

**Faculté de pharmacie
et des sciences biomédicales**

***Precision Medicine in Fabry Disease:
Integrating both Established and
Emerging Therapeutic Strategies***

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Résumé/Summary : Fabry Disease is an X-linked complex, multi-organ progressive lysosomal disorder caused by variants in the GLA gene that lead to deficiency or loss of enzymatic activity of α -galactosidase A. Years now there have been available therapies regarding FD, such as ERTs and/or pharmacological chaperone therapy. However, because of the clinical and molecular heterogeneity of the disease as well as because of unmet needs further research on the currently new and emerging therapies is deemed necessary. The heterogeneity of the disease such as gender, age, genotype-phenotype correlation, response to established treatment has led to the development of more individualized therapeutic approaches which are currently being approved or are still under investigation. However, the therapeutic approaches so far have limitations and thus the need for a more personalized approach is required. In this literature review, a more analytical approach towards genetics, pathophysiology, diagnosis, current and future therapeutic patterns is suggested. Additionally, the aim of this literature review is to critically present current and emerging therapeutic strategies for FD and to evaluate how these approaches contribute to the implementation of precision medicine in clinical practice.

Abbreviations

ADAs: anti-drug antibodies

α -Gal A: α -galactosidase A

CNS: Central nervous system

DBS: Dried blood spots

EOW: Every other week

E2W: Every two weeks

E4W: Every four weeks

eGFR: Estimated glomerular filtration rate

ERT: Enzyme replacement therapy

ESKD: End-stage kidney disease

FD: Fabry Disease

Gb3: Globotriaosylceramide

GLA gene: α -galactosidase A gene

GI: Gastrointestinal

IRRs: Infusion-related reactions

LVM: Left ventricular mass

Lyso-Gb3: Globotriaosil-sphingosine

MSSI: Mainz severity score index

SRT: Substrate reduction therapy

TEAEs: Treatment-emergent adverse events

VUS: Variant of uncertain significance

Summary

Fabry Disease is an X-linked complex, multi-organ progressive lysosomal disorder caused by variants in the *GLA* gene that lead to deficiency or loss of enzymatic activity of α -galactosidase A. Years now there have been available therapies regarding FD, such as ERTs and/or pharmacological chaperone therapy. However, because of the clinical and molecular heterogeneity of the disease as well as because of unmet needs further research on the currently new and emerging therapies is deemed necessary. The heterogeneity of the disease such as gender, age, genotype-phenotype correlation, response to established treatment has led to the development of more individualized therapeutic approaches which are currently being approved or are still under investigation. However, the therapeutic approaches so far have limitations and thus the need for a more personalized approach is required. In this literature review, a more analytical approach towards genetics, pathophysiology, diagnosis, current and future therapeutic patterns is suggested. Additionally, the aim of this literature review is to critically present current and emerging therapeutic strategies for FD and to evaluate how these approaches contribute to the implementation of precision medicine in clinical practice.

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Introduction

Fabry disease (FD) is a progressive X-linked lysosomal storage disorder resulting from pathogenic variants in the *GLA* gene, which encodes the lysosomal enzyme α -galactosidase A (α -Gal A) {1}. Impaired or absent α -Gal A activity leads to defective glycosphingolipid degradation, resulting in the progressive accumulation of globotriaosylceramide (Gb3) and its deacylated derivative, globotriaosylsphingosine (lyso-Gb3), within the lysosomes of various cell types. The aforementioned accumulation contributes to cellular dysfunction and progressive damage across multiple organ systems {1,2}.

Fabry disease is characterized by significant clinical heterogeneity, with its manifestations affecting the renal, cardiovascular, neurological, dermatological, gastrointestinal and ocular systems {3}. Common clinical features include angiokeratomas [**Figure 1**,{31}], cornea verticillata, hypohidrosis, neuropathic pain, gastrointestinal symptoms, cerebrovascular complications, cardiac hypertrophy and arrhythmias, as well as progressive renal impairment [**Figure 2**,{32}] {3}. The considerable variability in the clinical presentation is influenced by several factors, including the type of *GLA* variant, the level of residual α -Gal A activity, gender, and the pattern of X-chromosome inactivation in females {26}.

Clinically, Fabry disease is generally classified into two major phenotypes: classic Fabry disease and late-onset (non-classic) Fabry disease {30}. The former -the classic phenotype Fabry disease- is associated with severely reduced or absent α -Gal A activity and typically presents itself during childhood or adolescence with clinical manifestations such as neuropathic pain, angiokeratomas, hypohidrosis, and gastrointestinal symptoms. In contrast, the latter -onset Fabry disease- is associated with higher residual α -Gal A activity and typically presents itself during adulthood, predominantly affecting renal, cardiac or cerebrovascular systems, with few or no classic manifestations {1,2}.

Although Fabry disease is considered to be a rare disorder, it represents one of the most prevalent lysosomal storage diseases {30}. More importantly, its genetic and phenotypic variability results in differences in disease progression, organ involvement, and therapeutic response among affected individuals. This heterogeneity highlights the need for individualized

approaches to diagnosis, monitoring, and treatment, thus rendering Fabry disease as an important model for the application of precision medicine.



Figure 1: Angiokeratomas in a person with FD. This image presents benign skin growths on the abdomen area of a person afflicted with FD {31}.

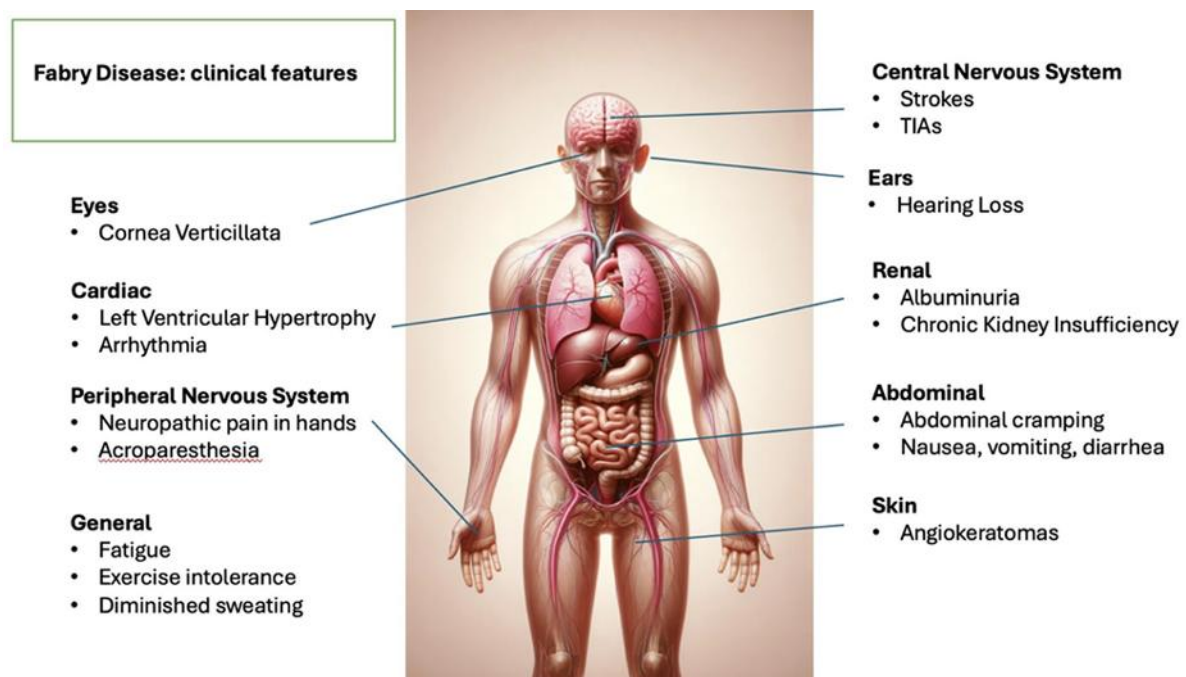


Figure 2: Clinical Manifestations of FD {32}.

Methods

This literature review was conducted using PubMed and google scholar databases. The search was based upon keywords such as “Fabry Disease”, “precision medicine”, “genetics”, “enzyme replacement therapy”, “chaperone therapy” and “emerging therapies in FD”. Selected original published articles were used to cover the scope of the matter under discussion in this literature review.

