmias that traditional exams may miss ^{74,75}
Cardiac intervention: septal myectomy or alcohol ablation	Symptomatic LVOTO, not manageable with medications and significant pressure gradients	Single study in FD ⁷⁰
Heart transplantation	End-stage Fabry cardiomyopathy ⁶²	Limited case series studies
Dialysis or kidney transplantation	ESRD	ERT should be continued in FD patients to reduce extra-renal complications ⁴⁵

Abbreviations - FD = Fabry disease; ACEIs = angiotensin-converting enzyme-inhibitors; ARBs = angiotensin receptor blockers; MRAs = mineralocorticoid receptor antagonists; HF = heart failure; LVH = left ventricular hypertrophy; LV = left ventricular; CCBs = calcium channel blockers; LVOTO = left ventricular outflow tract obstruction; SGLT2-i = sodium-glucose co-transporter 2 inhibitors; I.v. = intravenous; CHF = chronic heart failure; AF = atrial fibrillation; ERT = enzyme replacement therapy; ICD = implantable cardioverter defibrillator; PM = pacemaker; LR = loop recorder.

FABRY-RELATED NEUROLOGIC INVOLVEMENT

In FD, neurological manifestations may involve the central nervous system (CNS), the peripheral nervous system, and the autonomic nervous system^{79,80}. Signs and symptoms due to neurological involvement are among the most frequent, affecting up to 84% of males and 79% of females⁸¹. Pain and stroke are particularly relevant in terms of reduced quality of life, morbidity, and mortality.

Stroke prevalence in FD is reported to be between 11.1% and 25% in males and 15.7% and 21% in females⁸². Cryptogenic stroke has been considered a “red flag” for FD diagnosis for years; however, a recent systematic review concludes that screening for FD in patients with cryptogenic stroke is not cost-effective due to comparable frequency in the general population, suggesting screening only in recurrent cases⁸³. The average age of stroke onset in FD is 39 years in males and 51 years in females⁸⁴. The distribution of stroke types follows that of the general population, predominantly ischemic (87%), with the rest classified as hemorrhagic⁸². Lacunar infarcts are frequently found in brain imaging in FD⁸². In a study involving a small number of patients (n=21), the prevalence of signs of small vessel disease on imaging in patients with FD with a mean age of 50 years was 43%⁸⁵. Lacunar infarcts are strokes, generally <1.5 cm in size, involving deep brain areas, such as the thalamus, basal nuclei, periventricular areas, and sometimes the cerebellar vermis and pons. They usually have a favorable acute prognosis but tend to recur with possible involvement of multiple areas over time, leading mainly to cognitive impairment⁸⁶.

ERT does not cross the blood-brain barrier, and its effectiveness in addressing the CNS manifestations mentioned above is controversial⁸⁷. However, a meta-analysis showed a reduced risk of stroke recurrence in ERT-treated compared with treatment-naïve patients⁸⁸. Since CNS involvement may precede cardiac and renal involvement in terms of clinical events⁸⁹, early initiation of specific treatment may reduce stroke-related morbidity and mortality. Concerning supportive treatments for primary and secondary prevention of strokes in FD, specific literature is extremely poor. International recommendations suggest managing stroke risk factors, such as hyperlipidemia and hypertension, and promoting smoking cessation²⁵. Regarding the use of antiplatelet agents (e.g., aspirin or clopidogrel), guidelines for stroke prevention in the general population are recommended⁹⁰, with no clear evidence for their use in primary prevention. Some authors have observed that the occurrence or recurrence of stroke/transient ischemic attack is higher in patients with FD and without AF with some characteristics, i.e., previous stroke or transient ischemic attack, angiokeratoma, renal dysfunction, LVH, and global systolic dysfunction⁹¹. They proposed a clinical score for initiating antiplatelet agents for primary prevention in high-risk patients, but it has not yet been validated. Anticoagulants are usually recommended in case of AF or atrial flutter regardless of the CHADS2 or CHA2DS2-VASc scores unless contraindicated⁵⁸.

