Fabry disease and new advances in treatment

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Abstract
Fabry disease is an X-Linked lysosomal storage disease, caused by deficient activity of lysosomal enzyme α-galactosidase A. The accumulation of globotriaosylceramide (GL-3) in the lysosomes causes lysosomal and cellular dysfunction and this in turn triggers the cascade of cells and tissue ischemia and fibrosis. The classic phenotype of Fabry disease is seen in most males with no enzyme activity and it affects multiple organ-systems. The early clinical manifestation of the disease occur in childhood with episodes of severe pain in the extremities (acroparesthesia), hypohidrosis, corneal and lenticular changes, and skin lesions (angiookeratoma). The renal failure, cardiovascular disease and stroke are the major causes of morbidity and mortality occurring later in life. Due to random chromosome X inactivation (Lyonization), the carrier females of Fabry disease may experience Fabry disease-related symptoms including acroparesthesia, gastrointestinal complains, renal and cardiac disease and/or strokes. In this article, after brief review of clinical presentations and diagnostic tests for the disease, we review the present therapeutic approaches and future directions in management of patients with Fabry disease.

Key words: Fabry disease; Lysosomal storage disease, Treatment, Enzyme replacement therapy

Introduction
Fabry disease (FD) is an X-Linked lysosomal storage disease, caused by deficient activity of lysosomal enzyme α-galactosidase A. As the result of α-galactosidase A deficiency glycosphingolipids, predominantly globotriaosylceramide (GL-3) and galabiosylceramide, accumulate in the lysosomes of various cells, such as in the vascular endothelium of multiple organs (1). The accumulation of GL-3 in the lysosomes causes lysosomal and cellular dysfunction and this in turn, triggers the cascade of cellular and tissue ischemia and fibrosis. The estimated prevalence of Fabry disease is about one in every 117000 live born males.

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in most males with no enzyme activity and it affects multiple organs and systems. The early manifestation of the disease occur in childhood with episodes of severe pain in the extremities (acroparesthesia), hypohidrosis, corneal and lenticular changes, and skin lesions (angiokeratoma) (1). The rates of progression of the disease and specific organ damage demonstrate intra-and inter-familial variability. Renal failure, cardiovascular disease and stroke are the major causes of morbidity and mortality occurring in the fourth or fifth decade of life. As expected in X-linked disorders, males with deleterious mutations have little-to-no residual \( \alpha \)-galactosidase A activity, therefore, they experience the full spectrum of the disease symptoms. In female carriers, due to random chromosome X inactivation (Lyonization), the disease presentation is more variable and depends on the ratio of normal to mutant \( \alpha \)-galactosidase A in the different tissues. However, a significant number of carrier females may experience Fabry disease-related symptoms including acroparesthesia, gastrointestinal complaints, renal and cardiac disease and/or strokes. Treatment of Fabry disease for many years had been limited to palliative care and interventions for specific symptoms. Under this approach, the median survival time was about 50 years for men and 70 years for women (2,3). Enzyme replacement therapy is the new treatment presently available to the patients around the world. Agalsides alpha (Replagal) and agalsides beta (Fabrazyme) are recombinant enzymes, produced in a genetically engineered human cell line and genetically engineered Chinese hamster ovary cells, respectively. They are given intravenously to replace the defective enzyme. In Europe, both products are licensed to be used in treatment of symptomatic patients with Fabry disease. In USA, only agalsides beta has been approved by the Food and Drug Administration (FDA). After summarizing the clinical presentation and diagnosis of the disease, we will review the new therapeutic approaches, their developmental process, availability, and effectiveness.

**Natural History of Fabry Disease**

Patients with classic Fabry disease typically have less than 1% \( \alpha \)-galactosidase A activity and often demonstrate the full spectrum of the disease manifestations. In these patients, the progressive nature of Fabry disease reflects the involvement of various pathophysiological processes. Clinical characteristics of the disease may be reviewed according to the age of patients at the time of presentation of the symptoms, early manifestations and late, severe manifestations.

**Clinical Manifestations**

**Pain:** In the most of patients, the earliest symptom of the disease is intermittent or chronic acroparesthesia. These pain episodes are experienced as burning, tingling and numbness in the hands and feet. Extremity pain attacks, well known as “Fabry pain crises”, are experienced most commonly by male patients.