Epidemiology of FD

Fabry Disease is estimated to occur in approximately 1 in 40,000 to 60,000 males {4}. Although the disease also takes place in females, its prevalence among females remains vague {4}. The classic form of FD is estimated to take place in approximately 1 in 37,000 newborn males, whereas the overall prevalence of FD among newborns has been estimated in approximately 1 in 117,000 {5}. Late-onset FD is more frequent than classic FD with estimates suggesting a 3- to 10-fold higher prevalence. In certain populations, late-onset FD has been estimated to take place as frequently as about 1 in 1,500 to 1 in 4,000 individuals {6}.

Genetics of Fabry Disease

GLA Gene

Located on the long arm (q) of the X chromosome at position Xq22.1, the *GLA* encodes the lysosomal enzyme α -galactosidase A (α -Gal A) {7,8}. Variants in the *GLA* gene may result in a significant reduction in, or complete loss of, α -Gal A activity, leading to the progressive accumulation of the substrate glycosphingolipids such as Gb3 and its deacylated form; globotriaosylsphingosine (lyso-Gb3) [Figure 3]. Variants in the *GLA* gene impair lysosomal glycosphingolipid metabolism and cause Fabry disease {9}. The level of residual α -Gal A activity influences the nature and the age of the onset of clinical manifestations in FD {10,11}. In addition to residual enzyme activity, the specific type and severity of the *GLA* variant also contribute to the onset of the disease and its progression {11}.

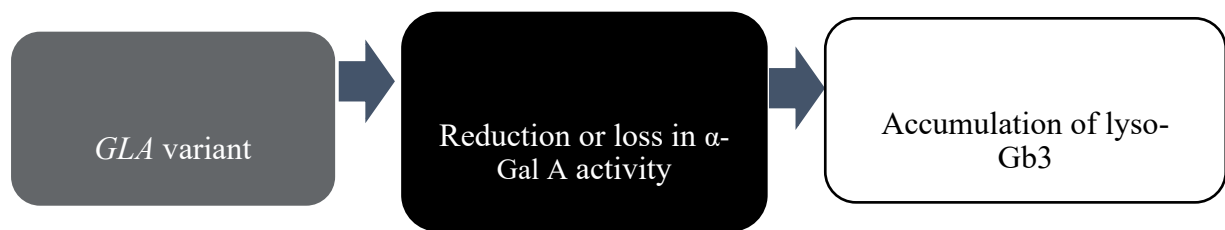


Figure 3: Pathogenic *GLA* variants lead to reduced or loss α -galactosidase A activity and subsequent lyso-Gb3 accumulation in FD.

Mutation versus Variant

A mutation is traditionally defined as a permanent alteration in the nucleotide sequence of DNA, whereas a polymorphism refers to a genetic variant with a frequency greater than 1% in a given population {27}. Although these terms have been extensively used in literature on genetics, they may lead to misconceptions by implicitly suggesting pathogenicity in the case of mutations and benignity in the case of polymorphisms. Consequently, current clinical genetics guidelines recommend replacing both terms with a more neutral “variant” term {27}.

ACMG - AMP Classification

Variants should be categorized in line with their clinical significance as “pathogenic”, “likely pathogenic”, “of uncertain significance” (VUS), “likely benign”, or “benign” {27}. More specifically, in 2015, the American College of Medical Genetics and Genomics (ACMG), a leading professional organization dedicated to advancing the practice of medical genetics and genomics, in collaboration with the Association for Molecular Pathology (AMP) introduced a standardized five-tier classification system for genetic variants. This system categorizes variants as “pathogenic” (class 1), “likely pathogenic” (class 2), “of uncertain significance”

(VUS) (class 3), “likely benign” (class 4), or “benign” (class 5) and constitutes the global standard for clinical interpretation {27}.

GLA Variants

Several types of variants have been identified in the *GLA* gene: “missense variants”, “nonsense variants”, “splice-site variants”, and “small insertions” or “deletions” {12}.

- **Missense** variants occur when a change in the codon sequence leads to the replacement of one amino acid with another {13}. The clinical impact of these variants can range from mild to severe, depending on the specific amino acid substitution {13}. Missense variants represent the most common type of variant in *GLA* gene accounting for approximately 61% of reported variants {12}. The majority of *GLA* missense variants are pathogenic and are associated with either classic or late-onset FD, as missense variants can lead to either a complete loss of enzyme function or to reduced residual α -Gal A activity {12}.
- **Nonsense** variants result in the creation of a stop codon where there was none previously {13}. Nonsense variants are associated with the classic FD phenotype and generate little or no α -Gal A activity {12}.
- **Splice-site** variants are nucleotide insertions, deletions, or substitutions that take place at the splice sites between the introns and exons of genes. During transcription, introns are removed, or spliced, out of the sequence, leaving only the exons in the transcribed RNA {14}. Splice site variants are associated with both classic and late-onset FD {12}.
- **Base insertions and deletions** can be classified as either in-frame or frameshift variants. In-frame variants occur when nucleotides are inserted or deleted in multiples of three nucleotides, thereby maintaining the integrity of the reading frame {13}. In contrast, frameshift variants are caused by insertions or deletions that involve a number of nucleotides not divisible by three, resulting in an alteration of the reading frame

{13}. Approximately, 25.5% of reported *GLA* variants are deletions or insertions that result in frameshifts, resulting in changes to the amino acid sequence of α -Gal A protein and are commonly associated with the classic FD {12}. Such alterations significantly affect both protein structure and protein function {12}.

To date, more than 1,000 *GLA* gene variants have been identified. Many of them are considered private as they have only been reported within a single family or have been observed in very few unrelated patients {26}. The presence of numerous VUS further complicates genetic interpretation as there are patients that present nonspecific clinical features and/or their profile does not fit the classic FD phenotype {26}.

In FD, VUS stands for: “Variant of Uncertain/Unknown Significance”, citing to a variant in the *GLA* gene for which there is lacking or inconsistent evidence to determine if this variant is pathogenic (disease-causing) or benign {28}.

Genotype - Phenotype correlation

As previously mentioned, Fabry disease (FD) can be broadly classified into two main clinical phenotypes: the classic form and the late-onset form {30}. The clinical manifestations of FD are influenced by the underlying *GLA* pathogenic variant and the level of residual α -galactosidase A (α -Gal A) enzyme activity.

The classic form is primarily observed in hemizygous males exhibiting less than 1% residual α -Gal A activity {30}. Symptoms typically take place during childhood or adolescence and include episodes of intense neuropathic pain involving the hands and feet known as acroparesthesia, angiokeratomas [Figure 1], reduced or absent sweating (hypohidrosis or anhidrosis), cornea verticillata [Figure 4], and gastrointestinal manifestations {30}. The progressive accumulation of glycosphingolipids may lead to involvement of multiple organs, particularly the kidneys, heart, and central nervous system. Renal function gradually deteriorates, frequently progressing to end-stage kidney disease (ESKD) between the third and

fifth decades of life {30}. In addition, untreated patients commonly develop hypertrophic cardiomyopathy, cardiac arrhythmias, and cerebrovascular complications. Consequently, renal, cardiac, and cerebrovascular disease constitute the leading causes of morbidity and mortality in individuals with classic Fabry disease {30}.

Although heterozygous females generally exhibit milder clinical symptoms than susceptible males, disease severity varies considerably {30}. Some women remain asymptomatic throughout their life, whereas other women develop clinical manifestations analogous to those observed in males with the classic phenotype {30}. This variability is largely attributed to random X-chromosome inactivation (lyonization), which determines the proportion of cells expressing either the normal or the pathogenic *GLA* allele {30}. Females in whom the X-chromosome carrying the pathogenic variant remains active in a greater proportion of cells are more likely to develop a more severe disease phenotype {30}. Common manifestations include cornea verticillata, acroparesthesia, angiokeratomas, hypohidrosis, and chronic abdominal pain. As the disease progresses, patients may present significant left ventricular hypertrophy (LVH), cardiomegaly, myocardial ischemia, cardiac arrhythmias, myocardial infarction, and transient ischemic attacks {30}.