Peripheral nervous system involvement is particularly relevant regarding decreased quality of life. Its pathogenesis is related to damage, of largely unknown etiology, of the posterior ganglia of the spinal cord and small-caliber nerve fibers, both myelinated and unmyelinated, resulting in a decrease in the number and density of small fibers with relative preservation of larger myelinated fibers⁹². As in many peripheral neuropathies associated with systemic diseases, damage distribution is length-dependent, with predominant involvement of the upper and lower extremities. The most frequently reported symptoms are pain and thermal hypoesthesia⁹², especially in the body extremities, while pallesthetic and mechanical perception are relatively preserved. Abdominal pain is common, reported in about one out of three patients⁹³, and is more likely due to autonomic dysfunction of gut motility. Globally, acute or chronic pain is reported by more than 60% of young patients, usually being the first reported symptom of disease². Acute pain is characterized by paroxysmal episodes of burning pain and is exacerbated by physical and psychological states, such as stress, fever, physical activity, heat, or fatigue⁹⁴. Although pain is more frequent in males, questionnaire results indicate a lower quality of life in females⁹⁵. Pain manifestations tend to decrease gradually with age, probably due to cumulative and irreversible loss of nerve fibers.

The onset of pain is an indication of ERT initiation²⁵. Specialized centers are usually able to perform quantitative sensory testing for a functional assessment of small nerve fibers and skin biopsies to quantify intra-epidermal nerve fiber density and Gb3 accumulation⁹⁶. FD pain-specific questionnaires, such as the Fabry-specific Pediatric Health and Pain Questionnaire⁹⁷ and the Würzburg Fabry Pain Questionnaire for adult patients⁹⁸, as well as general pain scales, such as the Brief Pain Inventory and/or pain diaries, are important tools for periodically reassessing pain in patients with FD and assessing response to treatments. After a comprehensive neurological evaluation, a holistic and tailored approach to the patient with pain is required, often in a multidisciplinary team, alongside specific treatment. Lifestyle modifications, such as maintaining adequate hydration, avoiding overheating and overtraining, using air conditioning, and prompt treatment of fever and infections, may help to avoid pain triggers⁹⁶. In acute pain episodes, taking off shoes and socks and reducing body temperature with cold water can help reduce pain attack duration and intensity⁹⁶. Patients who experience pain during exercise and exercise intolerance often tend to reduce physical activity later in life, with a detrimental cycle often associated with depression and increased cardiovascular risk. Cognitive-behavioral therapy and other forms of psychological care should be offered to patients with frequent pain episodes or chronic pain, especially when associated with anxiety and/

or depression⁹⁹. For a targeted pharmacological approach, acute and/or chronic pain and its underlying mechanism should be considered. Comparative studies on the efficacy of Fabry-related pain are limited. Therefore, current pharmacological strategies are essentially based on clinical experience and international guidelines for treating neuropathic pain¹⁰⁰. Carbamazepine, gabapentin, phenytoin, pregabalin, and duloxetine can be used in chronic neuropathic pain, with some caution regarding cardiac and renal restriction in selected patients⁹⁶. A recent case report showed a potential role of cannabis in reducing Fabry-related chronic neuropathic pain¹⁰¹. Non-steroidal anti-inflammatory drugs, such as ibuprofen and diclofenac, intravenous lidocaine, and opioid agonists, such as tramadol, oxycodone, and morphine, can be used in acute pain episodes⁹⁶, with caution regarding potential side effects, e.g., renal damage and gastrointestinal bleeding with non-steroidal anti-inflammatory drugs and worsening of gut motility and dependency with opioids. Some authors suggest using lidocaine or capsaicin cream as acute-pain prophylaxis before physical activity⁹⁶. Each drug should be titrated to the maximum tolerated dose to ensure pain control and reduce the risks of polypharmacy, such as drug interactions and adverse drug reactions.

Regarding autonomic dysfunction, clinical manifestations mainly affect the skin, the cardiovascular system, and the gastrointestinal tract. Generally, 53% of males and 28% of females present hypohidrosis, 25% of males and 4% of females present anhidrosis. Conversely, hyperhidrosis has an inverse epidemiology, affecting 11% of females compared with 6% of males¹⁰². Cardiovascular autonomic involvement is mainly manifested by decreased heart rate variability, reduced vasomotor response, and cardiac rhythm disturbances with a predisposition to developing AF and other arrhythmias, including ventricular forms that can lead to sudden cardiac death⁶⁹. Several gastrointestinal symptoms, such as abdominal pain, diarrhea, constipation, and nausea, are reported by 32.5%, 20.5%, 13.5%, and 12.3% of patients with FD, respectively^{93,103}. Supportive treatment of these manifestations mainly involves individualized physical exercise interventions (e.g., prevention of hypohidrosis and overheating, specific training programs to attenuate the effects of reduced heart rate variability), diet interventions (e.g., regimen low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols [FODMAPs]), and arrhythmia risk management, which are described in other sections in this review.