**Gastrointestinal:** Some patients suffer episodes of postprandial abdominal pain and bloating followed by multiple bowel movements and diarrhea, nausea, vomiting, and early satiety.

**Skin:** Angiokeratomas are cutaneous vascular
lesions appear as small, slightly raised, purplishred, non-blanching vascular ectasia. Among Fabry patients, anhidrosis or hypohidrosis is also frequently reported.

**Eyes:** Corneal manifestations are reported to be present in over 70-90% of patients. The best-known ocular sign of Fabry disease is the pattern of whitish spiral streaks in the corneal epithelium known as “cornea verticillata.”

**Late and Serious Clinical Manifestations:**

**Kidney:** Kidney involvement is a prominent feature and the main cause of premature death in classic Fabry disease. Microalbuminuria, proteinuria, and isosthenuria may be apparent in adolescence and early adulthood. The progressive kidney disease is marked by the progression of proteinuria, increased levels of serum creatinine and the reduction of glomerular filtration rate (GFR) during the third decade of life.

**Cardiovascular:** Fabry-related cardiac disease is a key cause of premature death. Early signs of cardiac involvement include interventricular septal and left ventricular hypertrophy (LVH), associated with valvular regurgitation. Progressive concentric LVH and diastolic dysfunction seen in advanced stages of the disease may be accompanied by clinical signs of congestive heart failure. Mitral valve prolapse and thickening also may be observed. Common initial electrocardiographic abnormalities include sinus bradycardia, nonspecific ST-segment changes, T-wave inversion, and shortened PR interval.

**CNS:** Central nervous system (CNS) involvement may be seen on brain MRI as white matter changes; noted as early as the second or third decade of life. Patients may present with transient ischemic attacks, vascular thromboses, seizures, or hemorrhagic or ischemic stroke.

**Others:** Paroxysmal attacks of severe rotational vertigo occur in large numbers of patients. Sensorineural hearing loss can be frequently documented in patients with Fabry disease. Peripheral neuropathy in Fabry disease predominantly involves small nerve fibers. The progressive loss of temperature and pain sensation should be assessed routinely. Obstructive and constrictive lung diseases have both been documented in a subgroup of patients, often presenting as wheezing, dyspnea, or bronchitis. Priapism has been associated with Fabry disease. Poor heat and exercise tolerance is commonly seen in patients. They typically are attributed to hypohidrosis and acroparesthesia. Patients may complain of generalized lack of energy and fatigue. Lymphedema of the legs is a poorly described and less common manifestation of Fabry disease.

**Laboratory Diagnosis**

**Enzyme activity:** α-galactosidase A activity may be measured in plasma, serum, leukocytes, tissue biopsies, or cultured skin fibroblasts. In affected males, with the classic or variant phenotypes of the disease is readily diagnosed by determination of low α-galactosidase A activity. Female carriers may have α-galactosidase A activity ranging from zero to within the normal range; thus, the enzyme assay is rarely helpful in determining female carrier status.
**DNA analysis:** DNA isolated from blood or biopsy specimens can be used for analysis of á-galactosidase A gene sequence to identify the disease-causing mutation. DNA testing is the preferred method for identifying and confirming the carrier status of females in whom enzyme activity is within or near the normal range.

**Therapeutic Approaches**
The disease management strategies should be individualized and planned according to the patient age and stage of the disease. These strategies include symptomatic management, disease-specific treatment, and adjunctive therapies and preventive measures.

**Symptomatic Management**
The aim of symptomatic treatment is to alleviate the symptoms has been used for many years. Some of these approaches continue to be beneficial in combination with newer forms of therapy.

**Pain management:** Daily prophylactic doses of neuropathic pain agents, such as phenytoin, carbamazepine, gabapentin or a combination of these agents provides some degree of relief. They are effective in decreasing the frequency and severity of Fabry pain episodes or pain crises in most of the patients. Some patients may require more potent analgesics (e.g., opioids) for their pain management (1).

**Gastrointestinal symptoms:** No specific treatment has been found to control the gastrointestinal symptoms in Fabry disease. However, pancrelipase, metoclopramide, histamine H2 blockers, loperamide hydrochloride can ameliorate gastrointestinal symptoms in some patients. Patients with abdominal symptoms often benefit from a change in eating habits, by having frequent and small meals (4).