In contrast, the late-onset form is associated with pathogenic *GLA* variants that are associated with higher residual α -Gal A activity {30}. Clinical manifestations usually appear during adulthood, most commonly between the sixth and eighth decades of life. In contrast with the classic phenotype, patients often do not exhibit early manifestations such as neuropathic pain, angiokeratomas, and hypohidrosis. Instead, the disease predominantly affects specific organ systems, particularly the kidneys and the heart, where patients may progress to ESKD and left ventricular hypertrophy, cardiomyopathy, and cardiac arrhythmias. In addition, cerebrovascular complications, including stroke and transient ischemic attacks, are also recognized features of the late-onset phenotype {30}.

Although many studies have investigated genotype–phenotype correlations in Fabry disease, establishing a clear association between specific *GLA* variants and clinical manifestations remains difficult. Many affected families have unique (private) *GLA* pathogenic variants, and patients with the same variant may still exhibit different clinical manifestations {30}. However, several trends have been observed. Males with the classic phenotype typically have

pathogenic variants that cause very low or absent α -Gal A activity, including missense, nonsense, and splice-site variants whereas, patients with the late-onset phenotype usually have variants that allow some residual enzyme activity. However, exceptions exist, and certain pathogenic variants, such as p. Arg112His, have been identified in patients with either the classic or the late-onset phenotype, highlighting how complex the relationship of genotype–phenotype in Fabry disease is {30}.

Table 1: summarizes the differences between classic and late-onset Fabry disease phenotypes based on selected clinical features {30}.

Feature		Classic	Late-Onset Variants
Age at onset		4-8 yrs	>25 yrs
Average age of death		41 yrs	>60 yrs
Manifestation	Angiokeratoma	++	–
	Acroparesthesia	++	–/+
	Hypohidrosis/anhidrosis	++	–/+
	Corneal/lenticular opacity	+	–
	Cardiac disease	LVH/ischemia	LVH/cardiomyopathy
	Cerebrovascular disease	TIA/stroke	–
	Kidney disease	ESKD	Proteinuria or ESKD
	Residual α -Gal A enzyme activity	<1%	>1%

Table 1 : Citation : Mehta et al. (2004), Eng et al (2007)

+ = present; – = absent; α -Gal A = alpha-galactosidase A; ESKD = end-stage kidney disease; LVH = left ventricular hypertrophy; TIA = transient ischemic attack {30}.

FD Inheritance

Variants in the *GLA* gene have different implications for males and females. Males are often more severely affected than females because they only have one X chromosome. The chance of inheriting Fabry disease is dependent on whether the affected parent is the father or mother {15-17}. Initially, FD was considered an X-linked disorder due to the hemizygous state in males, whereas females were thought to be asymptomatic or to present symptoms of mild severity. However, upon further studies, it turned out that females carrying the one pathogenic *GLA* variant may present clinical manifestations of the disease. Heterozygous females may manifest symptoms similar to affected males {29}. Hence, FD is now considered to be an X-linked disorder and not an X-linked recessive condition. In addition, the term “carrier” does not represent all affected females. In the majority of affected females, *GLA* variants are present in heterozygous state whereas it is extremely rare to be present in homozygous state. Regardless of gender, it is 50% possible for an heterozygous affected mother to transmit the *GLA* pathogenic variant to either her daughter or son [Figure 4, {29}].

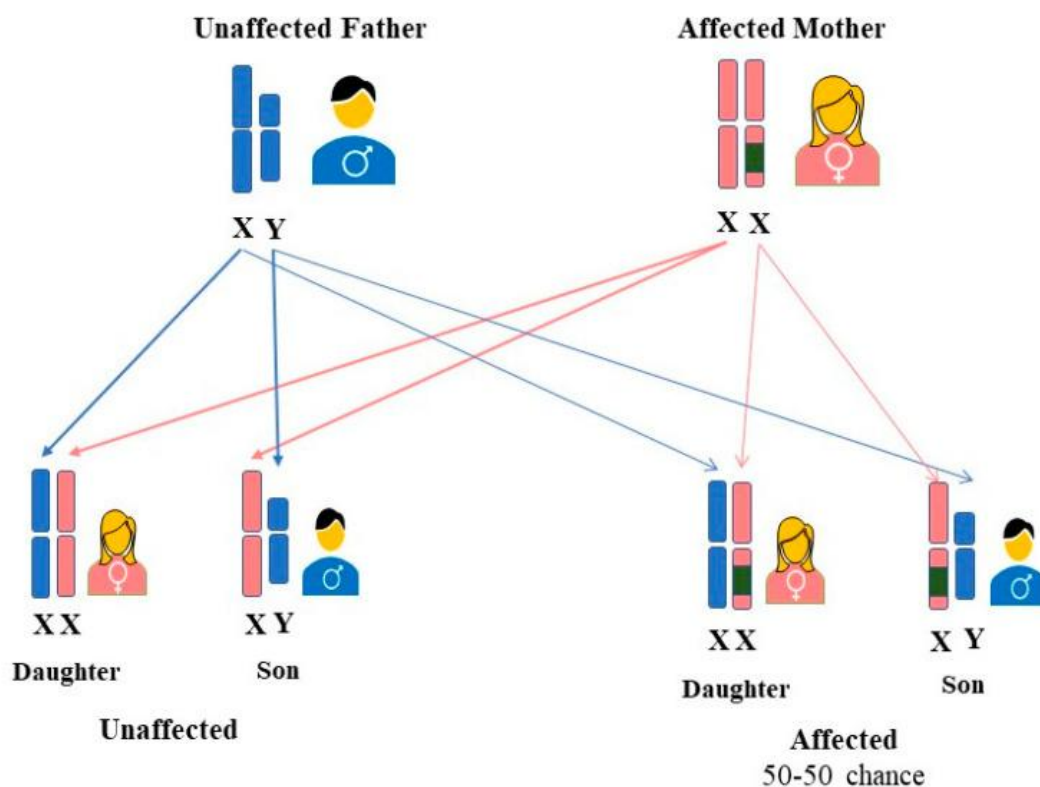


Figure 4: The chance of passing the *GLA* variant to children differs between males and females {29}. Affected males will pass the *GLA* variant to all their daughters, who will be heterozygous, while their sons will inherit the Y chromosome and will not be affected. Heterozygous women have a 50% chance of transmitting the *GLA* variant to their children, regardless of sex.

Pathophysiology of FD

The pathophysiology of Fabry Disease is primarily associated with a deficiency or loss of α -Gal A in the lysosomes, preventing cells from properly metabolizing and clearing Gb3 [Figure 5, {32}]. This results in the lysosomal accumulation of Gb3. So, when the normal metabolism of Gb3 does not take place the result is the conversion of Gb3 into the deacylated form Lyso-Gb3 by acid ceramidase {18}. In FD, lyso-Gb3 has been shown to accumulate simultaneously with Gb3, and lyso-Gb3 accumulates particularly in the bloodstream where its levels are significantly higher than normal {18}.

In FD, lysosomal accumulation of Gb3 occurs in cardiac and renal cells {19,20}. Renal cells include podocytes, distal tubular epithelial cells, vascular endothelial cells and smooth muscle cells of the kidney {19}. As mentioned above, FD accumulation of Gb3 and lyso-Gb3 occur in renal cells. A highly specialized renal cell that is affected by this accumulation is the podocyte. Podocyturia occurs when injured podocytes detach from the kidney glomerulus and are excreted via urine {21}. Podocyturia is evident from the early stages of FD, thus rendering it a reliable biomarker for early detection of FD {22}. At this point, it is worth noting that nephropathy is one of the major manifestations of FD {19} and there is a highly solid biomarker that facilitates the task of precision medicine.

Cardiac cells include cardiomyocytes and, valvular fibroblasts, endothelial cells and vascular smooth muscle cells of the heart {20}. Gb3 accumulation in cardiomyocytes leads to progressive hypertrophy and inflammation as a result of cell death and possibly myocardial fibrosis. Hypertrophic Cardiomyopathy (HCM) is the main cardiac manifestation in FD, with Left Ventricular Hypertrophy (LVH) being present in 43% of males and 26% of females with FD {23}. The severity and incidence of LVH increase with age, exhibited in more than 75% of patients above the age of 75 {23}.

In addition, Gb3 can also accumulate in vascular endothelial cells of the skin (angiokeratomas), as well as in cells of the nervous system {19}.