A summary of the main supportive treatments and strategies for neurologic involvement in FD is reported in Table 3.

HOLISTIC APPROACH TO OTHER ISSUES

Physical Exercise

Fatigue and exercise intolerance are common early findings in patients with FD². The most frequent causes include hypohidrosis, exercise-induced acroparesthesia, reduced exercise capacity, and chronotropic incompetence^{68,104,105}. Additionally, chronic fatigue is often reported, leading not only to reduced activities of daily living but also to a significant negative impact on quality of life and psychosocial development, especially in young people¹⁰⁶. Simultaneously, sedentary behavior exacerbates physical function decline, cardiorespiratory capacity reduction, fatigue, frailty, muscle atrophy, loss of strength, and the risk of depression^{107,108}. These factors promote a vicious cycle of reduced physical activity and exercise intolerance in FD. Lack of physical exercise shortens life expectancy and increases mortality from at least 35 chronic diseases¹⁰⁹. The benefits of physical activity in maintaining and improving cardiovascular health and muscular fitness are well established¹¹⁰. Exercise also plays a role in preventing and controlling hypertension, osteoporosis, and osteoarticular diseases. It also reduces the risk of dementia and cognitive impairment, as well as relieves anxiety, stress, and loneliness. Nevertheless, exercise contributes to improved mental health by promoting the release of neurohumoral mediators such as serotonin and endorphins, enhancing general well-being. Possible benefits of improving health perception, self-image, and self-esteem should also be considered¹¹¹.

Although limited, studies on exercise in FD have shown promising results. Schmitz et al¹¹² conducted a pilot study to evaluate exercise intolerance and the effect of an adapted strength/circuit exercise program in a small population of patients with FD. The 12-month exercise program involved 14 patients (six women with an average age of 46 years). Before the program, the participants reported muscle soreness; no acroparesthesia or pain attacks occurred during exercise. At the end of the study, 58% reported reduced fatigue, and 67% found the program beneficial for overall well-being and fitness. Powell et al¹¹³ found no adverse effects of exercise on arrhythmic load or heart rate response in patients with FD.

Table 3. Supportive treatments in Fabry neurologic involvement.

Treatment/therapeutic strategy	Therapeutic target	Specific considerations/challenges in FD
Management of stroke risk factors such as hyperlipidemia, hypertension, and smoking	Stroke prevention	No specific studies in Fabry cardiomyopathy
Anti-platelet agents	Stroke recurrence in patients without atrial fibrillation or flutter	Use in primary prevention in high-risk FD patients is not validated ⁹¹
Anticoagulants	Stroke prevention in atrial fibrillation or flutter	Since conventional risk scores are not validated to estimate the probability of cardioembolic events in FD, anti-coagulation is usually recommended despite CHADS2 and CHA2DS2-VASc scores ⁵⁸
Lifestyle modifications, such as maintaining adequate hydration, avoiding overheating and overtraining, using air conditioning, and prompt treatment of fever and infections	Avoid pain triggers	
Psychological support	Make the pain more acceptable	It helps patients with frequent pain episodes or chronic pain, especially if associated with anxiety and/or depression ⁹⁹
Carbamazepine, gabapentin, phenytoin, pregabalin, and duloxetine	Chronic neuropathic pain	<ul style="list-style-type: none"> • Limited comparative studies of efficacy in FD⁹⁶ • Caution on cardiac and renal restriction in selected patients⁹⁶ • Potential role for cannabis in reducing Fabry-related chronic neuropathic pain¹⁰¹
NSAIDs, intravenous lidocaine and opioid agonists	Acute pain episodes	<ul style="list-style-type: none"> • Limited comparative studies of efficacy in FD⁹⁶ • Caution regarding renal damage and gastrointestinal bleeding with NSAIDs • Consider possible worsening of gut motility and dependency on opioids

Abbreviations - FD = Fabry disease; NSAIDs = non-steroidal anti-inflammatory drugs.

