Review Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: www.ijrpns.com

https://doi.org/10.36673/IJRPNS.2023.v12.i03.A11

A REVIEW ON FABRY DISEASE

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ABSTRACT

Fabry disease (FD) is a progressive, X-linked inherited disorder of glycosphingolipids that is caused by the deficiency of α-galactosidase A that affects males and shows disease expression in heterozygotes, is associated with dysfunction of many cell types and includes a systemic vasculopathy. As a result of the aberrant buildup of glycosphingolipids, there are a number of clinical symptoms, significant morbidity and mortality. Males who are hemizygous for the disease yet have no remaining -galactosidase. The disease's hallmark neurological, cutaneous, renal, cardiovascular, cochleo-vestibular and cerebrovascular signs may all be displayed by an individual, whereas heterozygous females may only experience mild to moderate symptoms. There is an enzyme replacement therapy for Fabry disease, but it is an expensive intravenous medication. Small molecule chaperone treatment and other alternative therapeutic modalities are actively being investigated. Other small molecule compounds, such as non-inhibitory chaperones, enzyme activators, molecules that decrease GLA substrate and molecules that activate GLA, can be found using high throughput screening (HTS) methods.

KEYWORDS

Fabry disease, Enzyme replacement therapy, X-linked inherited disorder and α-galactosidase A.

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INTRODUCTION

Fabry disease overview

A lack of -galactosidase A results in Fabry disease (FD), a progressive, X-linked hereditary condition of glycosphingolipids[1]. In body fluids and lysosomes of cells, including those that are particularly relevant to disease pathology, such as cardiomyocytes, conduction system cells, vascular endothelial and smooth muscle cells and fibroblasts, podocytes, tubular, glomerular, mesangial and interstitial cells and neurons in

autonomic and p53-positive cells, globotriaosylceramide GLA mutants that practically have no enzymatic activity (<5% of the normal mean) are associated to severe and early onset classical phenotypes, while mutations leading to a residual enzymatic activity are associated to attenuated and late-onset phenotypes[2,3]. The characteristics of classical phenotypes include early development of acroparesthesias, neuropathic pain, hypohydrosis, heat, cold and exercise intolerance, cornea verticillata, angiokeratomas, gastrointestinal symptoms and proteinuria. Along with sensorineural hearing loss, adult patients also exhibit cardiac, renal and cerebrovascular symptoms. Unlike early-onset phenotypes, late-onset phenotypes appear as cardiac, renal and/or cerebrovascular symptoms in adulthood; the involvement of an organ, such as the heart or kidneys, may have a significant influence on the phenotype[2-5]. Examples of cardiac symptoms include left ventricular hypertrophy (LVH), heart failure, angina, dysrhythmias, anomalies in cardiac conduction, and sudden death. Renal involvement may lead to end-stage renal failure, and brain involvement is indicated by the frequency of strokes or transitory white matter lesions (WML) in the brain[2-5]. In this X-linked condition, heterozygote females are more than just carriers; they can also develop a full-blown disease that is just as severe as it is in affected men[6,7.]

Background

Fabry disease (OMIM 301500) is a hereditary, X-linked lysosomal storage disorder[1] first described by the dermatologists William Anderson and Johann Fabry in 1898. As a result, the body's cells begin to accumulate globotriaosylceramide, a type of fatty substance. Most of the body's cells contain globotriaosylceramide, which is made up of three sugars and a fatty molecule called ceramide. The condition is estimated to affect 1 in 40,000 to 117,000 males worldwide. Lack of the lysosomal enzyme -galactosidase A (GLA) leads to an accumulation of the glycosphingolipid globotriaosylceramide (Gb3) in various cells and organs, particularly in endothelial cells and smooth muscle cells of blood arteries, which is the underlying cause of the disorder[8,9]. In most cases, symptoms first appear in childhood. By middle age, untreated patients frequently suffer life-threatening problems. Hemizygous males are not the only ones that exhibit symptoms of this illness; heterozygous females also do. People who are not treated may experience pain, skin, eye, and gastrointestinal issues. Potentially fatal complications from Fabry disease can include kidney damage, heart attack, and stroke. Enzyme replacement therapy, which substitutes the lacking or insufficient enzyme with either agalsidase alfa or beta, is one form of treatment available[9].