Gastrointestinal (GI) manifestations are very common in FD, affecting up to 50% of females and almost 60% of untreated children with FD. Most reported GI symptoms in FD include abdominal pain, bloating, early satiety, intermittent/chronic diarrhea, constipation, nausea and vomiting, and low weight gain {24}. GI symptoms are among the earliest and most underestimated signs of FD since they are often confused with symptoms of other gastrointestinal disorders such as irritable bowel syndrome or inflammatory bowel disease. In many cases, GI symptoms may be underreported by patients, so it is important to educate patients with FD as well as specialists about the appearance of GI symptoms in FD so as to improve or prevent the progression of these symptoms {24}.

Summarizing, Gb3 accumulation may cause a cascade of adverse conditions such as cellular death, compromised energy metabolism, small vessel injury, oxidative stress, impaired autophagosome maturation and irreversible cardiac and renal tissue fibrosis {11}. Long-term exposure to elevated Gb3 causes chronic toxicity, cell death and breakdown of tissues {19}.

As observed, Gb3 and lyso-Gb3 are two vital and commonly used biomarkers of Fabry Disease. For example, measurements of plasma and urinary levels of Gb3 and lyso-Gb3 are used as complementary tests for diagnosing Fabry disease as well as for monitoring response to FD treatment.

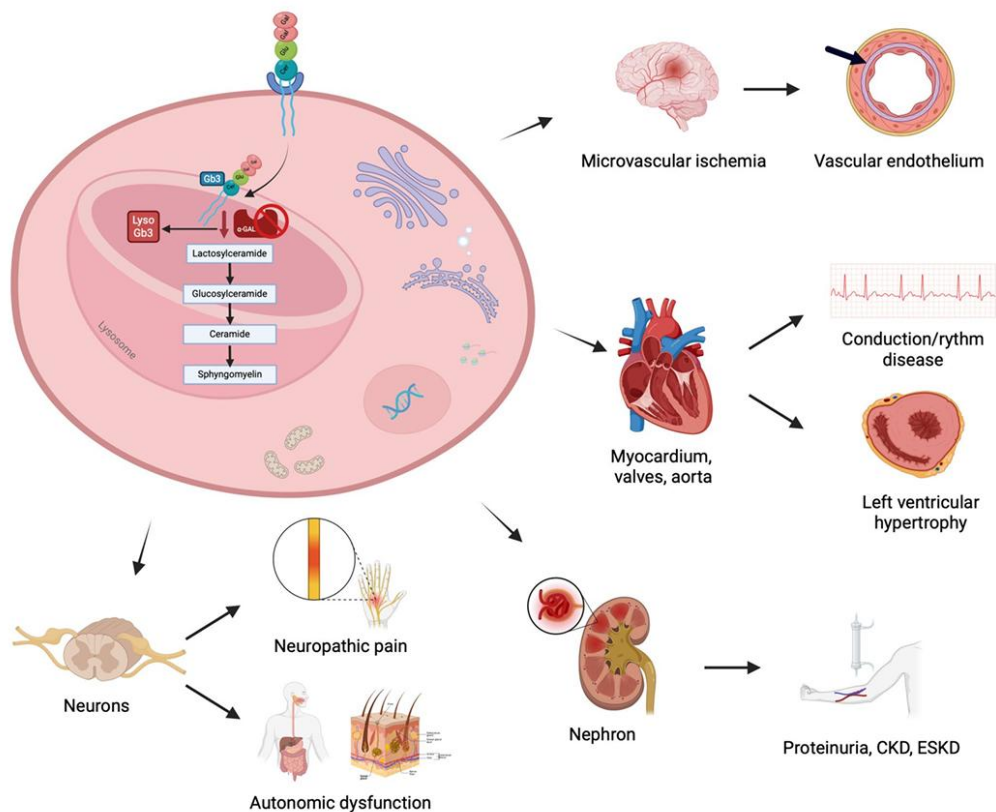


Figure 5: Pathophysiology of FD {32}.

Diagnosis

FD is caused by variants in the *GLA* gene that lead to a loss or deficiency in α -Gal A lysosomal enzyme activity {9}. Thus, there are both biochemical and genetic tests that measure α -Gal A activity and identify FD-causing *GLA* variant respectively {11}.

To investigate a possible FD case and thus, to diagnose FD, some significant characteristics should be taken into consideration, such as:

- **Family history;** family history of neuropathic pain, heart disease, kidney disease, or stroke can lead to a speculation of FD {11}.

- **Patient history;** patients with a history of neuropathic pain, proteinuria, kidney disease (prior to the age of 50), arrhythmia, heart failure, stroke, heat/cold intolerance, exercise intolerance, and/or missing school as a child are presumed to have FD {11}.
- **Physical exam results;** when a physician presumes FD based on medical exams along with some patients' characteristics such as Fabry Facies, angiokeratomas, and/or cornea verticillata [Figure 6, {33}]{11}.
- **High-risk populations;** non-classic individuals with late-onset symptoms of FD i.e. chronic kidney disease, unexplained hypertrophy, young stroke patients to be screened {11}.



Figure 6: Cornea Verticillata {33}

As mentioned above, both biochemical and genetic tests are used for the screening and diagnosis of Fabry disease (FD). However, the diagnostic approach differs between males and females because FD is an X-linked disorder {11}.

In **males**, the initial diagnostic test is the measurement of α -galactosidase A (α -Gal A) enzyme activity, which is commonly performed using dried blood spots (DBS). If reduced enzyme activity is detected, the result may be borne out by measuring α -Gal A activity in leukocytes, particularly when a more reliable assessment is required.

Molecular analysis of the *GLA* gene is then performed to confirm the diagnosis by identifying a pathogenic variant and to support genotype–phenotype correlation {11}.

In **females**, α -Gal A enzyme activity may be within the normal range because random X-chromosome inactivation can preserve sufficient enzyme activity in some cells. Therefore, molecular analysis of the *GLA* gene is recommended as the primary diagnostic test in females with presumed Fabry disease {11}. The diagnostic path is represented in **figure 7**, [Figure 7, {34}].

DBS samples can also be used for molecular genetic testing. Pathogenic variants in the *GLA* gene are identified by DNA sequencing, most commonly using Sanger sequencing or next-generation sequencing (NGS). In patients with inconclusive biochemical or genetic findings, particularly those carrying variants of uncertain significance (VUS), plasma lyso-Gb3 measurement provides additional diagnostic information to be interpreted along with the patient's clinical presentation, enzyme activity, and genetic results {25}.

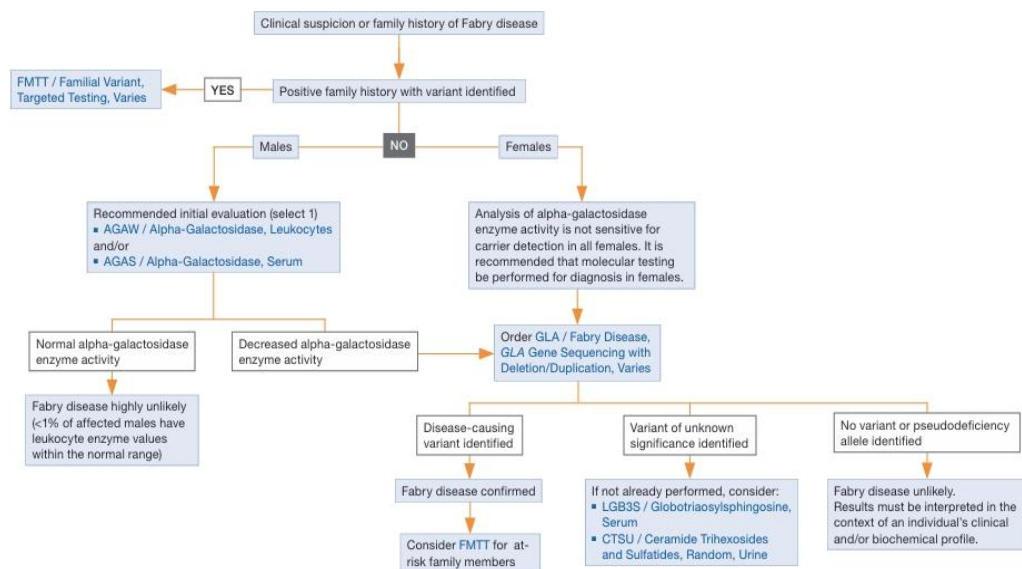


Figure 7: Fabry Disease Diagnostic Testing Algorithm {34}.