**Skin:** The results of various laser methods in treating the angiookeratomas of Fabry disease have not been promising for patients who are not receiving enzyme therapy (5).

**Others:** Symptomatic treatment of renal, cardiovascular and cerebrovascular complications is warranted.

**Surgical care:** In cases of renal transplant, the engrafted kidneys from an unaffected and non-carrier individual corrects kidney function and remains free of GL-3 storage. Thus, these patients should be provided with enzyme replacement therapy to halt the progress of the vascular disease of the heart and brain (6).

**Diet:** A "renal diet" is recommended for patients with proteinuria and renal failure. Low-protein, low-sodium diets should be supervised by a nutritionist.

**Activity:** Patients are advised to self-monitor their activity level in order to avoid factors that precipitate symptoms; for example, in case of pain, it is recommended that patients hydrate adequately prior to any physical activity, and to avoid exposure to extreme temperatures.
Disease-specific Treatment

With the advancement in the field of molecular and biochemical genetics the strategies that directly address the underlying cause of the disease have become the focus of investigations for lysosomal storage diseases in general and Fabry disease in particular. These strategies aim is to delay and prevent the serious organ damage related to the disease.

Enzyme replacement therapy: Enzyme replacement therapy (ERT) provides the patient with the biologically functional protein. The infused enzyme is taken up into lysosomes through specific receptors located on the surface of the target cells. Reversal of the metabolic and pathologic abnormalities in the cells and tissues are the key therapeutic goals of enzyme replacement therapy. These changes should in turn result in improvement of symptoms and the prevention of complications of the disease. Multiple clinical trials with recombinant α-galactosidase A were under taken to investigate the safety and efficacy of enzyme replacement in patients with Fabry disease. These enzymes include Fabrazyme (Genzyme Corporation, Cambridge, Mass) and Replagal (TKT Corporation, Cambridge, Mass)

1) Evaluation of Fabrazyme: Preclinical studies of recombinant human α-galactosidase A (r-hαGaLA) infusions in knockout mice which demonstrated reduction of GL-3 in tissues and plasma, provided rationale for a phase 1/2 clinical trial (7). Phase 1/2 clinical trial was an open-label, dose-ranging study of Fabrazyme treatment in 15 patients. Each patient received five infusions at one of five dose regimens. During this trial, it was demonstrated that the infused enzyme generally was well tolerated. Rapid and marked reductions in plasma and tissue GL-3 were observed biochemically, histologically and/or ultrastructurally. Clearance of plasma GL-3 was dose-dependent. GL-3 deposits were cleared to near normal or were markedly reduced in the vascular endothelium of liver, skin, heart, and kidney, on the basis of light- and electron-microscopic evaluation of these tissues(8). In the phase 3 trial of enzyme replacement therapy, a multicenter, randomized, placebo-controlled, double-blind study, 58 patients were treated with Fabrazyme or placebo at 1mg/kg every 2 weeks for 20 weeks. It was demonstrated that with this regimen, GL-3 deposits cleared from plasma and capillary endothelium of the major sites of pathology in Fabry disease such as the kidney, heart, and skin. This trial provided the “proof of concept” that enzyme replacement could reverse the GL-3 accumulation in key sites of pathology (9). The investigation of clinical benefit of ERT with Fabrazyme in patients with advanced Fabry disease was undertaken in a phase 4 clinical study, which had a double-blind, placebo-controlled design. During this study it was documented that the rate of progression of renal, cardiac, and cerebrovascular complications and death among patients who received active drug was reduced in comparison to the patients who received placebo. Therefore, it is reasonable to conclude that in order to prevent irreversible damage to the organs ERT should be started early in the course of the disease (10,11).

2) Evaluation of Replagal: A phase 1 trial involving 10 affected males demonstrated that a single dose of 0.007-0.1 mg/kg of Replagal could
reduce the accumulated GL-3 in the liver and urinary sediment, but no dose effect was seen (12). Phase 2/3 clinical trials with Replagal was designed as a single center, double-blind, placebo-controlled study involving 26 male patients with neuropathic pain who received 0.2 mg/kg every two weeks for 22 weeks. Mean (SE) Brief Pain Inventory score for severity of neuropathic pain declined from 6.2 (0.46) to 4.3 (0.73) in patients treated with Replagal vs. no significant change in the placebo group (p=0.02). Mean creatinine clearance increased by 2.1 ml/min (0.4 ml/s) for patients receiving Replagal. There was an approximately 50% reduction in plasma glycosphingolipid levels, a significant improvement in cardiac conduction, and a significant increase in body weight (13).