Despite the recognized benefits of exercise, there are no specific recommendations for prescribing exercise to patients with FD. Planning an exercise program requires a personalized approach that considers individual needs, limitations, and goals. The American College of Sports Medicine¹¹⁴ guidelines, based on the frequency, intensity, time/duration, type, volume, and progression (FITT-VP) principle, provide a framework for tailoring exercise programs to specific needs¹¹⁵. Given the specific needs of patients with FD, the guidelines mentioned above should be adapted by integrating exercise into the multidisciplinary management of patients¹¹⁶. Silva et al¹¹⁷ recommended daily submaximal-intensity aerobic activities (e.g., walking, swimming, cycling) and endurance exercises for patients with FD to improve cardiovascular fitness and muscle strength. Muscogiuri et al¹¹⁶ emphasized the importance of frequent physical activity for individuals with FD, aligning with guidelines from KDIGO 2021 and ESC 2020. Gambardella et al¹¹⁸ suggested adapting physical activity programs conducted in various chronic conditions for patients with FD.

Anemia and Iron Deficiency

Anemia and iron deficiency (ID) are common complications of chronic heart failure (CHF) and CKD. Anemia has been described in 34% of patients with FD, often associated with CKD, CHF, and inflammation¹¹⁹. It is reasonable to assume that it is mainly caused by ID, the most common cause of anemia, especially in chronic inflammatory conditions such as CKD and CHF^{120,121}. The prevalence of ID in selected patients with FD might be even higher; for example, it is estimated to be around 60% in patients with HF with preserved EF¹²², but specific studies on FD are lacking. Anemia and ID may be favored by several processes associated with CKD and CHF, i.e., erythropoietin dysregulation, renin-angiotensin system activation, hyperparathyroidism, chronic inflammation with increased TNF-alpha and IL-6 production, inflammation-driven hepcidin production, reduced erythropoiesis and erythropoietin resistance in bone marrow, iron retention into macrophages, malnutrition and hemodilution¹²³. Iron homeostasis in skeletal and cardiac muscle is crucial for mitochondrial function and adenosine triphosphate generation¹²⁴. Indeed, ID has detrimental effects on exercise capacity and quality of life in patients with CHF, independently of anemia and left ventricular EF^{125,126}. Accurate assessment of iron status and anemia is still poorly studied in patients with FD and probably not sufficiently highlighted in disease management recommendations^{25,127}. Periodic assessment of iron status and anemia is recommended by major international guidelines in all patients with CKD and eGFR <60 mL/min and in patients with CHF^{128,129}. Appropriate management of anemia with possible intravenous iron supplementation may be a simple, cost-effective measure to improve physical function, quality of life, and outcomes in adult patients with FD, given its well-established benefit in CKD and CHF¹²⁶.

Diet

Dietary management is considered a complementary approach in the management of FD. Specific dietary approaches in CKD and arterial hypertension have been discussed previously. Recently, a potential role for diet low in FODMAPs has been suggested to alleviate gastrointestinal symptoms associated with FD, such as abdominal pain, constipation, indigestion, and diarrhea¹³⁰. Patients with FD may experience improved gastrointestinal symptoms and overall quality of life by reducing the intake of poorly absorbed carbohydrates^{130,131}. Furthermore, green tea, rich in polyphenols such as epigallocatechin gallate, has antioxidant and anti-inflammatory properties, which may offer potential benefits in mitigating cellular damage and oxidative stress associated with FD^{132,133}. Although further research is needed to elucidate the specific mechanisms and potential efficacy of these dietary interventions in managing FD, integrating dietary modifications into the comprehensive care of affected individuals holds promise in optimizing health outcomes and enhancing their quality of life.