In addition to enzymatic and molecular analysis, the use and the measurement of disease-specific biomarkers has been rendered a crucial element in the section of diagnosis of FD. Among these biomarkers, lyso-Gb3 has arisen as an importantly valuable biomarker due to its association with the existence of the disease and its severity. Elevated plasma lyso-Gb3 was observed in males FD patients in 2008 {26}.

Plasma lyso-Gb3 concentrations are remarkably high in males with classic FD, with levels reported to be up to 100-fold higher than those observed in healthy individuals {26}. Lower concentrations of lyso-Gb3 were observed in males with mild phenotype and heterozygous females; however, these values were above the normal range. The degree of lyso-Gb3 elevation is also influenced by the type of *GLA* variant as higher concentrations of lyso-Gb3 have been observed in patients carrying severe loss-of-function variants i.e. nonsense and frameshift variants {26}.

Measurement of plasma lyso-Gb3 refers to an additional powerful diagnostic tool in cases where genetic findings are dubious. More specifically, lyso-Gb3 levels may support the interpretation of *GLA* VUS as in that case lyso-Gb3 can contribute to determining if this variant is likely to be clinically relevant or not {26}. However, it is worth mentioning that normal plasma lyso-Gb3 levels do not exclude the presence of FD; this concerns mainly female patients as they may have a non-affected X chromosome. Thus, relevant results are to be interpreted with a-Gal A activity, genetic analysis and clinical findings. Furthermore, lyso-Gb3 measurement may offer prognostic information except for diagnostic information as several studies have correlated plasma-lyso Gb3 levels and disease burden, involving cardiac and neurological manifestations {26}.

Precision Medicine: Standard and Emerging Therapies

Rationale of Precision Medicine in Fabry Disease

Fabry Disease is characterized by significant clinical and genetic heterogeneity. As described above, the *GLA* gene can be affected by a wide range of pathogenic variants, which may result in different levels of residual α -Gal A activity and diverse clinical manifestations. Moreover, disease expression varies according to gender, as heterozygous females may exhibit a broad spectrum of symptoms ranging from asymptomatic cases to severe organ involvement. In addition, the interpretation of genetic findings can be challenging, particularly in individuals carrying variants of non-significance (VUS), further emphasizing the complexity of diagnosis and therapeutic decision-making in FD. Because of this variability, the need for precision medicine approach is essential in FD, as treatment decisions should be tailored in line with each patient's characteristics.

Special attention needs to be drawn to the fact that still there is no curative treatment for Fabry Disease {35}. Current therapeutic goals for FD focus mainly on: reduction and management of symptoms, preventing the evolution of organ manifestations, particularly in kidneys, heart and CNS, thus enhancing the quality of life of patients as well as promoting the advancement of life expectancy {35}.

Standard Therapies of Fabry Disease

Currently, the standard treatments for Fabry disease include enzyme replacement therapies (ERTs) and pharmacological chaperone therapy. These therapeutic approaches have significantly improved disease management by slowing disease progression, reducing glycosphingolipid accumulation, and preventing irreversible organ damage. However, Fabry disease is a multisystemic disorder, and the efficacy of current therapies may vary depending on several patient-specific factors, including gender, genotype, disease stage, and the extent of organ involvement. This heterogeneity highlights the need for individualized therapeutic strategies, rendering Fabry disease an important model for the application of precision medicine.

Introduction to ERTs

In the context of Fabry disease, enzyme replacement therapies (ERTs) use recombinant human α -galactosidase A (α -Gal A) to replace the deficient enzyme activity, thereby reducing

glycosphingolipid accumulation and preventing further tissue and organ damage {36}. More specifically, ERTs provide an exogenous source of recombinant human α -galactosidase A (α -Gal A), replacing the deficient endogenous enzyme activity. Following intravenous administration, recombinant α -Gal A circulates in the bloodstream and is taken up by target cells through mannose-6-phosphate receptors (M6PRs) {11}. The enzyme is subsequently transported to lysosomes, where it catalyzes the hydrolysis of accumulated globotriaosylceramide (Gb3). As a result, Gb3 accumulation is reduced, thereby limiting progressive cellular and tissue damage {11}. The mechanism of action for ERTs is presented in **Figure 8**.

Since their introduction in 2001, ERTs have become the standard treatment for Fabry disease {35}. Currently, three ERTs are available: agalsidase alfa (Takeda, Tokyo, Japan), agalsidase beta (Sanofi Genzyme, Cambridge, MA, USA), and the most recently approved enzyme replacement therapy, pegunigalsidase alfa (Chiesi, Parma, Italy). Agalsidase alfa and agalsidase beta are administered by intravenous infusion every two weeks {35}, whereas pegunigalsidase alfa can be administered either every two weeks (E2W regimen) or every four weeks (E4W regimen) with the regimen of E4 weeks to be administered in stable patients {37}.

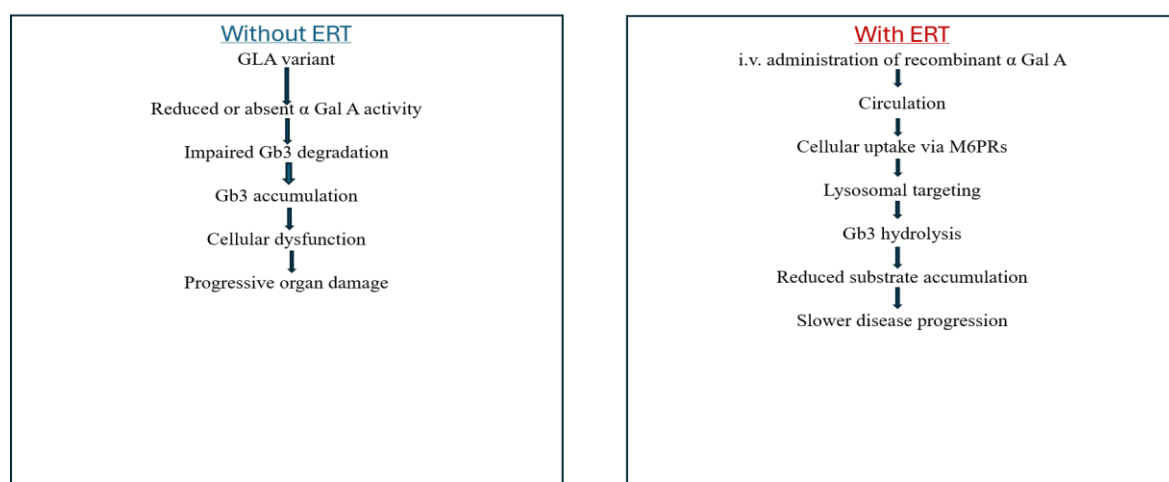


Figure 8: Mechanism of action of ERT.

Agalsidase alfa

Agalsidase alfa was approved in Europe in 2001, though, it has not been approved in the United States. It is a recombinant human α -Gal A enzyme produced in a human cell line, specifically in human fibrosarcoma HT-1080 cells. Agalsidase alfa is administered by intravenous infusion at a dose of 0.2 mg/kg over approximately 40 minutes. Treatment with agalsidase alfa has been approved for patients aged seven years and older {35}.

Agalsidase beta

Agalsidase beta was approved in Europe in 2001, whereas it was approved in the United States in 2003. It is a recombinant human α -Gal A enzyme produced in Chinese hamster ovary (CHO) cells. Agalsidase beta is administered by intravenous infusion at a dose of 1.0 mg/kg over approximately 280 minutes. In line with recent literature, the duration of infusion can be gradually reduced to 90 minutes {35}, provided that the patient demonstrates good tolerance. Treatment with agalsidase beta has been approved for patients aged eight years and older {35}.

Overall efficacy and safety of agalsidase alfa and beta

As the first approved ERTs, the efficacy and safety of agalsidase alfa and agalsidase beta have been extensively studied and re-evaluated over time {38}. A broad clinical study program and long-term clinical experience have demonstrated their efficacy and safety in patients with Fabry disease {38}.