The outcomes of clinical studies summarized above were the basis for approval of Fabrazyme and Replagal in most European countries in 2001, and for Fabrazyme in the US in 2003. The enzyme is infused intravenously at 0.2 mg/kg for Replagal and at 1 mg/kg for Fabrazyme every 2 weeks. The commercial availability of both enzyme formulations has provided treatment for many patients around the world. This has allowed further assessment of effect of ERT on various clinical manifestation of the disease. Today there is a growing body of evidence that demonstrates ERT is beneficial in improving most of the disease symptoms. However, the response to ERT may vary, depending in part on tissue specific differences in drug delivery, and disease stage at the time of treatment initiation. The effect of ERT on the various manifestations of the disease may be extended to other organ system; such as improvement of GI symptoms (4), improvement in the function of C-, Aδ-, and Aβ-nerve fibers (14), stabilization of deteriorating renal function (15) and improved cardiac function (16,17).

**Treatment Recommendations**

Currently, it is recommended that ERT should be initiated as early as possible in all males with Fabry disease (including those with end-stage renal disease). The symptomatic female carrier of Fabry disease with serious organ-system at risk should also be assessed as a candidate for ERT (5,18-21).

The following signs and symptoms are among the important evidence of serious implications of Fabry disease in females that warts initiation of enzyme treatment, the only available disease specific treatment:

1- Uncontrolled pain at any age that requires alteration of lifestyle and interferes with quality of life
2- Presence of and a progressive increase in proteinuria, exceeding 300 mgs/24 hours; or a renal biopsy result which shows significant renal involvement
3- Patients on dialysis or transplanted
4- Ischemic heart disease with or without cardiac dysfunction; Moderate to severe heart enlargement (LVH)
5- Cardiac arrhythmias
6- Significant brain involvement or MRI changes
7- Frequent and severe vertigo episodes
8- Severe fatigue

**Substrate Reduction**

The principle of substrate reduction therapy is to inhibit partially the biosynthetic cycle to reduce substrate influx into the catabolically
compromised lysosomes. Substrate reduction therapies have proven effective for other forms of lysosomal storage disorders such as for Gaucher disease type 1 (21), and are under investigation for Fabry disease.

**Enzyme Enhancement Therapy**
In general, certain missense mutations and some small in-frame deletions may cause polypeptide misfolding, but may not (or only slightly) impair the functionally essential domains of the mutant protein (the active site, receptor-binding site, etc.) Pharmacological chaperones, such as substrate analogues that selectively binds to the target protein may facilitate the stabilization of misfolded proteins, helps it fold into the correct threedimensional shape and functioning effectively (22). It has been reported that an orally active, small molecule drug demonstrates favorable results in enhancing alpha-galactosidase A activity. Presently this molecule is being tested in clinical trials.

**Gene Therapy**
Even though, there is still a long way to go before gene therapy can be used in human and treatment of Fabry disease, gene-based therapy may overcome the limitation of ERT, as it may allow constant delivery of a therapeutic protein to the whole body or to targeted organs.

**Adjunctive Therapies and Preventive Measures**
In addition to the enzyme replacement therapy, other measures that are considered standard of care should be used to optimize the disease management and reduce the rate of disease progression in advanced disease stages. Some of these adjunct therapies are summarized below (22):
1. Use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor antagonists in patients with proteinuria to reduce urinary protein and albumin excretion to the absolute minimum amount
2. Control of hypertension
3. Management of dyslipidemia (most commonly, hypercholesterolemia)
4. Prophylaxis with anti-platelet or anticoagulant medication for patients who have had transient ischemic attacks or a stroke
5. Permanent cardiac pacing in high risk patients
6. Hearing aids in cases of hearing loss and avoiding excessive noise exposure
7. Encourage the patients to maintain a healthy lifestyle, such as avoiding smoking

**Consultations**
A multidisciplinary healthcare team approach is essential. This team should include a medical geneticist, a nephrologist, a cardiologist, an ophthalmologist, a pain specialist, and a neurologist understanding Fabry disease. Emotional support and family counseling should be an integral part of patient care.

**References**
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