Therapeutics and Clinical Risk Management

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REVIEW

Experts' Opinion in Fabry Disease Management and the Unmet Medical Need: The Saudi Perspective

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Abstract: Fabry disease (FD) is an X-linked lysosomal storage disorder caused by α-galactosidase A gene mutations. Its global incidence ranges from 1:40,000 to 1:170,000. This expert review evaluates the available guidelines, the status of diagnosed but untreated patients with FD, and the challenges in diagnosing and managing FD in the Kingdom of Saudi Arabia (KSA). An advisory board meeting (ABM) was conducted in two phases, with a survey that aimed to receive insights on the current unmet needs in the management of patients with FD in November 2022, and a second, offline meeting in February 2023. The goal of this ABM was to discuss current unmet needs in the management of Fabry patients in the Kingdom of Saudi Arabia. In the first ABM, experts opined on the best practices in the diagnosis, screening, and management of FD for healthcare professionals. These opinions on the management of FD relied on data from research and expert clinical judgments. In the second ABM, the same panel discussed different aspects of FD diagnosis, treatment, and management in the member countries of the Gulf Cooperation Council. The experts discussed the stigma associated with FD, patient awareness and knowledge, genetic screening, biomarkers, and home infusion therapy. They reviewed international guidelines and clinical criteria for enzyme replacement therapy (ERT). Furthermore, they also discussed the diagnosis of FD in men and women, the current guidelines followed for monitoring patients with FD, monitoring untreated patients with FD, Fabry Stabilization IndeX (FASTEX) as an assessment tool for the diagnosis of FD, FD management in KSA, challenges encountered while prescribing ERT in patients with FD, and the clinical criteria for starting ERT. The discussions led to the conclusion that currently, ERT is the only available therapy to manage FD and research should be focused on the early diagnosis and management of FD.

Keywords: classical, enzyme replacement therapy, Fabry disease, late-onset, monitoring, phenotype

Introduction

Fabry disease (FD) is an X-linked, multisystem, lysosomal storage disorder that is caused by pathogenic mutations in the α-galactosidase A gene (*GLA*), which results in deficient/undetectable α-galactosidase A (α-Gal-A) activity and increasing lysosomal buildup of globotriaosylceramide (Gb-3). This initiates a chain of cellular and tissue reactions of fatal conditions that damage the heart, kidneys, and central nervous system.[1,2] The estimated worldwide incidence of FD is 1:40,000–1:170,000.[2] FD remains underdiagnosed in Arab countries as evident from the very few reports. It has been suggested that FD may be more common in KSA than previous estimates.[3] Compared to many other countries in the Arab world and Europe, KSA has a higher incidence of FD.[4] This review presents expert opinions on the diagnosis and treatment of FD, reviews the status of diagnosed but untreated FD, and discusses the challenges in diagnosing and managing FD in the Kingdom of Saudi Arabia (KSA). A panel of FD experts gathered to opine on the management of

Received: 26 April 2024
Accepted: 26 August 2024
Published: 13 September 2024

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FD based on their practical experience and available high-level evidence. The opinions provided by the experts will aid medical personnel in establishing screening standards and developing strategies for treating men and women with FD.

Methods

The meeting was planned in two phases, with the first meeting being conducted virtually in November 2022, and the second conducted in person in February 2023. At the first advisory board meeting (ABM), eight questions were discussed by a panel of eight experts. A literature analysis of studies published on FD in pediatric and adult populations, as well as suggestions from current guidelines were critically reviewed by the panel. The literature selection process involved a review of peer-reviewed articles, clinical guidelines, and expert opinions relevant to FD. The search strategy included databases such as PubMed, MEDLINE, and Cochrane Library. Articles were selected based on their relevance to the diagnosis, treatment, and management of FD, particularly in the context of KSA. The search terms employed included combinations of keywords such as "Fabry Disease", "enzyme replacement therapy", "genetic screening", "clinical management", "diagnosis", "treatment guidelines", and "Saudi Arabia". The discussion points were chosen based on their relevance to the current challenges and unmet needs in the diagnosis and management of FD in the KSA. These points were identified through preliminary expert consultations and a review of existing literature, ensuring that they reflect the issues faced by healthcare professionals in this region.

In the second ABM, the same panel of eight experts discussed the diagnosis, treatment, and management of FD in the member countries of the Gulf Cooperation Council (GCC). Key insights from the first ABM were also presented to the panel of experts.

The second ABM focused on the following domains:

- Diagnosis of FD in men and women in the KSA.
- FASTEX (Fabry Stabilization IndeX) as an assessment tool for monitoring disease progression or stabilization of FD.
- Unmet needs in FD management in the KSA.
- Challenges encountered while prescribing enzyme replacement therapy (ERT), which is the only approved specific therapy in KSA, for patients with FD.
- The clinical criteria for specific therapy initiation.
- The current guidelines followed for monitoring treated and untreated patients with FD.