Psychological Support

Neuropsychiatric manifestations, such as anxiety, depression, cognitive dysfunction, suicidal ideation and attempts, and psychosis, are common in patients with FD and have a multifactorial and not fully elucidated pathogenesis^{134,135}. Pain, reduced physical activity, social and relational problems, stigma, reaction to coping with a chronic progressive disorder, as well as organic alterations, such as progressive micro-ischemic brain damage, are probably major contributing factors^{136,137}. Psychological disorders and cognitive dysfunction significantly impact the quality of life of patients with FD^{135,138,139}. Körver et al¹⁴⁰ identified pain, negative health perception, and dysfunctional coping styles as major variables in the quality of life of patients with FD. Neuropsychological impairment often involves executive functioning, information processing speed, and attention, while general intellectual functioning, naming, memory, and perceptual functioning are preserved^{139,140}. Psychometric tests have revealed complex personality traits and psychological alterations in patients with FD, including suspiciousness, feelings of isolation, and social maladjustment¹⁴¹.

The effects of untreated neuropsychological disorders can be dramatic on patient outcomes and treatment compliance. Supportive psychiatric and psychological treatment should consider this complexity, and Fabry referral centers should offer in-house counseling and/or tele-counseling¹⁴² as part of the multidisciplinary care. Modifiable factors, such as coping behaviors, can be targeted in psycho-

logical and rehabilitation approaches^{139,143}. Cognitive-behavioral therapy can help patients identify and modify factors that drive unhelpful behaviors, such as stress and overexertion. A recent pilot study by Ali et al¹⁴² showed the usefulness of this approach in improving depression and quality of life in participants with FD.

Genetic Counseling and Preimplantation Genetic Diagnosis

Genetic counseling plays a crucial role in providing comprehensive information to patients with FD and their families regarding the inheritance pattern, FD manifestation, and available testing options. It offers support, guidance, and education to help families understand the FD genetic basis, assess their reproductive risks, and make informed decisions regarding family planning and prenatal testing^{25,144}.

In classical prenatal FD diagnosis, the first step involves determining the sex of the fetus. For female fetuses at risk for FD, enzymatic testing is usually not performed because of the high risk of false negatives. Indeed, assessing α -galactosidase A activity and analyzing *GLA* mutations are mandatory, while LysoGb3 analysis remains controversial. On the other hand, for male fetuses at risk for FD, the α -galactosidase A activity test has shown high sensitivity and can be performed on chorionic villi or cultured amniocytes. Sequencing of the *GLA* gene is required only if α -galactosidase A activity is reduced¹⁴⁴.

Recently, with advances in reproductive technologies, preimplantation genetic diagnosis (PGD) has emerged as a valuable tool for couples at risk of transmitting FD to their offspring¹⁴⁵. PGD involves screening embryos created through *in vitro* fertilization to identify those free from disease-causing mutations before implantation, thus offering the opportunity to conceive unaffected offspring¹⁴⁵. Early experiences in lysosomal storage disorders, including FD, have been described, with an overall pregnancy rate/embryo transfer of 38%¹⁴⁶. Although PGD could be efficient and feasible in preventing FD transmission, ethical considerations, and psychological impact should be carefully considered. Comprehensive counseling and collaborative efforts among genetic counselors, reproductive specialists, case managers, and couples ensure personalized and ethical decision-making.

Fertility and Pregnancy Support

Literature on fertility and pregnancy management in patients with FD is limited^{147,148}. An analysis of self-reported data on reproductive fitness in 376 patients with FD (134 males and 242 females) showed increased reproductive activity¹⁴⁷. However, the same self-reported survey found that infertility rates were significantly higher among males (36%) and females (20.3%) than in the general population (7% in males and 12% in females)¹⁴⁶. Additionally, access to assisted reproductive technology increased for both men and women with FD, 9% and 13%, respectively, compared with 0.7% in the general population¹⁴⁷. Hauser et al¹⁴⁹ observed that ovarian, testicular, and adrenal functions in 13 patients with FD were substantially comparable to that of the general population. Although a correlation has been described between Gb3 accumulation in Leydig cells, vessels, connective tissue, and muscle of the testicular interstitium and an abnormality in semen¹⁵⁰, this does not appear to impact fertility in male patients. In a prospective, multicenter, cross-sectional study, Papaxanthos-Roche et al¹⁵¹ analyzed seminal abnormalities and their effect on fertility in 18 male patients with FD. The study revealed that 52.9% of patients had at least one clinically significant abnormality in their semen analysis, primarily due to a decrease in sperm count, volume, or viability. However, these observed alterations in sperm did not significantly impact fertility and did not appear to correlate with disease severity¹⁵¹.