PATHOPHYSIOLOGY

The pathological abnormalities can be divided into disease-specific and secondary changes that are not disease-specific but reflect organ abnormalities and dysfunction[8]. Beyond the lysosome, there seem to be other cellular effects of -GalA deficiency. Cell viability is mediated by the autophagy-lysosome pathway (ALP), a crucial recycling process. Lysosomal storage disorders, such as Fabry disorders, frequently feature ALP disruption. Similar to this, it has been observed that sphingolipid illnesses such Gaucher disease and Fabry disease have impaired mitochondrial activity and energy balance. Further evidence that inflammation plays a part in tissue destruction comes from the observation of lymphocyte and macrophage infiltration in FD tissues, including the heart. Organ damage may be facilitated by oxidative stress and persistent inflammation in FD[8,9].

It is commonly known that Gb3 builds up in lysosomes after -GalA deficiency, but the ensuing pathways leading to cellular malfunction and, eventually, symptoms, are still poorly understood. The observed mitochondrial dysfunction in fibroblasts from FD patients is likely caused by impaired autophagic flux, including mitophagy, as is the case with other hereditary glycosphingolipidoses. The observed elevation of

the unfolded protein response in cells from some FD patients further suggests that endoplasmic reticulum malfunction may occur. Pathogenesis appears to be heavily influenced by oxidative stress, fibrosis, and inflammation. LysoGb3 has been proposed as a potential pathogenic component in FD. For classic male and female FD patients, a statistically significant connection between lifetime lysoGb3 exposure and total disease severity was observed. Indeed, lysoGb3 encourages the proliferation of smooth muscle cells, which is consistent with the thickened intima media and stiffer blood vessels in FD. Additionally, it has been shown that lysoGb3 destroys nociceptive neurons at the level found in FD males, which is congruent with the observed discomfort in the classic FD males' extremities. The upper limb's thermal and cold detection thresholds were observed to substantially correlate with lifetime exposure to lysoGb3. The loss of podocytes and glomerulus fibrosis, two significant features of renal illness in FD patients, are also likely to be impacted by lysoGb3. Finally, it has been discovered that lysoGb3 inhibits endothelial nitric oxide synthase (eNOS) at amounts reported in FD patients, suggesting that it may be a factor in the vasculopathy seen in FD.

Beyond the lysosome, there seem to be other cellular effects of -GalA deficiency. Cell viability is mediated by the autophagy-lysosome pathway (ALP), a crucial recycling process. Lysosomal storage disorders, such as Fabry disorders, frequently feature ALP disruption. Disrupted mitochondrial activity and energy balance have also been reported in sphingolipid illnesses such Gaucher disease and Fabry disease (for a fantastic review on this subject, see Ivanova *et al*. 2020). Further evidence that inflammation plays a part in tissue destruction comes from the observation of lymphocyte and macrophage infiltration in FD tissues, including the heart. Organ damage may be facilitated by oxidative stress and persistent inflammation in FD (for a review, see Rozenfeld *et al*[9].

Symptoms of Fabry Disease[10]

The buildup of GL-3, which begins to accumulate before birth and continues throughout a person's life, is what causes the symptoms of Fabry disease. The severity of a person's sickness, their age, the activity of their enzymes, and the sort of genetic variant they have can all affect how severe their symptoms are. Some signs could be:

Chest pain
Corneal whirling (marble-like patterns in the eyes)
Digestive problems, such as diarrhea, abdominal pain, early satiety (feeling full after only a little food), and nausea
Kidney disease
Hearing loss
Heart disease
Inability to sweat
Ministrokes or transient ischemic attacks (TIAs)
Hand and foot discomfort
Reddish or purple spots on the skin
Temperature sensitivity
Tinnitus.

Some symptoms could deteriorate over time without the sufferer realizing it. If untreated, Fabry disease can shorten a person's lifespan by 20 years for men and 15 years for women.

Symptom Management[10]

Along with unpleasant symptoms, Fabry disease can result in significant and perhaps fatal complications such a stroke, heart attack, and kidney damage. Because of this, your doctor may suggest additional drugs to help with symptom treatment. These consist of:

Gabapentin, phenytoin, or carbamazepine. These anti-seizure medications may be prescribed by your doctor to treat bouts of excruciating burning pain in your hands and feet.