Furthermore, the experts discussed the social stigma associated with FD, patient knowledge and understanding of the progressive nature of FD, family screening, reliable biomarkers for FD diagnosis, and the relevance of home infusion therapy (HIT) in managing FD.

After the ABMs the experts decided that their opinions must be summarized into a manuscript to provide healthcare professionals (HCPs) with a list of best practices for FD diagnosis, screening, and management. The experts' opinions were based on evidence from published literature and the clinical expertise of the HCPs.

Results and Discussion

Epidemiology of Fabry Disease

According to estimates, FD has an incidence rate of 1 in 40,000 men and 1 in 117,000 women.[5] However, this number may be an underestimate. In genetic screening studies, as mentioned in a systematic review of high-risk populations by van der Tol et al,[6] the overall proportion of individuals having *GLA* gene abnormalities, including genetic variants of undetermined significance (GVUS), was 0.62%. The prevalence of FD with a definitive diagnosis, however, was only 0.12%.[6,7] An analysis of 45 screening studies on FD concluded that a more accurate measure of prevalence can be obtained by considering patients with pathogenic *GLA* mutations. The prevalence of pathogenic *GLA* variants in high-risk populations was reported as 0.2% in males and 0.05% in female patients undergoing hemodialysis, 0.3% in males and 0% in female patients with renal transplants, 0.8% in males and 0.9% in female patients with cardiac disease, and 0.034% in males and 0% in female patients with stroke.[8]

Data from Saudi children born between 1983 and 2008, gathered over 25 years by the Saudi Aramco Medical Services Group, revealed an FD incidence rate of 5 per 100,000 live births.[9] Additionally, in the KSA, 4.8 out of 1000 hemodialysis patients were diagnosed with FD.[9]

Expert Opinion on the Available Epidemiological Data on Fabry Disease in the Kingdom of Saudi Arabia

- Creating a comprehensive database on FD in the KSA is the need of the hour.
- The gaps in epidemiological information on FD could be due to a lack of resources and knowledge about the disease in the KSA.
- It is important to differentiate between the different phenotypes of FD, namely, the classical and late-onset FD phenotype.
- Addressing the gaps in the phenotype–genotype correlations in FD can ensure prompt diagnosis and management of FD in the KSA. Hence, based on a comprehensive knowledge of the phenotype, HCPs can determine the screening process.
- A research center focused on FD needs to be established in the KSA.

Clinical Manifestations of Fabry Disease

The classical phenotype of FD is a severe form that is frequently observed in men with FD who have almost no α-Gal-A activity; the nonclassical (late-onset) phenotype, however, is a milder variant of the disease.[9] Classical patients with FD exhibit neuropathic pain, ophthalmological symptoms, angiokeratoma, as well as cardiological and nephrological problems.[10] Patients with "late-onset" phenotypes present predominately with cardiac and less often with renal manifestations.[11] Approximately, 15%–62% of patients with FD are frequently depressed, especially if they are experiencing pain.[12] Eight clinical cases of FD diagnosed in KSA were presented to the expert panel to set the context and initiate the discussion on the diagnosis and management of FD in the second ABM. The details of the cases that were discussed are presented in Supplementary Table S1.

The mutations in the *GLA* genes often have unidentified consequences and determining the genotype–phenotype association is challenging.[13] Identifying the clinical features of FD is particularly challenging in women and people with uncommon genetic variants.[7]

Women with FD usually have variable symptoms ranging from being pre-symptomatic to having serious complications.[14] Men with classical FD usually exhibit bothersome symptoms during early infancy or adolescence.[15] In women with late-onset FD, the symptoms usually manifest between the third and sixth decades of life. While central nervous system dysfunction and cardiac issues are the most prevalent clinical symptoms in women, renal failure is very rare.[16]

The variations observed in classical and late-onset FD in men and women include:

- Renal problems: A greater risk for chronic kidney disease was observed in men with classical FD than that seen in men with late-onset FD. However, no differences in the risk of chronic kidney disease were found between men with the late-onset form of FD and women with either late-onset or classical forms of the disease.[10]
- Cardiac involvement: Echocardiography shows that the left ventricular mass (LVM) was greater in patients with classical FD as compared to those with late-onset FD. Additionally, men with classical FD had higher LVMs than women with classical FD. The LVM values were observed to be comparable in women with classical FD and men with late-onset FD. Furthermore, an increased late gadolinium enhancement (LGE) risk was observed in men with classical FD than in men with late-onset FD and women with classical FD. This risk was comparable between men with late-onset FD and women with late-onset or classical FD. While left ventricular hypertrophy observed on a cardiac MRI predicted LGE risk in men, it did not correlate with LGE risk in females.[10]
- Cerebrovascular manifestations: White matter lesions (WMLs) were more commonly observed in men with classical FD than men with late-onset FD and women with classical FD. Women with classical FD had a greater risk of WML than women with late-onset FD. However, the risk of WMLs was similar in men and women with late-onset FD.[10]

Deacylated derivative of globotriaosylceramide (Lyso-Gb-3): The concentration of lyso-Gb-3 is a reliable predictor of the disease course.[10] Plasma concentrations of lyso-Gb-3 have been linked to disease severity in both men and women with nonclassical FD. However, this association was not observed in patients with the classical form of the disease, potentially due to a ceiling effect. In these patients, lyso-Gb-3 levels above a certain threshold do not correlate with increased disease severity.