Appropriate counseling by qualified medical professionals is important in the management of potential pregnancies in women with FD¹⁵². The clinical implications of specific treatment and potential teratogenic and nephrotoxic supportive medications should be discussed before pregnancy. Specialists should also inform the patient and their partner about alternative options to natural procreation, such as preimplantation genetic analysis, early diagnosis with chorionic villus sampling or amniocentesis, adoption, or gamete donation¹⁵². Following the onset of pregnancy, women with FD should receive evaluation and monitoring by a maternal-fetal specialist along with standard antenatal assessment. Close monitoring of proteinuria is of utmost importance, and patients with FD should be informed about the possibility of specific symptoms worsening, such as acroparesthesia, during pregnancy^{148,152}. A retrospective analysis of 41 pregnancies revealed a significantly higher incidence of proteinuria and hypertension in women

with FD¹⁴⁸; hence, close monitoring is imperative. Postnatal depression was found in 17% of patients (seven out of 41 pregnancies analyzed), a finding that does not appear to be statistically significant when compared with the general population¹⁴⁸.

Since ERT during pregnancy has been poorly investigated, initiating, continuing, or discontinuing ERT should be made on a case-by-case basis, considering the risks and benefits for each patient^{148,152,153}. Overall, studies report that both agalsidase alfa and agalsidase beta can be continued safely during pregnancy for patients with symptomatic FD, with no significant adverse effects on either the mother or fetus¹⁵⁴⁻¹⁵⁶. Gb3 accumulation in the maternal placental tissue has been described regardless of ERT¹⁵⁶. This study revealed that Gb3 accumulation at both maternal and fetal levels could occur if the fetus inherited the mutation¹⁵⁶. Migalastat is contraindicated for pregnant and lactating women because of potential toxicity to the fetus. However, preclinical studies in rabbits have shown that toxicity to the fetus only occurs at doses that are toxic to the mother¹⁵⁷. A patient with FD took migalastat up to 18 weeks of pregnancy without experiencing any complications except for low gestational weight¹⁵⁷. However, due to insufficient data, migalastat remains unrecommended¹⁵⁷.

Management of Other Organs' Involvement

Cochleo-vestibular alterations are common in FD and are not limited to males and/or classic phenotypes¹⁵⁸. Up to 72.3% of adult patients complain of hearing loss, tinnitus, or vertigo¹⁵⁸. Pure tone audiometry revealed that hearing thresholds per frequency, at the same age, are worse in patients with FD than in the general population¹⁵⁹. ERT efficacy is not well established in cochleo-vestibular outcomes. Regular cochleo-vestibular assessment is required as part of the multidisciplinary evaluation of patients with FD to detect those who might benefit from hearing aids or cochlear implants. Sudden hearing loss is usually managed with an infusion of vasodilators and steroids. Vertigo episodes may require anti-nausea drugs. Tinnitus is usually difficult to manage and may require the use of devices blocking the effects of tinnitus²⁵.

Ocular alterations, especially cornea verticillata, are important in the early recognition of FD and evaluation of the phenotype². Cornea verticillata can be detected with a slit-lamp evaluation. Vessel tortuosity can be observed in the conjunctiva and retina and, as with cornea verticillata, is associated with a more severe clinical phenotype¹⁶⁰. Vision is usually normal in patients with FD, except in ischemic events or the development of lenticular opacities known as "Fabry cataracts"¹⁶¹. Ophthalmologic evaluation is usually recommended at baseline and subsequently only if there is a clinical need²⁵.

Dermatological alterations include angiokeratoma and lymphedema. Angiokeratomas are associated with the classic FD phenotype². They are clinically harmless but can cause distress, especially if located in the genital area. Laser and other cosmetic techniques may be considered with caution because of the risk of scarring, especially for confluent angiokeratoma¹⁶². Lymphedema can cause significant discomfort in patients due to a feeling of heaviness or tightness in the affected limbs. Physical exercise, the use of compression stockings, and lymphatic draining massage can help manage this complication¹⁶².