ACE blockers

This particular blood pressure drug doubles as a kidney protector if you already have high blood pressure. That lessens the possibility that you might require kidney transplantation or possibly dialysis. An erratic heartbeat is more prevalent in those who have Fabry disease. As a result, you could also need other cardiac drugs.

Gastrointestinal medications

If you experience nausea, vomiting, diarrhea, constipation, or other gastrointestinal issues, the doctor can prescribe these.

Skin treatments

Your face's little blood vessels may enlarge if you have Fabry disease. During a consultation, your dermatologist can have them taken off.

Hearing aids

They may provide relief for symptoms such as tinnitus, vertigo, or hearing loss brought on by the constriction of blood vessels in the ears.

Tests to monitor fabry disease

Your entire body is affected by Fabry disease. And as you age, the symptoms usually become worse. Therefore, it's crucial to monitor your general health.

Regular health examinations are essential. If you have additional diseases like renal disease or heart problems, you could require these tests more frequently than once a year.

Blood tests

Your electrolytes, white and red blood cell counts, as well as the functionality of your liver and kidneys, are all examined.

Urine tests

These examine your urine for blood or protein, which can be a warning sign of renal disease.

Electrocardiogram

Your heart's electrical activity is being recorded in order to look for an irregular cardiac rhythm.

Echocardiogram

It captures an image of your heart using sound waves. This will look for issues with your heart's valves or chambers.

Hearing test

You could need this every year.

Brain imaging

This may be performed every two years to check for changes in the brain's blood arteries that could indicate a stroke risk[10].

TREATMENTS FOR FABRY DISEASE

Diagnosis

Patients with certain diagnostic symptoms, such as angiokeratoma in the skin or vascular ectasia in the buccal or conjunctival mucosa, are suspected of having Fabry disease. During an eye exam, the cornea will typically be found to have verticillata, and a funduscopy will demonstrate increased tortuosity of the retinal blood vessels. The condition is characterized by non-specific but significant anomalies such as pain neuropathy, hypohidrosis and renal insufficiency. Low -galactosidase levels are required to confirm a suspected diagnosis of Fabry disease. a procedure on cultivated skin fibroblasts or peripheral blood white cells. In general, values below 20% of the normal range should be regarded as diagnostic, while activity levels below 35% should raise Fabry disease suspicion. Increased urine sediment Gb3 measurements made after a 24-hour collection are particularly helpful in Fabry disease diagnosis[8].

Treatment

Although there is no known cure for Fabry disease, therapy can lessen symptoms, restore alpha-GAL function, avoid organ damage and replace the lost alpha-GAL enzyme. Treatments consist of[11].

Enzyme Replacement Therapy

Recombinant GLA is given to cells during enzyme replacement therapy (ERT), which also corrects several metabolic and pathologic problems. Since 2001, ERT has been used to treat Fabry disease; it is given intravenously once every two weeks[12]. Agalsidase alfa (Replagal, Shire Human Genetic Therapies, Cambridge, MA, 0.2mg/kg per infusion) and agalsidase beta (Fabrazyme, Genzyme Corporation, Cambridge, MA, 1mg/kg per infusion) are the two recombinant GLA preparations that are available for ERT. The FDA has only given Fabrazyme approval for usage in the USA. Early-stage renal and heart symptoms have been proven to benefit from ERT, which reduces discomfort and enhances quality of life. However, there is still debate over the long-term clinical advantages of ERT for Fabry patients, particularly with relation to its capacity to avert avertable strokes[13,14].

Recombinant enzyme injections can potentially trigger immunological reactions in some people. Other restrictions on ERT include the enzyme's short half-life and the requirement for periodic administration of substantial doses of the enzyme. Additionally, people with Fabry disease are burdened by the exorbitant cost of ongoing treatment[8,15].

Alternative Therapies

While ERT is the recommended course of treatment, supportive and palliative methods can be used to address various symptoms of Fabry disease. In many patients, daily preventive dosages of neuropathic painkillers such phenytoin, carbamazepine, and gabapentin are helpful in reducing the frequency and intensity of pain episodes. For the treatment of pain, some patients require stronger analgesics, such as opioids. Pancrelipase, metoclopramide, H2 blockers, loperamide and hydrochloride can all be helpful for gastrointestinal issues. Angiokeratomas have been treated with a variety of laser procedures, however they were ineffective. Liquid nitrogen can be used to treat pedunculated lesions as an alternative to laser therapy.