In summary, FD symptoms in the classical and late-onset phenotypes are different. Men with classical FD have a more severe form of the disease than men and women with the late-onset phenotype. Additionally, both LVM and renal function are worse in men with classical FD than in men or women with late-onset FD. The course of the disease is comparable between women with classical FD and men with late-onset FD. Women with late-onset phenotypes have the least severe form of the disease. Overall, cardiac hypertrophy is more common in men than in women.[10]

Differences in Diagnostic Criteria in Men and Women

The diagnosis of FD requires the family history of the patient; his/her genealogy; and the results of physical and clinical examinations, biochemical tests, genetic screening, and imaging procedures, all of which must be evaluated by an expert.[7]

The laboratory FD diagnostic algorithm is given in Figures 1 and 2.[17]

Management of Fabry Disease

For more than a decade, ERT (agalsidase-beta and agalsidase-alfa) has been considered the mainstay in FD management. A few treatment modalities such as chaperone therapy with migalastat have also been approved for use in managing FD. Pegunigalsidase-alfa (a recently approved ERT), gene-based therapies, and substrate reduction therapies (venglustat and lucerastat) are certain treatment options that hold promise in the management of FD. The Food and Drug Administration (FDA)[18] and European Medicines Agency (EMA)[19] approved pegunigalsidase-alfa in May 2023. Despite the steps taken to improve the management of FD, a cure for FD is yet unavailable. Chaperone therapy is approved for patients with mutations that result in the misfolding and premature dissolution of the mutant protein; in patients without such mutations, ERT remains the treatment of choice.[20] Agalsidase alfa and agalsidase beta are the available options in KSA.[9] Gene therapy for FD is a promising approach that aims to address the underlying genetic cause of the condition by introducing functional copies of the defective GLA gene into the patient's cells. This innovative treatment method offers the potential for long-term supraphysiologic enzyme expression, potentially leading to sustained therapeutic benefits. Unlike enzyme replacement therapy, gene therapy may provide a more targeted and efficient way to address the root cause of FD, potentially reducing the need for lifelong treatments and minimizing the risk of developing anti-α-GAL antibodies. Research in gene therapy for FD continues to advance, offering hope for improved outcomes and quality of

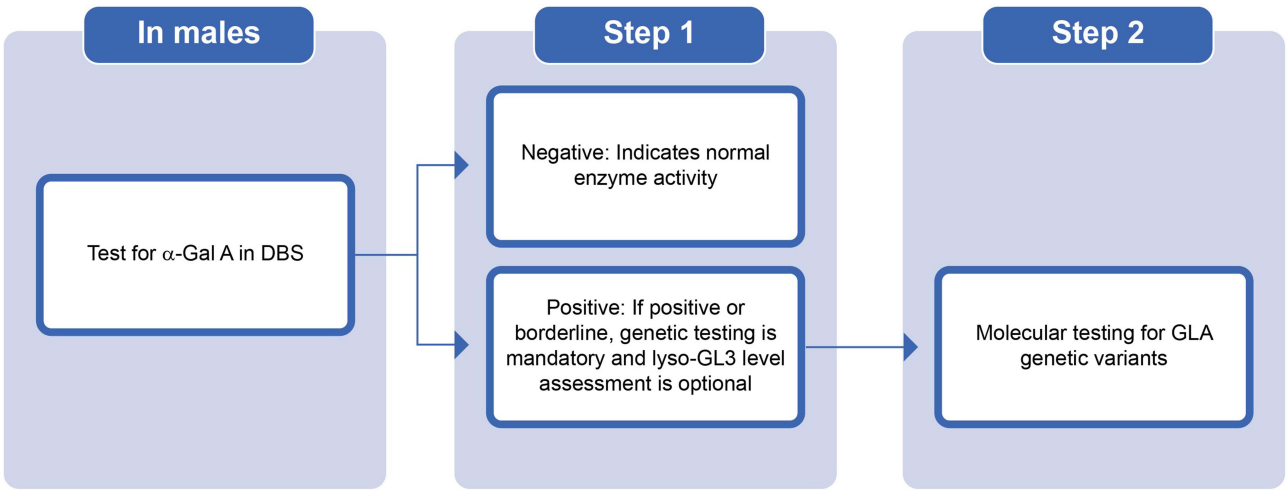

Figure 1 Diagnostic algorithm for FD in men.[17]
Abbreviations: DBS, Dried blood spots; α-Gal-A, α-Galactosidase-A; GLA, α-Galactosidase-A gene; lyso-Gb-3, Globotriaosylsphingosine.