Both molecules are indicated for patients with confirmed Fabry disease and reduced glycosphingolipid accumulation by facilitating the hydrolysis and clearance of globotriaosylceramide (Gb3) {35}. Both enzymes have been shown to decrease plasma Gb3 and lyso-Gb3 levels, as well as urinary Gb3 levels and Gb3 deposition in the kidney, contributing to stabilization or slower decline of estimated glomerular filtration rate (eGFR). Regarding cardiac involvement, both enzymes have demonstrated stabilization or reduction of

left ventricular mass (LVM), improvement of neurological outcomes, reduction in the severity of gastrointestinal symptoms and pain, and improvement in patients' quality of life {35}.

However, treatment response is not uniform among all patients and may be influenced by disease stage, gender, genotype, and the presence of irreversible organ damage at treatment initiation. Despite these demonstrated benefits, ERTs present several limitations that have driven the development of newer therapeutic approaches; one of the most important limitations being immunogenicity {39}. Anti-drug antibodies (ADAs) have been reported in a high proportion of patients receiving agalsidase beta, particularly among males with classic Fabry disease {39}. According to real-world studies, the development of ADAs may negatively affect treatment response, as persistent lyso-Gb3 elevation has been observed in some patients. Furthermore, infusion-related reactions (IRRs) represent an additional safety concern associated with ERT administration {39}.

Dose reduction/Switching between the two ERTs

Recent studies have investigated dose reduction strategies for agalsidase beta {40}. One study evaluated a reduced-dose regimen, decreasing the dose from 1.0 mg/kg every other week (EOW) to 0.3 mg/kg EOW over an 18-month period. Although this regimen maintained renal Gb3 clearance and preserved the reduction of Gb3 deposits in different renal cell types, an increase in urinary Gb3 deposits was also observed following dose reduction. Another study investigated a reduced-dose regimen from 1.0 mg/kg EOW to 0.5 mg/kg per month for one year and reported a significant increase in plasma lyso-Gb3 levels in male patients, without differences in pain severity, disease severity scores such as the Mainz Severity Score Index (MSSI), estimated glomerular filtration rate (eGFR), or left ventricular mass (LVM) {40}.

Several studies have also evaluated the effects of switching between ERTs, particularly from agalsidase beta to agalsidase alfa, with inconsistent findings {40}. More specifically, according to one study, patients who initially received either agalsidase beta 1 mg/kg every other week (EOW) or a reduced dose of 0.3–0.5 mg/kg EOW and were subsequently switched to agalsidase alfa 0.2 mg/kg EOW exhibited a greater decline in estimated glomerular filtration

rate (eGFR) and a significant worsening of gastrointestinal symptoms, pain, and Mainz Severity Score Index (MSSI) scores {40}. In contrast, another study reported that patients who switched from agalsidase beta 1 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW showed no significant differences in plasma lyso-Gb3 levels, eGFR, proteinuria, or left ventricular mass (LVM) during a two-year follow-up period {40}. These findings highlight the need for therapeutic strategies that optimize treatment efficacy while reducing treatment burden, supporting the development of next-generation ERTs.

Pegunigalsidase alfa

Pegunigalsidase alfa is a PEGylated recombinant human α -Gal A and constitutes the most recently approved enzyme replacement therapy for Fabry disease. Pegunigalsidase alfa received approval from both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) in May 2023 for the treatment of adult patients aged ≥ 18 years with Fabry disease {35}. Pegunigalsidase alfa is administered by intravenous infusion at a dose of 1.0 mg/kg every two weeks (EOW), with an infusion of at least 3 hours duration {35} which can reach the 90min if the patients exhibit good tolerance. In addition, a 2.0 mg/kg every four weeks (E4W) dosing regimen has recently been approved by the EMA for eligible stable adult patients receiving enzyme replacement therapy {37}. This extended dosing interval may provide greater treatment flexibility and may reduce treatment burden while maintaining clinical efficacy in appropriately selected patients.

As mentioned above, pegunigalsidase alfa is a PEGylated recombinant human α -Gal A enzyme. PEGylation refers to the chemical conjugation of polyethylene glycol (PEG) molecules to the enzyme, aiming to modify its pharmacokinetic properties. Pegunigalsidase alfa is chemically modified through the attachment of 2 kDa homo-bifunctional polyethylene glycol molecules to two plant cell-derived α -Gal A subunits {39}.

The PEG moieties may partially mask immunogenic epitopes of the enzyme, potentially contributing to a favorable immunogenicity profile compared to non-PEGylated enzyme replacement therapies {39}. PEGylation can modify the molecular surface in a way that limits the exposure of specific epitopes to immune recognition and, consequently, reduces

the likelihood of an immune response {41}. However, the clinical impact of PEGylation on anti-drug antibody development remains under investigation and is to be interpreted within the context of available clinical data.

One of the main consequences of PEGylation is the prolongation of the circulating plasma half-life of the enzyme. The plasma half-life of pegunigalsidase alfa has been reported to be approximately 80 hours, compared to approximately 90–110 minutes for agalsidase alfa and 80–120 minutes for agalsidase beta {39}. This prolonged pharmacokinetic profile may contribute to sustained enzyme exposure and has supported the evaluation of extended dosing intervals {35}.

The efficacy and safety of pegunigalsidase alfa have been evaluated in three phase III clinical studies: BALANCE, BRIDGE, and BRIGHT {35}.

The BALANCE study was a phase III head-to-head clinical trial that evaluated the efficacy and safety of pegunigalsidase alfa in comparison to agalsidase beta in adult patients with Fabry disease. Over a two-year period, pegunigalsidase alfa demonstrated non-inferior efficacy regarding eGFR slope and showed a favorable safety profile regarding treatment-emergent adverse events (TEAEs) and infusion-related reactions (IRRs). Furthermore, a lower frequency of neutralizing ADAs observed in patients receiving pegunigalsidase alfa providing additional data regarding its immunogenicity profile {39}.

The BRIDGE study was a phase III switch study evaluating the transition from agalsidase alfa to pegunigalsidase alfa in patients with Fabry disease. Following the switch, pegunigalsidase alfa demonstrated non-inferiority regarding eGFR slope, suggesting stabilization of renal function in patients previously treated with agalsidase alfa. In some patients, a stabilization of disease progression was observed, including patients with a rapidly progressive disease course who subsequently exhibited a more stable clinical trajectory. Regarding safety, pegunigalsidase alfa demonstrated a favorable safety profile {42}.

The BRIGHT study was a phase III, a 52-week clinical trial conducted in adult patients with Fabry disease who had previously received stable treatment with agalsidase alfa or agalsidase beta every two weeks (E2W) for more than three years. The results demonstrated that switching to pegunigalsidase alfa at a dose of 2.0 mg/kg every four weeks (E4W) was well tolerated in clinically stable patients with Fabry disease. Overall, treatment-emergent

adverse events (TEAEs) and infusion-related reactions (IRRs) were reported at low frequencies, while anti-drug antibodies (ADAs) were detected in 3.4% of patients receiving pegunigalsidase alfa {37}.

Limitations of ERT

According to the literature, ERTs present several limitations {40}. One important limitation is their variable tissue distribution and substrate clearance. Despite their ability to circulate and reduce Gb3 and lyso-Gb3 levels, ERTs may exhibit differences in enzyme delivery and substrate clearance among various tissues, particularly in organs affected by advanced disease, such as the kidney and heart {40}. Another important limitation is the occurrence of infusion-related reactions (IRRs), which may affect treatment tolerability and constitute a challenge during long-term therapy {40}. Although newer ERT approaches, such as pegunigalsidase alfa, have been developed aiming to improve pharmacological properties and treatment tolerability, IRRs have not been completely eliminated. Therefore, additional therapeutic strategies continue to be investigated to further optimize Fabry disease management. Another major limitation of ERTs is immunogenicity. The development of anti-drug antibodies (ADAs), particularly in males with classic Fabry disease, may negatively influence treatment response associated with persistent biomarker elevation and infusion-related reactions {40}. The incidence of ADA development appears to vary between different ERTs. For instance, agalsidase beta has been associated with ADA development in up to 91% of male patients with classic Fabry disease, whereas lower rates have been reported with agalsidase alfa (approximately 20%) {40}.

Importantly, not all ADAs have the same clinical impact. Neutralizing ADAs represent a clinically relevant subgroup, as they can bind to the therapeutic enzyme and reduce its enzymatic activity, potentially decreasing treatment efficacy. Therefore, the assessment of neutralizing antibodies is important for understanding individual variability in response to ERT {40}.