The main goals of therapeutic management are the control of proteinuria, cholesterol and blood pressure. Patients with proteinuria should take ACE inhibitors and/or blockers. The proper management of hypertension and hypercholesterolemia is necessary. Patients who have had ischemic episodes or strokes should undergo permanent cardiac pacing, and high-risk patients should consider prophylaxis with anticoagulants. Patients must also be inspired to continue living a healthy lifestyle. It may be beneficial to alter your eating routine to incorporate frequent little meals. Dialysis or kidney transplantation can extend life in patients with advanced renal illness, even though renal failure is the most common cause of death in people with classic Fabry disease. However, other organ system damage persists even with the engrafted kidneys, particularly vascular disease that affects the heart and brain. It is obvious that additional therapies and preventative actions are required to manage Fabry disease even with ERT.

EMERGING TREATMENT STRATEGIES FOR FABRY DISEASE

Emerging Fabry disease treatment options include the development of small molecule drugs, which are widely employed in the treatment of a range of disorders. Small compounds account for roughly 80-90% of all commercialized medications. Small molecule medications are typically efficacious, have rapid effects, and can be used orally. They can also pass the blood-brain barrier, do not trigger autoimmune reactions and have lower manufacturing costs. Gene therapy has also been investigated as a treatment for Fabry disease. Because viral vectors were used to induce in vivo gene transfer in murine models, the experimental outcomes were limited. Some emerging drug development strategies for small molecule therapy of Fabry disease are illustrated and outlined in more detail below.

Chaperone therapy

Several missense mutations in FD patients result in a mutant protein with normal GAL A catalytic activity. The decrease in overall GAL The altered protein's severely reduced stability has been linked to enzymatic activity in people with these GLA mutations. Protein misfolding and subsequent premature breakdown cause this. The purpose of chaperone therapy is to improve the stability of the mutant protein by enhancing its proper folding. Galactose was employed in the earliest *in vitro* investigations on the effect of a chaperone in FD. In vitro enzyme activity was boosted by adding galactose to the growth media of COS-1 cells with the p.Q279E mutation. Galactose boosted enzyme activity in COS-1 cells and lymphoblasts for several GLA mutations, but not all (e.g., no reaction for the p.G328R mutant). The only clinical research on galactose to far involves a male FD patient with the p.G328R mutation who received 1g/kg galactose intravenously every other day for two years. In contrast to the in vitro data, endo-myocardial biopsy tissues showed a 180% increase in enzymatic activity and a reduction in heart mass. Following

chaperone investigations primarily employed the galactose analogue 1-deoxygalactonojirimycin (formerly known as Migalastat, Amicus Therapeutics), in which the oxygen atom in the ring is replaced with a nitrogen atom, resulting in an iminosugar. Migalastat is a powerful inhibitor of GAL A, although it also boosts enzymatic activity for some GLA mutations at lower dosages (Figure No.1). It is thought that the attachment of the iminosugar to the catalytic domain of GAL A causes the enzyme to fold properly and that after transport to the lysosome, the competitive inhibitor is replaced by the enzyme's natural substrate. An *in vitro* enzyme activity assay is used to establish whether a patient is eligible for Migalastat treatment. In a nutshell, wild type HEK-293 cells are transiently transfected with plasmids harboring mutant GLA DNA and then treated with Migalastat. Endogenous enzyme activity is measured in empty vector-transfected cells and subtracted from total enzyme activity in cells transfected with mutant DNA. Patients with such mutations in the GLA gene are judged suitable for therapy with Migalastat if the corrected GAL A activity increases at least 1.2-fold, with an absolute increase in activity of >3%. The increase in GAL A activity within the qualifying population ranges from 1.2 to 30.4-fold and is related to baseline enzyme activity. The wide range of GAL A activity increases in response to Migalastat treatment may explain, at least in part, the extremely variable (biochemical) response to Migalastat treatment in the clinical investigations mentioned below. Furthermore, because the investigations were performed in wild-type cells rather than GLA-knock out cells, the results should be interpreted with caution as endogenous GAL. A activity varies by cell and cell count varies by plate[16].