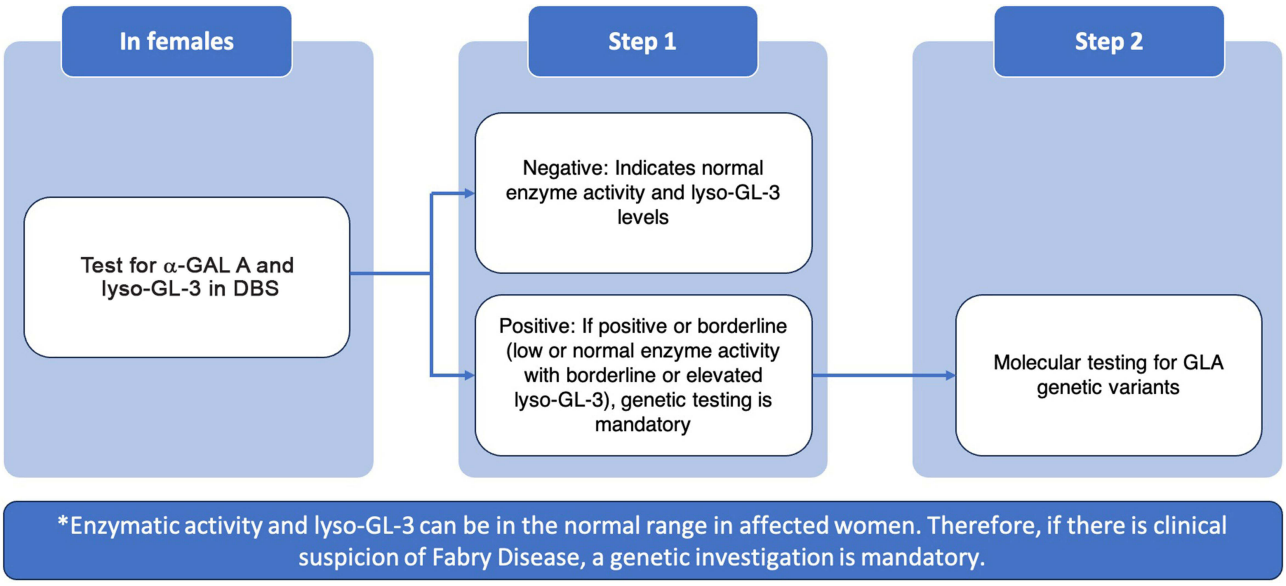

Figure 2 Diagnostic algorithm for FD in women.[17]
Abbreviations: DBS, Dried blood spots; α-Gal-A, α-Galactosidase-A; GLA, α-Galactosidase A gene; lyso-Gb-3, Globotriaosylsphingosine.

life for patients with this rare genetic disorder.[21] Limitations of gene therapy for FD include challenges in efficient gene delivery to target cells, potential immune responses to viral vectors, achieving long-term gene expression, and the high cost of treatment. Overcoming these limitations is crucial for enhancing the safety, efficacy, and accessibility of gene therapy for Fabry Disease.[21]

The management of FD is based on its clinical manifestations and symptoms as illustrated in Figure 3.[22]

Expert Opinion on Managing Fabry Disease in the Kingdom of Saudi Arabia

- Although family screening can identify undiagnosed cases, it is difficult to gain patient cooperation mostly due to social stigma associated with assigning genetic disease to a family. Transitioning patients from pediatric clinics to adult clinics may lead to loss of follow-up of FD patients; however, this is not observed during family screening.
- All the relatives of patients with FD should volunteer for screening. Additionally, experts agreed that prenatal diagnosis and genetic screening for FD be carried out. Programs for newborn screening can also enable early diagnosis and treatment of FD.
- There is a need for patient awareness and education about FD in the Arabic language. Mainstream media, the Internet, and social media can also aid in spreading awareness about FD among the masses.
- It is desirable that patients with FD be referred to clinical geneticists for answering queries on marriage, fertility, and pregnancy. Patients should be informed about the disease and given reading material about FD.
- Given the intricate multisystemic nature of FD symptoms, multispecialty care for patients with FD is desirable. Additionally, measures should be taken for concomitant infusion of ERT in patients undergoing hemodialysis.