Immunogenicity is an important limitation of ERTs and has contributed to the development of newer ERT approaches, such as pegunigalsidase alfa. PEGylation may contribute to altered

pharmacokinetic properties and may partially mask immunogenic epitopes, potentially influencing the immunogenicity profile of the enzyme {32}. However, despite these advances, immune responses may still occur, highlighting that immunogenicity remains an important consideration in the personalized management of Fabry disease.

Furthermore, the requirement for lifelong intravenous infusions represents an additional limitation of ERTs, increasing treatment burden and potentially affecting patients' quality of life and adherence to the regimen {32}.

Pharmacological chaperone therapy

Migalastat is the first and currently the sole oral pharmacological chaperone therapy approved for the treatment of Fabry disease. It was approved in Europe in 2016 and is administered orally at a dose of 123 mg every other day {32}. It is an iminosugar analogue of the terminal galactose residue of Gb3 with a low molecular weight which acts as a selectively competitive inhibitor of α -Gal A {32}. In more detail, *GLA* gene encodes the α Gal A enzyme. In many patients, especially in patients with missense variants, the enzyme is produced but it is wrongly folded (misfolded, the 3D structure is abnormal). Because of this abnormal folding, the cellular quality-control system recognizes the enzyme as defective, retains it within the endoplasmic reticulum (ER), and targets it for degradation before it reaches the lysosome. Consequently, little or no functional α -Gal A reaches the lysosome, resulting in the accumulation of Gb3 {40}, [Figure 9].

Migalastat, unlike ERT, does not replace the enzyme but enters the cell and binds to mutant α Gal A enzyme. This reversible binding stabilizes the mutant enzyme allowing it to fold correctly and traffic from the ER to the lysosome. Inside the lysosome, the environment has low pH. Within the acidic environment of the lysosome, migalastat dissociates from the enzyme, allowing the active site to become available for substrate (Gb3) hydrolysis, preventing in that way Gb3 accumulation {40} [Figure 9]. The mechanism of action for chaperone is presented in Figure 9.

At this point, an important characteristic of migalastat therapy should be highlighted. Unlike enzyme replacement therapy, migalastat is indicated only for patients carrying amenable *GLA* variants. These variants usually result in the production of a mutant α -galactosidase A (α -Gal A) enzyme that is misfolded but retains residual enzymatic activity and can therefore be stabilized by migalastat {32}. But what exactly does amenable mean? A variant is considered amenable when migalastat increases the activity of the mutant enzyme according to predefined assay criteria, indicating that the enzyme can be stabilized and retain sufficient activity to reach the lysosome and function {32}. Hence, migalastat is not suitable for patients carrying variants that result in absent or severely reduced α -Gal A production, such as large gene deletions as no functional enzyme is available {32}. The amenability of *GLA* variants is assessed via an in vitro assay in which Human Embryonic Kidney Cell Lines (HEK-293) are transfected with particular variants and produce mutant proteins {32}. Therefore, genetic testing is indispensable before treatment initiation to identify patients with amenable *GLA* variants, making migalastat a representative example of precision medicine in Fabry disease.

Migalastat's efficacy has been demonstrated in two phase III clinical trials: the FACETS trial, in which migalastat was compared to placebo, and the ATTRACT trial, in which migalastat was compared to enzyme replacement therapy (ERT). In both trials, migalastat demonstrated beneficial effects on cardiac and renal outcomes, including a reduction in left ventricular mass index (LVMI) and stabilization of the estimated glomerular filtration rate (eGFR) slope {32}.

Limitations of pharmacological chaperone

Migalastat is, to date, the only oral therapeutic option targeting patients with amenable *GLA* variants; this is an inherent limitation as migalastat cannot be used in patients carrying non-amenable variants. In addition, in line with the current literature, limited data are available to support the use of migalastat in patients aged ≥ 75 years old or patients younger than 16 years of age, and pregnant breastfeeding women. Finally, another limitation of migalastat is that it is not recommended in patients with $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ {40}.

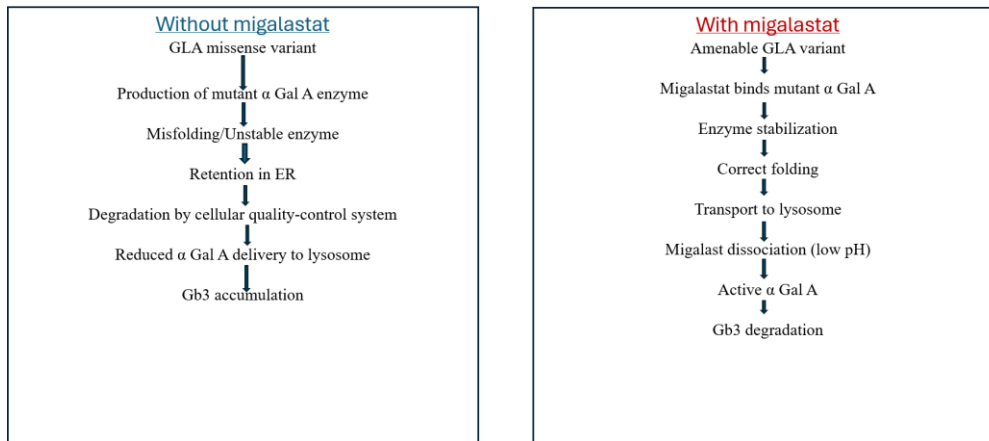


Figure 9: Mechanism of action of chaperone.

Treatment costs

Available therapies for FD are associated with a substantial financial burden due to their high cost. In Belgium, as far as concerned ERTs, the hospital prices are €404 and €2,925 for 5 mg and 35 mg vials of agalsidase beta, respectively, €1,564 for the 3.5 mg vial of agalsidase alfa, and, €404 and €1,616 for 5mg and 20 mg vials of pegunigalsidase alfa, respectively. For migalastat, the hospital price is €17,802 for a pack of 14 capsules {CBIP, 47}. These prices highlight the considerable cost of FD therapies. Certainly, the price is associated with the dosage and patient-specific factors i.e. body weight for ERTs.

Emerging therapies

SRT

Whereas ERT aims to correct the enzymatic deficiency by providing an exogenous source of functional α -Gal A and migalastat aims to stabilize amenable *GLA* variants, substrate reduction therapy (SRT) emerges as a new and different therapeutic approach by reducing the synthesis of Gb3 and lyso-Gb3, and thus limiting Gb3 accumulation {35}.

Three different drugs are currently under clinical investigation:

Lucerastat (Idorsia), per os administration, at a dose of 1g twice daily. It is a low-molecular-weight iminosugar which acts as an inhibitor of glucosylceramide synthase (GCS), thereby reducing lyso-Gb3 levels in plasma {43}. Further studies are ongoing {35}.

Venglustat (Sanofi, Genzyme), per os administration, at a dose of 15 mg per day {35}. It is a ceramide analogue which also acts as GCS inhibitor (like Lucerastat) {35}. Venglustat has been developed for the treatment of various lysosomal storage disorders. It has been investigated for its ability to cross the blood-brain barrier (similar to Lucerastat) and target CNS. Despite its favorable safety and tolerability profile, a small number of patients exhibited severe psychiatric AEs, resulting in the discontinuation of the treatment {44}. Nevertheless, phase III clinical studies are underway {35}.

AL01211 (Acelink Therapeutics), is a novel GCS inhibitor (similar to Lucerastat & Venglustat) with high selectivity that is currently being evaluated in a phase II clinical trial {35}.

Gene Therapy

Gene therapy constitutes a promising therapeutic option not only for FD but also for a wide range of genetic disorders.

Gene therapy for FD is based on correcting the underlying defect at the level of the *GLA* gene; meaning that scientists may introduce genetic material containing the instructions for a functional *GLA* gene into the patient's cells. Hence, the patient's cells are able to produce functional α -Gal A. To deliver genetic material into the cells, a vector is needed, with the most commonly used approaches including lentiviral vectors and adeno-associated virus vectors (AAV) {35}.

Lentiviral vectors can be used in both in vivo and ex vivo approaches. However, the ex vivo approach is mainly used, in which hematopoietic stem cells are genetically modified outside the body and then reintroduced into the patient. In the first clinical trials, lentiviral gene therapy showed an increase in α -Gal A activity and a reduction in lyso-Gb3 levels. However, over time, enzyme activity declined and remained insufficient to ensure a stable therapeutic proposition. Despite the increase in α -Gal A activity and reduction of lyso-Gb3 levels observed in subsequent trials, many challenges remain in lentiviral gene therapy for FD {35}.