Migalastat is the only oral medication for FD that has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Israel, Australia, and Canada are among the countries that have approved Migalastat in addition to the United States and the European Union. Migalastat may lower Gb3 buildup in podocytes after 6 months of therapy, according to a recent study. In the same trial, Migalastat-treated individuals had better gastrointestinal symptoms than placebo-treated patients. An 18-month open label trial in 57 FD patients evaluating a transition from Fabrazyme or Replagal to Migalastat found no significant differences in renal function deterioration (the study's primary goal). A new Migalastat publication revealed a 5% reduction in heart mass on echocardiography in FD patients, as well as a mean rise in GAL. The previously untreated group showed A activity in patient leucocytes and a 45% drop in plasma lysoGb3. However, as previously stated, echocardiographic measures of heart mass are highly varied (inter-observer variability 15%-19%, de Simone *et al* 1999), making any conclusions based on only 14 patients challenging. Future research could employ cMRI (inter-observer variability 4%-10%) for a more exact assessment of heart mass. Furthermore, native T1 values, late gadolinium enhancement, and extracellular volume fractions (ECV) could be evaluated to examine the formation and progression of cardiac fibrosis, albeit the latter should be performed only in individuals with an eGFR greater than 30mL/min. Furthermore, the increase in enzymatic activity as well as the decrease in plasma lysoGb3 did not occur in all patients; in fact, one patient experienced an increase in lysoGb3 after discontinuing ERT. Although the rate of lysoGb3 elimination may change between treatments due to differences in bio-distribution and operating mechanism, a rise in lysoGb3 after switching from ERT to chaperone therapy suggests substrate re-accumulation. Lenders et al. recently demonstrated that Migalastat medication significantly reduced plasma lysoGb3 levels while increasing leucocyte GAL A activity in patients with the p.N215S mutation. Enzyme activity did not increase in FD patients with the p.L294S mutation, however lysoGb3 levels increased dramatically in these patients following treatment. Further research revealed that when amenability was examined in GLA-knockout HEK-293 cells and patient-derived cell lines, there was no response to Migalastat in

cells containing the p.L294S mutation, supporting the clinical findings. *In-vivo* response monitoring, including leukocyte GAL A activity, plasma lysoGb3 alterations, and extensive clinical evaluation, will aid in selecting individuals who are most likely to benefit from Migalastat treatment.

Substrate reduction therapy

Another oral therapy for FD is substrate reduction therapy (SRT), which aims to reduce the synthesis of metabolites that cannot be eliminated due to the underlying enzyme deficiency. Dosing should be done with prudence because the total abolition of a single enzyme reaction has the potential to disturb cell homeostasis, influencing processes such as apoptosis, cell proliferation and differentiation. SRT may be adequate in patients with residual enzyme activity to reduce substrate generation to a level compatible with the remaining enzyme activity. Additional methods for clearing stored Gb3 in FD patients, such as biliary excretion, may also contribute to the balance between accumulation and degradation of Gb3 in FD patients, as has been demonstrated for glucosylceramide in Gaucher disease.SRT may not be sufficient as a single therapy in individuals with minimal to no residual enzyme activity, but it may be beneficial in conjunction to ERT. One of the other possible advantages of iminosugars (SRTs and chaperone treatment) is that, unlike ERT, they do not cause ADA formation and may be capable of crossing the blood-brain barrier.

The glucose-based iminosugar N-butyldeoxynojirimycin was the first SRT used to treat an SD (for example, Gaucher illness). N-butyldeoxynojirimycin inhibits glucosylceramide synthase (GCS), the first step in glycosphingolipid synthases and the medicine was approved for the treatment of Gaucher disease as Miglustat (Actelion Pharmaceuticals). Later, the more selective GCS inhibitor Eliglustat (Sanofi Genzyme) was introduced, which is effective in the treatment of Gaucher disease but is ineffective in the treatment of Fabry disease due to its effect on cardiac conduction.The ceramide-based Venglustat (Sanofi Genzyme) and the galactose derivative Lucerastat (Idorsia Pharmaceuticals, Switzerland), both of which inhibit GCS, were later developed and tested for FD. The additional file mentions variations in specificity and inhibitory ability. A slow but gradual clearance of Gb3 from the superficial skin capillary endothelium and a gradual decline in plasma lysoGb3 in the majority of included patients over the course of 3 years of treatment are suggested by preliminary data from clinical trials evaluating the effect of Venglustat in Fabry patients who have not received treatment[16].