Enzyme Replacement Therapy

In 2001, the EMA approved two types of ERT for managing FD. These are lifelong treatments and are administered as an intravenous infusion.[1,22] The two forms of ERT available are agalsidase-alfa, which is obtained from human fibroblasts and administered biweekly at a dosage of 0.2 mg/kg, and agalsidase-beta, which is obtained from Chinese hamster ovary cells and administered biweekly at a dosage of 1.0 mg/kg. These ERTs can clear Gb3 from podocytes, mesangial cells, and endothelial cells. Long-term ERT has resulted in significant reductions in renal and cardiovascular complications in patients with FD. Recently, the FDA and EMA have approved pegunigalsidase-alfa for the management of FD in

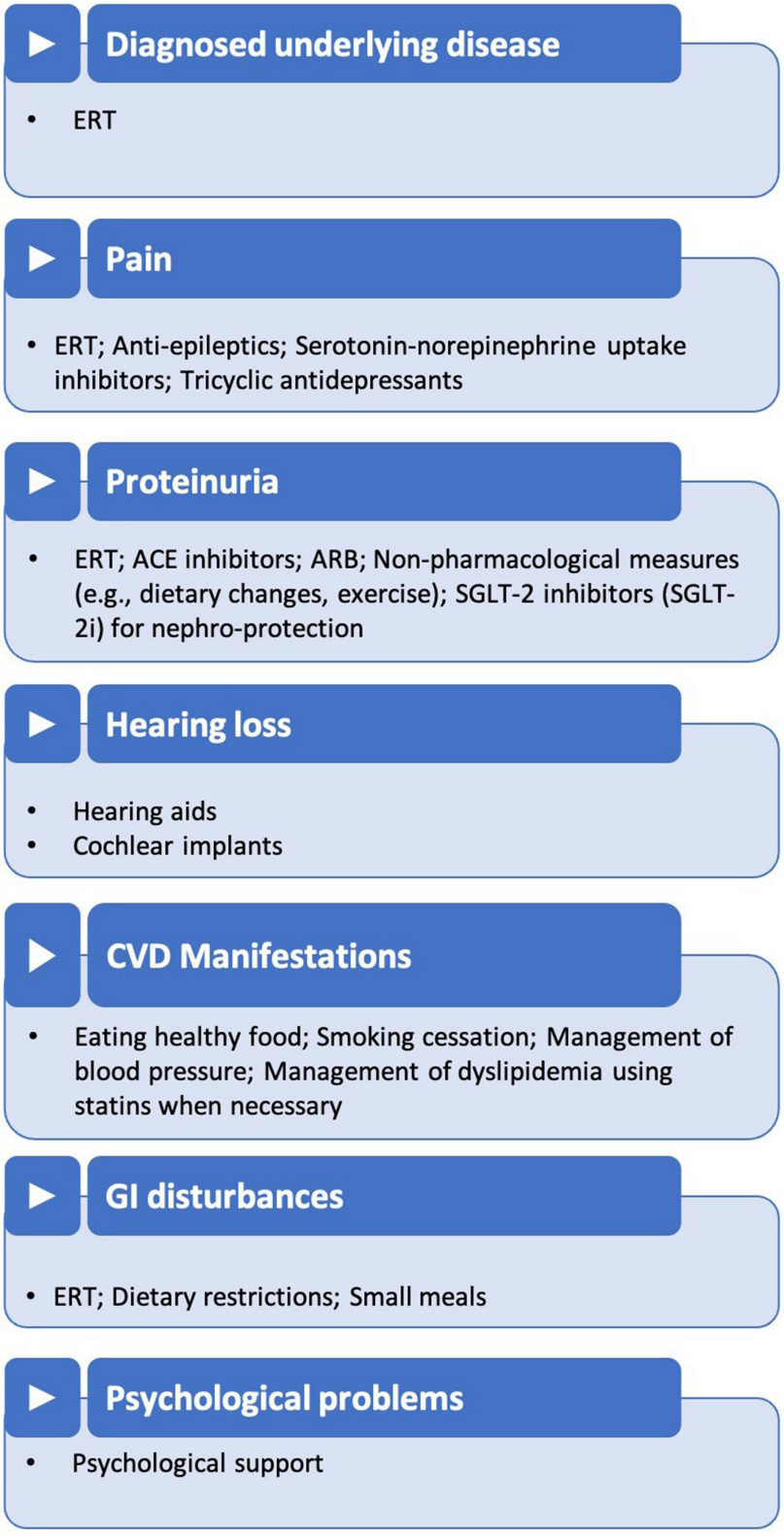

Figure 3 Choice of therapy in patients with Fabry disease based on the clinical manifestations.[22]
Abbreviations: ACE: Angiotensin-converting enzyme; ARB: Angiotensin II receptor blocker; BP: Blood pressure; CVD: Cardiovascular; ERT: Enzyme replacement therapy; GI: Gastrointestinal.

adults.[19,23] Previously, agalsidase-beta was the only FDA-approved ERT.[24] Early treatment improves disease outcomes. Therefore, the early identification and management of FD before organ damage can occur is crucial.[20]