Among respiratory alterations, obstructive lung disease and sleep disorders have been described in patients with FD. Obstructive lung disease is associated with dyspnea, wheezing, and dry cough¹⁶³. Interstitial lung disease is rare. Sleep disorders may manifest with sleep apnea, excessive daytime sleepiness/chronic fatigue, exercise intolerance, and hypertension¹⁶⁴. Spirometry, including response to bronchodilators, treadmill exercise testing, oximetry, and chest X-ray, are recommended at baseline and every 2 years during the follow-up in adult patients²⁵. Bronchodilators may be prescribed to relieve airway obstruction. Periodic assessment of sleep disturbance symptoms can help identify patients who may benefit from supportive strategies, such as continuous positive airway pressure treatment. Smoking cessation should be pursued in each patient, eventually with drugs or psychological support.

Osteopenia and osteoporosis are common in adults with FD and can be complicated by pathological fractures¹⁶⁵. Vitamin D deficiency caused by poor sunlight exposure, malabsorptive gastrointestinal disease, and deficient activation due to CKD and/or the use of antiepileptic drugs may play a role. Periodical evaluations with dual-energy X-ray absorptiometry are recommended in adults with FD²⁵. If osteopenia or osteoporosis is detected, careful assessment of risk factors and osteoclastic/osteoblastic activity should be performed to choose the more proper bone-specific supportive therapy.

Home Therapy

Stable patients who tolerate in-hospital infusions and have an adequate home environment are generally eligible for nurse-assisted home infusions¹⁶⁶. Patients, their families, and clinicians generally welcome this opportunity, but it has national and regional differences in applicability. The COVID-19 pandemic has increased and accelerated the availability of home-based ERT¹⁶⁷, which is generally safe and can improve patient-centered care and quality of life, reducing constraints on hospital resources. Both agalsidase alfa and beta are suitable for home therapy. Recent studies have demonstrated the good tolerability of shorter infusion regimens with agalsidase beta, showing a low incidence of antibody formation and infusion-associated reactions^{168,169}, which could be an advantage for home infusions.

A summary of the above-mentioned holistic strategies in FD is reported in Table 4.

Table 4. Other holistic approaches in FD.

Treatment/therapeutic strategy	Therapeutic target	Specific considerations/challenges in FD
Individualized physical exercise	Improve exercise and pain tolerance, psychologic and cardiovascular well-being	Specific training programs showed promising results in FD patients ¹¹²
Complementary dietary strategies	Gastrointestinal symptoms	<ul style="list-style-type: none"> The low-FODMAP diet has been suggested to alleviate gastrointestinal symptoms associated with FD¹³⁰ Green tea has antioxidant and anti-inflammatory properties, which may offer potential benefits in FD¹³³
Psychological support	Disease acceptance, pain, and neuro-psychiatric manifestations	Specific interventions showed good results in patients with FD ^{142,143}
Genetic counseling, fertility, and pregnancy support	Inform patients with FD and families about the inheritance pattern, fertility, and pregnancy issues	<ul style="list-style-type: none"> ERT can be generally continued in pregnant symptomatic women Migalastat is contraindicated during pregnancy and lactation Assess the risk/benefit of supportive medication before pregnancy PGD has emerged as a novel opportunity in FD; an overall pregnancy rate/embryo transfer of 38% has been described in LSD¹⁴⁶
Management of other organ involvement (e.g., cochlear-vestibular, pulmonary, and dermatologic alterations, osteopenia, and osteoporosis)	Address specific patient issues	Efficient multidisciplinary team is required

Abbreviations - FD = Fabry disease; FODMAPs = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; ERT = enzyme replacement therapy; PGD = preimplantation genetic diagnosis; LSD = lysosomal storage disorders.

CONCLUSIONS

Specific treatments are essential in FD to reduce disease morbidity but should be associated with the rational use of supportive care to boost therapeutic potential. Supportive treatments often include a careful titration of antiproteinuric agents, pain management, and appropriate management of renal, cardiac, and neurological involvement with disease-specific challenges. The availability of SGLT2 inhib-

itors, which can prevent secondary processes induced by substrate accumulation in the kidney and heart, is hoped to further improve renal and cardiac outcomes in patients with FD. A holistic approach, often in a multidisciplinary team, promoting individualized physical exercise programs, diet, psychological support, and genetic counseling can significantly improve patient-centered care and quality of life. Further studies are needed to better understand the progression of FD with proper use of the best supportive and specific treatments currently available, set appropriate treatment goals, and better evaluate responses.

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