Residual Enzyme Activation

It is well known that tiny molecule activators can increase enzyme activity. In patients with Fabry disease, enzyme activators may improve mutant GLA's residual activity in the lysosomes, reducing the amount of substrate stored there and reducing symptoms. These activators, however, could not be advantageous if their efficacy is too high or if the residual activity of mutant GLA is insufficient. Finding enzyme activators in compound library screens is far more challenging than finding inhibitors from the perspective of drug discovery. As a result, tests that are particularly designed to identify small molecule enzyme activators are required.

GLA Promoter Activation

By promoting the production of the target protein, specific small molecule promoter activators may enhance the concentration of GLA in lysosomes. In this instance, a promoter activator attaches to the GLA promoter in cell nuclei to increase GLA transcription and raise the production of mutant GLA protein. Since the boost of mutant enzyme expression could correspondingly increase protein trafficking to the lysosome, this leads to an increase in GLA in the lysosomes. Therefore, a small molecule promoter activator may address lysosomal storage in Fabry patients with high residual GLA enzyme activity by increasing the amount of enzyme in lysosomes. A permanent cell line that has been modified with a cDNA plasmid carrying the promoter region of the GLA gene connected with a reporter gene such as luciferase must be produced in order to find small molecule GLA

promoter activators[14]. High throughput screening of this reporter gene cell line against the compound library may discover promoter activator lead compounds. Chemistry optimization and compound development can start once lead compounds have been found[15].

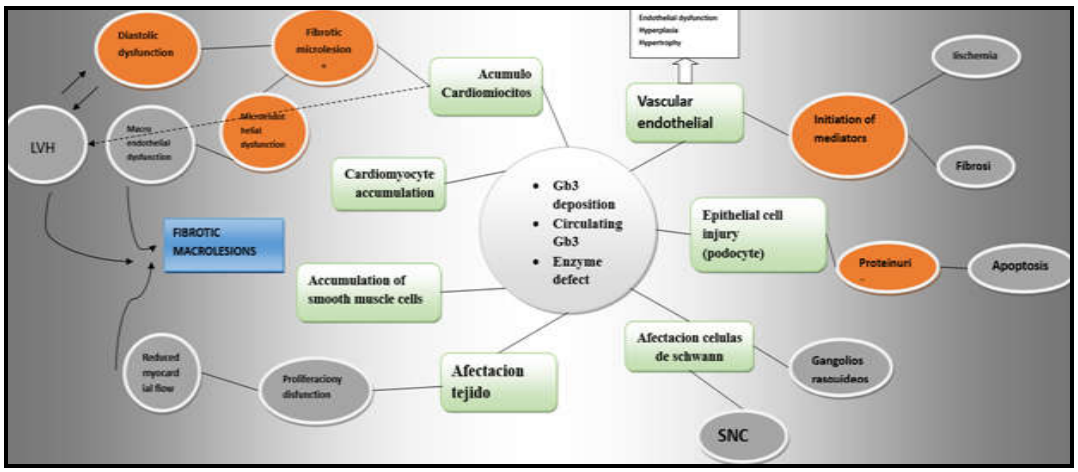
Protein Homeostasis Regulation (Proteostasis)

Altering the proteostasis network in cells, which comprises of numerous tightly controlled biological pathways that affect protein synthesis, folding, trafficking, disaggregation, and degradation, is another therapy approach. By expanding the proteostasis network capacity, small molecule proteostasis regulators may be used to enhance the amount of folded protein in the endoplasmic reticulum. This is accomplished by improving signaling pathways and/or by translating and trancribing parts of the proteostasis network[16]. Protein folding or breakdown can be facilitated by such alterations in the proteostasis network capacity. Diltiazem and verapamil, two well-known calcium channel blockers, have recently been shown to have largely restored mutant glucocerebrosidase folding, trafficking, and enzyme function in patient fibroblasts[17]. Although therapeutic levels of these calcium channel blockers cannot be achieved in people, this novel target may be used to produce tiny molecules. Additionally, although this theory needs to be confirmed, the combination of proteostasis regulators and small molecule chaperones may further increase the amount of folded protein trafficked to lysosomes and hence boost the therapy.