Clinical Criteria for Starting Enzyme Replacement Therapy

The initiation of ERT in FD patients requires a tailored approach, differentiating between male and female patients as well as between classical and non-classical FD phenotypes. The importance of the timing of the initiation of ERT has been highlighted in the literature. The European Fabry Working Group (EFWG) has published consensus criteria in 2015 for the initiation of ERT in patients with FD.[25] While the EFWG guidelines provide a valuable framework for clinical decision-making, the need for revision of such recommendations has been suggested to incorporate recent advances.[26] A multidisciplinary approach is recommended to decide when ERT should be initiated in a patient with FD. The clinical criteria for starting ERT for patients with classical FD are given in Table 1 and those for late-onset FD are given in Table 2.[1]

ERT may be appropriate for children ≥2 years of age (of either sex) experiencing neuropathic pain, pathological albuminuria, severe gastrointestinal issues, stomach discomfort, or cardiac involvement. If a pathogenic *GLA* variation, a family record of serious illness, and undetectable *α-GAL-A* activity are detected in a boy, early ERT may be

Table 1 Clinical Criteria for Starting ERT for Classical FD

Adult Patient Population	International Recommendations for the Initiation of ERT
Classical Fabry disease	
Men, symptomatic or asymptomatic	ERT should be administered to individuals of any age; however, older age and comorbidities may impact treatment options.
Women, symptomatic	Indications for the initiation of ERT are signs and symptoms that suggest significant involvement of major organs, including: - Neuropathic pain, severe pain, or FD neuropathy - Proteinuria/albuminuria that cannot be attributed to other conditions and signs of renal impairment, which, if present alone, could indicate a need for a renal biopsy - Stroke or transient ischemic attacks - Symptoms of a heart condition, such as dyspnea, palpitations, syncope, or chest discomfort, none of which can be explained by other factors - Constant diarrhea or persistent gastrointestinal dysfunction that is incapacitating, but other possible conditions apart from FD are ruled out - Intolerance to physical activity and reduced perspiration
Women, asymptomatic	If laboratory, histological, or imaging data indicate kidney, heart, or CNS damage, ERT should be considered. This includes: • Renal disease, defined as a low GFR (<90 mL/minute/1.73 m^2 adapted for age >40 years [GFR category ≥G2]), constant albuminuria >30 mg/g (albuminuria category A2 or A3), podocyte foot process effacement, or glomerulosclerosis on renal biopsy, moderate or severe GL-3 inclusions in a range of renal cell types • Cerebral white matter lesions or undetected strokes on brain MRI • Asymptomatic heart diseases, such as cardiomyopathy, arrhythmia, or cardiac fibrosis, detected by contrast cardiac MRIs • ERT should also be considered when there is a skewed X-chromosome inactivation pattern with predominant expression of the mutant *GLA* allele with or without deficient α-Gal-A activity in the context of disease signs and symptoms • If determined, the X chromosome inactivation profile could impact female patients' therapy decisions. The presence of the mutant *GLA* allele is often linked with rapid disease progression, necessitating surveillance , and early intervention

Notes: Adapted from Ortiz A, Germain DP, Desnick RJ et al Fabry disease revisited: Management and treatment recommendations for adult patients. *Mol Genet Metab*. 2018;123(4):416–427. Creative Commons https://creativecommons.org/licenses/by-nc-nd/4.0/.[1]

Abbreviations: α-Gal-A, α-galactosidase A; CNS, Central nervous system; ERT, Enzyme replacement therapy; FD, Fabry disease; GFR, Glomerular filtration rate; GLA, α-galactosidase; GL-3, Globotriaosylceramide; MRI, Magnetic resonance imaging.

Table 2 Late-Onset FD Caused by Missense Galactosidase α Variants of Uncertain Significance (GLAVUS)

Late-Onset Fabry Disease Caused by Missense *GLA VUS*	
• For men and women	• ERT should be considered and recommended if there is laboratory, histological, or imaging evidence of damage to the kidney, heart, or CNS as described in Table 1, even in the absence of the characteristic symptoms of FD. It should be possible to link the anomalies to FD, although this may need a histological analysis or biochemical proof of GL-3 buildup. • When determining the pathogenicity of any VUS, it is advisable to seek the counsel of a geneticist and FD management specialist. • ERT should not be used to treat patients who have benign *GLA* polymorphisms that are well-characterized. • ERT may not be required in the absence of tissue pathologies or clinical symptoms associated with FD, especially in heterozygous women. A multidisciplinary care team should routinely check on such individuals.