AAV vectors represent one of the most promising approaches in gene therapy. They are particularly used for in vivo gene delivery into patients' cells with the liver being one of the most commonly targeted organs. In comparison to other viral vectors, AAV vectors exhibit lower immunogenicity. However, immune responses against the capsid of the virus and the transferred genetic material constitute major challenges. Several AAV-based gene therapy approaches are currently investigated in FD {35}. STAAR study, using isaralgagenecivaparvovec (ST-920), exhibited encouraging results including increase in α -Gal A activity, decrease in lyso-Gb3 levels and the possibility of ERT discontinuation in treated patients {clinical trials.gov}. Other AAV-based approaches are under clinical investigation; however, safety concerns and immune responses remain crucial limitations. According to Lenders M. et al., ST-920 represents one of the most advanced AAV-based gene therapy approaches in FD {35}.

In **Figure 10** {35}, therapeutic targets of current and future treatments for Fabry disease are presented. Current and future treatments for FD have as their main aim to reduce the accumulation of Gb3 in various cells via different therapeutic approaches including ERT, pharmacological chaperone therapy, SRT, and gene therapy.

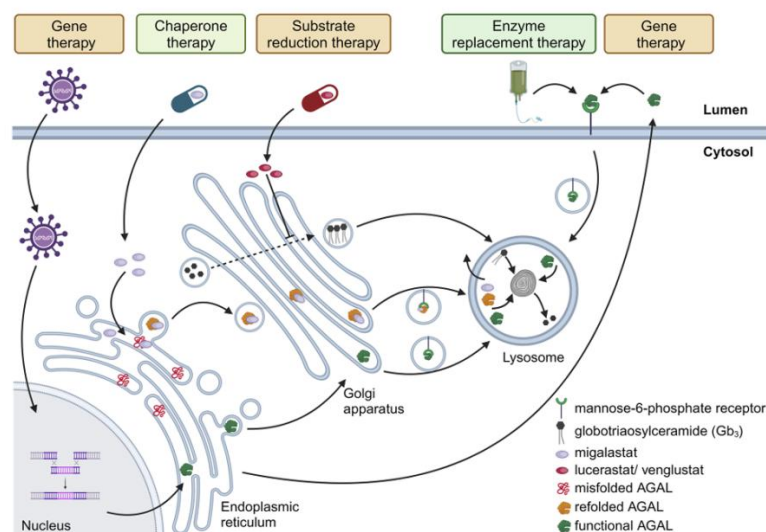


Figure 10: Therapeutic targets of current and future treatments for FD {35}.

Future perspectives in treatment

In addition to the emerging therapies described above, there are several other therapeutic approaches that are still in the preclinical stage of development. One of these is mRNA therapy, which uses lipid nanoparticles to deliver mRNA, encoding the functional α -Gal A, and thus allowing the endogenous production of the enzyme. Preclinical studies of the mRNA therapy have exhibited increased α -Gal A activity and reduced lyso-Gb3 levels {45}. Another promising approach is vesicle-based ERT that aims to improve enzyme stability, circulation time and cellular uptake via nanoliposomes that act as carriers for the therapeutic enzyme {46}.

Discussion

The findings discussed throughout this review indicate that Fabry Disease is characterized by considerable clinical and molecular heterogeneity, thus highlighting the need for individualized therapeutic approaches. Due to the complexity of the disease and its multi-organ involvement, the management of this disorder increasingly relies on the principles of precision medicine reflecting the considerable interindividual clinical variability observed among patients with FD. Factors such as gender, age, genotype-phenotype correlation, extent of organ involvement, disease stage, immunogenicity, particularly the development of anti-drug antibodies, play a crucial role in the selection of the optimal therapeutic strategy.

Although ERTs represent a major therapeutic advancement in the management of FD, the development of more individualized therapeutic approaches continues to represent an unmet clinical need. Pegunigalsidase alfa constitutes an example of next-generation ERT that has been developed through PEGylation - a chemical modification designed to enhance its therapeutic profile by improving pharmacokinetic properties and potentially reducing immune recognition through the masking of immunogenic epitopes; this approach reflects the ongoing transition toward personalized therapeutic strategies. Another significant step toward individualized therapeutic strategies in relation to FD management is pharmacological chaperone therapy, which introduced a genotype-guided therapeutic approach into the management of patients with FD. Unlike ERTs, which provide enzyme replacement, chaperone therapy targets patients carrying amenable GLA variants. In addition, its oral administration compared to the intravenous administration required for ERTs may improve patient convenience and

adherence to the treatment. However, its development targeting amenable variants constitutes simultaneously both its strength as a precision medicine approach and its main limitation as it restricts its applicability to a subset of patients.

A notable point not to be neglected is the fact that the established therapies do not fully prevent disease progression, therefore, research into novel therapeutic strategies remains significantly active. Hence, emerging therapies such as SRT and gene therapy are under clinical research with the aim of overcoming the limitations of current treatments. SRT, compared to both ERTs and pharmacological chaperone therapy, targets a different step into the disease pathway by reducing substrate synthesis, and thus limiting the accumulation of lyso-Gb3. Therefore, SRT may represent an alternative therapeutic approach, potentially broadening the therapeutic options available for FD. Overall, it is evident that the available and emerging therapeutic strategies differ not only in their mechanism of action but in their therapeutic target as well. Thus, this therapeutic revolution reflects the principles of precision medicine.

ERT replaces the deficient enzyme, pharmacological chaperone therapy stabilizes the endogenous enzyme, SRT reduces substrate accumulation whereas gene therapy seeks to correct the underlying genetic defect of the disease and thus, it can be considered an etiology-directed therapeutic approach. However, always having in mind the benefit and the well-being of the patient, despite the preliminary encouraging results of both emerging therapies, further data are required to establish their long-term safety and efficacy.

In addition, the principles of precision medicine do not only address therapeutic approaches but also include patient monitoring. Lyso-Gb3 measurement represents a valuable biomarker that helps in both the diagnosis and monitoring of the disease as well as in the assessment of disease burden. Therefore, lyso-Gb3 represents a link between diagnosis, disease monitoring and assessment of treatment response. Measurement of anti-drug antibodies (ADAs) represents another biomarker that is used as an indicator of treatment-related immunogenicity. Increase in ADAs and especially neutralizing antibodies may be associated with reduced therapeutic response. Overall, lyso-Gb3 provides information about disease status and treatment response whereas ADAs provide information about the patient's immunological response to treatment. Although these biomarkers represent significant tools, the full implementation of precision medicine requires a combination of biomarkers, genetic information and clinical characteristics, as no single parameter can fully reflect the complexity of Fabry disease.

Fabry disease represents a paradigm where precision medicine is indispensable due to its clinical and molecular heterogeneity. Relevant therapeutic approach is shifting from a general strategy towards a more individualized therapeutic strategy. Treatment of patients with FD should be managed by a multidisciplinary clinical team so as a more individualized decision to be taken. Treatment selection will be based on taking into consideration several parameters such as clinical characteristics, genotype, biomarkers, disease progression, treatment response. The goal is not just treatment selection but also enhancing the quality of life and preventing irreversible organ damage, always having as main goal the well-being of the patient.

Conclusion

Fabry disease is characterized by considerable molecular and clinical heterogeneity, illustrating the importance of the application of precision medicine in its management. The standard and available therapeutic strategies such as ERTs and pharmacological chaperone therapy, along with emerging therapies such as SRT and gene therapy, provide different therapeutic approaches for addressing this complex disease. The integration of biomarkers, genetic information and clinical characteristics may contribute to better and individualized treatment selection and patient monitoring. However, further evidence is required to prove the long-term safety and efficacy of emerging therapies. Overall, the positive aspect is that extensive research is being conducted for the management of FD, with the ultimate goal of improving patients' lives.

Limitations

This work is based on a bibliographic literature review, so the results are dependent on the quality and availability of the published bibliography. Fabry disease has considerable molecular and clinical heterogeneity, so the results from different studies cannot be directly compared. Emerging therapies are under clinical investigation, so their long-term efficacy and safety are not yet defined. To conclude, the prices of available therapies and the process of regulatory approvals differ between countries and may change over time.

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