Chemical Chaperone Therapy

A promising therapeutic approach for Fabry disease has recently been identified as chemical chaperone therapy (CCT). Small molecules known as chemical chaperones bind to mutant enzyme proteins to help with their proper maturation, folding and trafficking to their functional site, such as the lysosome. Some enzyme inhibitors and receptor antagonists have been said to act as chaperones for mutant enzymes and receptors because of how strongly they bind to the target protein. For a number of lysosomal storage disorders, including Fabry disease, Gaucher disease, Pompe disease, Tay-Sachs/Sandhoff disease and GM1-gangliosidosis, the effects of chemical chaperones have been investigated. Chemical chaperones have been demonstrated to increase the effectiveness of enzyme replacement therapy for Gaucher disease, Pompe disease, and Fabry disease, according to recent studies. In a phase 3 clinical trial, 1-deoxygalactonojirimycin, one GLA inhibitor, is being investigated as a chaperone treatment drug for Fabry disease[18].

In vivo, however, boosting mutant enzyme activity with an inhibitor would not be the best course of action because doing so could undermine the chaperone action's functionality. Theoretically, a pure enzyme binder with chaperone action or an enzyme activator would make excellent drug development candidates. When employed as a therapeutic, enzyme activators would improve lysosomal enzyme activity through their combined chaperone and enzyme stimulatory effects. There aren't any small molecule activators with chaperone action on the market right now. It is still unknown how to construct the right assays and run compound library screenings to find novel lead compounds. A new approach that may be helpful for identifying prospective chaperone chemicals in library screens is cell-based chaperone tests employing tagged GLA proteins[13,17].



Pathophysiology

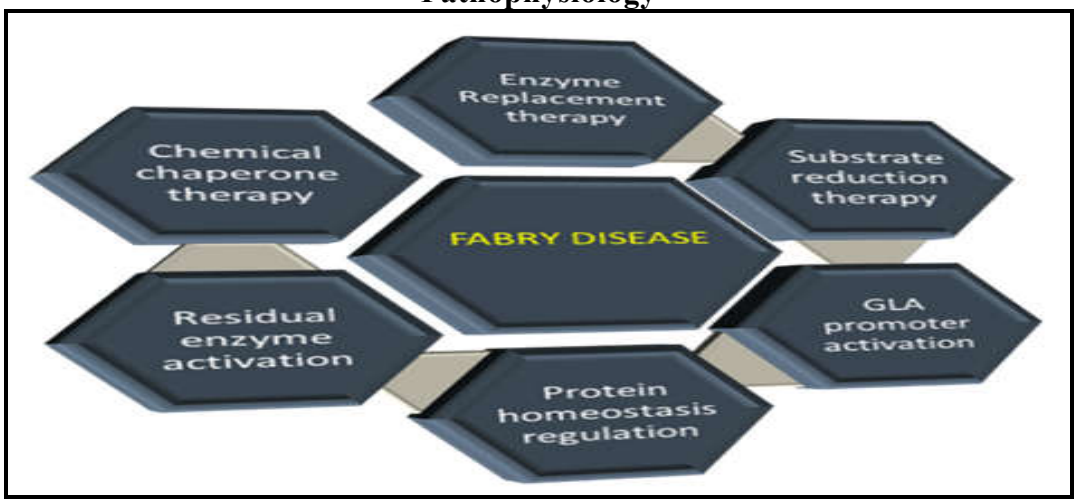


Figure No.1: Illustration of current and emerging treatment strategies for Fabry disease. The currently available treatment is highlighted in black

CONCLUSION

FD is a multisystem disease with a wide range of symptoms and indications. Diagnosis in symptomatic individuals necessitates a high index of suspicion and screening of particular at-risk populations. ERT was the first particular therapy devised and while it can halt renal failure and relieve symptoms, it has minimal effect on cardiovascular and cerebrovascular outcomes. These patients and their families may benefit from enzyme replacement therapy for Fabry disease's later, life-threatening cardiovascular and cerebrovascular consequences.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Department of Pharmaceutics, T. John College of Pharmacy, Banglore, Karnataka, India for providing necessary facilities to carry out this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Pallavi H R *et al*. A review on fabry disease, *International Journal of Research in Pharmaceutical and Nano Sciences,* 12(3), 2023, 73-82.