Notes: Adapted from Ortiz A, Germain DP, Desnick RJ et al Fabry disease revisited: Management and treatment recommendations for adult patients. *Mol Genet Metab*. 2018;123(4):416–427. Creative Commons https://creativecommons.org/licenses/by-nc-nd/4.0/.[1]
Abbreviations: CNS, Central nervous system; ERT, Enzyme replacement therapy; FD, Fabry disease; *GLA*, α-galactosidase A; GL-3, Globotriaosylceramide; VUS, Variants of unknown significance.

beneficial.[1,27,28] Fabrazyme® (agalsidase-beta) has been approved by the FDA for use in patients 2 years of age and older.[28] Replagal (agalsidase-alfa) is approved by EMA for the treatment of FD among children aged 7 years and older.[29] Anti-agalsidase antibody (ADA) titers should be assessed during the initial visit and every 6 months thereafter. The role of ADAs in the context of ERT for FD is increasingly recognized as an important factor influencing clinical outcomes. ADAs can significantly reduce the effectiveness of ERT by neutralizing the therapeutic enzyme. Additionally, non-neutralizing antibodies, while not directly inhibiting the enzyme's function, can alter the pharmacokinetics of the drug by increasing its clearance from the bloodstream. Moreover, the presence of ADAs is closely linked with infusion-associated reactions (IARs), which are common, especially in male patients with classical FD. These reactions can manifest as sudden onset of fever, chills, nausea, and general malaise, typically resolving quickly after stopping the infusion. The development of ADAs can exacerbate these reactions, making them more frequent or severe. The formation of ADA-drug complexes is another potential complication. These complexes can accumulate in the vascular walls or kidneys, leading to serious conditions such as vasculitis, thrombosis, and renal failure. These complications highlight the need for careful monitoring of patients undergoing ERT for the development of ADAs and associated adverse effects.[30] The ERT dose should adhere to the Summary of Product Characteristics, and patients must be monitored for adverse responses to the infusions. The ERT should be based on the natural history of the condition and the process of the treatment must be explained to families.[1]

It is critical to confirm or verify the pathogenicity of discovered *GLA* variations as some are benign; people carrying such mutations should not be considered patients with FD and should not be given ERT. The decision to initiate ERT in children must be taken collaboratively by the pediatrician, geneticist, patient, and family after careful consideration of the advantages and disadvantages of lifelong biweekly infusions. Home infusion can be explored for patients who manage hospital infusions well, and under the appropriate conditions, can reduce the burden of the biweekly treatments.[1]

Expert Opinion and Unmet Needs Related to Enzyme Replacement Therapy for Patients with Fabry Disease in the KSA

- ERT is not prescribed in about 20%–80% of patients in the KSA as they are considered asymptomatic or oligosymptomatic. Closer monitoring of those patients is essential.
- Half the experts faced economic challenges when prescribing ERT for patients with FD.
- According to a few experts' experience, most physicians underestimate the impact of ERT on the clinical outcomes of the patients.
- The HCPs in the Middle East also face challenges in providing timely ERT to their patients due to logistic issues.
- A huge unmet need is social stigma associated with the disease. Prejudice and stigma against FD and its treatment affect the prognoses of patients with FD.

- Patients are often unwilling to undertake treatment due to the lack of transition care from pediatric to adult clinics. The patients have a fear of the complications of the treatment or have family members who have had complications due to the treatment.
- For men, ERT should be initiated as soon as classic FD is diagnosed, regardless of age or symptoms; however, for women, ERT should be initiated only if symptoms appear or organ damage is confirmed.
- Other indications for the immediate requirement of ERT are cardiomyopathy and renal involvement. Furthermore, ERT may be continued during renal transplantation. For infants with FD who are asymptomatic, ERT must be initiated based on guidelines framed specifically for the pediatric population. The minimum age at which ERT may be initiated is ≥2 years.[27,28] In classical FD, treatment must begin before 16 years of age.
- There is a need to devise a local FD treatment guideline for the KSA regarding ERT.
- It is important to set appropriate expectations for patients with FD. The patients and their families should be made aware that ERT does not reverse the damage caused by FD but can help slow down the disease progression. It can avert morbidity and the need for renal transplants.

Home Infusion Therapy for Patients with Fabry Disease

A study among patients and nurses involved in providing healthcare delivery at home in the form of ERT for patients with Gaucher disease, FD, and mucopolysaccharidosis II showed an adherence rate of 92.9% and an improved quality of life (QoL) of 88.5%; 77% of the patients expressed that they were comfortable with the treatment, 69% felt that the treatment could be adjusted with daily activities, and 58% found that the treatment was flexible enough to allow them to lead nearly normal lives.[31]

Expert Opinion on Home Infusion Therapy

- There was a combination of responses from the experts on the use of HIT. Some considered it to be unsafe, others felt that patients who missed their ERT sessions due to logistic issues could benefit from HIT.

Monitoring Fabry Disease

Periodic monitoring of patients with FD in whom ERT is yet to be initiated is essential; this can help to record disease progression and to correlate genotypic and phenotypic findings, when available. On initiating ERT, regular assessment of the effect of ERT on all organ systems is strongly recommended. A baseline tissue biopsy, particularly of the kidney, can be a useful marker for evaluating disease progression if the patient's condition worsens.[1] Supplementary Table S2 outlines the aspects to be considered for monitoring the response to ERT.[32]

Expert Opinion on Monitoring Patients with Fabry Disease in the KSA

- The experts suggested monitoring patients with FD by performing clinical assessments, such as evaluating the plasma concentrations of lyso-Gb-3, renal and heart decline, neurological involvement, and QoL; these expert opinions match the international guidelines.
- Monitoring protocols, including the evaluation of serum lyso-Gb-3 levels, vary based on the HCPs' decision and on the guidelines that are being followed.
- Biomarkers for monitoring: The presence and severity of albuminuria, proteinuria, and serum levels of lyso-Gb-3 need to be evaluated every 6–12 months. Lyso-Gb-3 is a valuable biomarker of FD, especially to assess disease stabilization or progression. This combination of testing is helpful in the early detection of organ injury and for assessing the effectiveness of ERT. However, standardization of biomarkers for monitoring FD needs to be done. Biomarkers are valuable in assessing activity and disease stabilization.
- Routine monitoring to test for progression of FD:
  - In cases where α-Gal-A deficiency is not apparent, but patients are symptomatic, frequent monitoring is required to understand if symptoms are attributable to FD.
  - Patients are monitored using cardiac magnetic resonance imaging (MRI), echocardiography and electrocardiography; the frequency of these depends on the severity of the disease.

- Ophthalmological examinations must be done every year. However, in cases with severe ocular symptoms, such as those caused by unilateral occlusion of the central retinal artery, monitoring must be done every 6 months.[33]
- Clinical examinations, dermal biopsies, and thyroid function tests should also be carried out every 6 months.
- Most experts evaluate patients' glomerular filter rate (GFR) every 6–12 months for patients >18 years of age.

FASTEX: A Fabry Disease Assessment Tool

A severity score system called FASTEX can be used to evaluate a patient's clinical stability during treatment. The tool assigns a raw score to each of the recognized FD domains and converts it into percentages. The severity of the disease can be visualized between two points and an overall stability analysis can be carried out by summing up the respective scores. The global evaluation criterion is a score of >20%; a score of ≤20% shows consistency or improvement in the clinical condition. It also measures changes in the patient's condition over time. Physicians from various international organizations should utilize the FASTEX tool to verify its validity and applicability, which may improve clinical evaluation and treatment of patients with FD.[34]

Expert Opinion on Monitoring of DNT Fabry Disease Patients Using the FASTEX Tool

Most experts opined that there were no clinical guidelines for monitoring untreated patients with FD in the KSA. However, untreated patients with FD can be monitored by using the FASTEX tool.

Conclusion

The expert panel suggested that spreading awareness about FD in the KSA and educating the general population about the disease is of utmost importance. In the KSA, it would be desirable to create a database and establish a research center for FD, to differentiate between classical and late-onset FD, and to identify phenotype-genotype correlations to aid in the early diagnosis and management of FD. Family and newborn screening, and consultation with a clinical geneticist have been suggested for early identification of FD. Early treatment with ERT must be initiated to prevent disease progression in FD patients. ERT is the only available therapy for managing FD in the KSA and the Middle East, with agalsidase-alfa and agalsidase-beta being the available ERTs in KSA. Additionally, referral to multispecialty care is desired. Furthermore, the use of the FASTEX tool should be encouraged to facilitate the monitoring of patients with FD staying untreated.

Abbreviations

ABM, Adboard Meeting; ERT, Enzyme Replacement Therapy; eGFRs, Estimated Glomerular Filtration Rates; EMA, European Medicines Agency; FD, Fabry Disease; FDA, Food and Drug Administration; FASTEX, Fabry Stabilization IndeX; Gb-3, Globotriaosylceramide; GVUS, Genetic Variants of Undetermined Significance; GCC, Gulf Cooperation Council; HCPs, Healthcare Professionals; HIT, Home Infusion Therapy; KSA, Kingdom of Saudi Arabia; LGE, Late Gadolinium Enhancement; LVM, Left Ventricular Mass; MRI, Magnetic Resonance Imaging; QoL, Quality of Life; WMLs, White Matter Lesions; α-Gal-A, α-Galactosidase A; GFR, Glomerular filter rate; GLA, α-Galactosidase A Gene.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analysed.

Acknowledgments

The need for this paper with expert opinion evolved during the first advisory board held in 2022 requested by the experts. Sanofi was neither involved in the creation nor the content of the paper, they only funded the logistics and the two advisory board meetings through third-party, authors did not get any payment in favour the content creation and development, it was voluntary work from the advisors. Advisory board members have been paid only for participation in the meetings as per fair market value. We would like to thank BioQuest Solutions Pvt. Ltd. for their editorial support.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

Sanofi funded the logistics of the advisory board meeting, including honoraria for attendees' time but did not pay for their time for developing the manuscript.

Disclosure

Dr Konstantinos Fourtounas reports honoraria from Sanofi, during the conduct of the study. The authors declare that they have no competing interests.

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