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Mini Review

A Review of Current and Future Treatment Strategies for Fabry Disease: A Model for Treating Lysosomal Storage Diseases

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Abstract

Fabry disease (FD) is an X-linked lysosomal storage disease (LSD) that results in accumulation of the glycosphingolipid globotriaosylceramide (GL-3) in various tissues of the body due to deficient activity of the lysosomal enzyme alpha-galactosidase A (a-Gal A). Accumulation of the undegraded substrate seriously affects the renal, cardiac, and cerebrovascular systems, resulting in a reduced lifespan and quality of life for Fabry patients. Periodic infusion of recombinant human a-Gal A, known as enzyme replacement therapy (ERT) is the current FDA-approved treatment for FD. Alternative treatments are being investigated, including chaperones, substrate reduction therapy (SRT), stem cell transplant, and gene therapy. In this article, we review the latest available data regarding ERT, its use, safety, and effect on the main presentations of FD and also the ongoing studies of novel agents and modalities currently under investigation.

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ABBREVIATIONS

FD: Fabry Disease; LSD: Lysosomal Storage Disease; GL-3: Globotriaosylceramide; A-Gal A: Alpha-Galactosidase A; ERT: Enzyme Replacement Therapy; SRT: Substrate Reduction Therapy; IV: Intravenous; ACE: Angiotensin-Converting Enzyme; ARB: Angiotensin-Receptor Blocker; GFR: Glomerular Filtration Rate; ESRD: End Stage Renal Disease; LVH: Left Ventricular Hypertrophy; Lvmass: Left Ventricular Mass; TIA: Transient Ischemic Attack; GI: Gastrointestinal; Gvhd: Graft-Versus-Host Disease; ZFN: Zinc-Finger Nuclease; TALEN: Transcription Activator-Like Effector Nuclease; CRISPR–Cas:Clustered Regularly Interspaced Short Palindromic Repeat–CRISPR-Associated;ER: Endoplasmic Reticulum; PC: Pharmalogical Chaperones; GCS: Glucosylceramide Synthase

INTRODUCTION

Fabry disease (AKA Anderson-Fabry disease) was first described in 1898 by Johannes Fabry and William Anderson as a hereditary, X-linked lysosomal storage disease [1-3]. The lysosome is a critical organelle responsible for breaking down and recycling various substrates, including sphingolipids [4]. In Fabry disease (FD), lysosomal function is disrupted due to deficient activity of the lysosomal enzyme, alpha-galactosidase A (a-Gal A), resulting in an accumulation of globotriaosylceramide (GL-3) in a variety of cell types [1]. This accumulation of GL-3 has devastating consequences with a multi-organ pathology that most seriously affects the renal, cardiac, and cerebrovascular systems [5]. Cellular dysfunction and production of mediating molecules [6,7] due to accumulation of GL-3 or other possible metabolites [8] is believed to trigger a cascade of events including cellular death (apoptosis or necrosis) [9] compromised energy metabolism [10], small vessel injury, calcium channel dysfunction [11], oxidative stress, alterations in autophagy [12], tissue ischemia, and development of irreversible cardiac and renal tissue fibrosis [13]

The prevalence of FD has been estimated to be 1 in 40,000 to 117,000 male's worldwide [14]. However some recent newborn screening studies have shown a higher incidence for FD and its variants (1 per 3000-4000 live births)[15-17]. Early manifestations begin in childhood and adolescence with neuropathic pain, hypohidrosis, gastrointestinal symptoms, and angiokeratomas. Later in life chronic kidney disease, cardiomyopathy and cerebral events are the most important findings [18,19]. Women heterozygous for FD may express disease with variable severity as the enzyme is not completely absent [19]. For both heterozygous females and hemizygous males, the impairment of major organ systems and other pathologies of FD result in a diminished quality of life, as well as a notable reduction in lifespan of about 15-20 years [20-23].

Not including treatments that address the symptoms of FD, enzyme replacement therapy (ERT) is the only FDA-approved treatment available. Therapeutic alternatives (e.g. chaperones, substrate reduction therapy (SRT), stem cell transplant, and gene therapy) are also under investigation for FD. Other therapeutic potentials like proteostasis regulators [24] or anti-apoptotic/ anti-necrotic therapies [25], which are under investigation for other LSDs, may be tested for FD in the future.

ENZYME REPLACEMENT THERAPY (ERT)

Currently, two different recombinant enzyme replacement drugs are commercially available for the treatment of Fabry patients: agalsidasealfa (Replagal) and agalsidase beta (Fabrazyme). They both contain recombinant human a-Gal A [26,27] and exhibit identical biochemical properties, with only minor differences in glycosylation, composition, and mannose-6-phosphate receptor mediated cellular uptake [28,29]. However, agalsidasealfa (Not approved by the FDA) is produced in a human cell line by gene activation, where as agalsidase beta (Approved by the FDA) is produced in Chinese hamster ovary cells by recombinant techniques [30]. While both drugs are administered by slow intravenous (IV) infusion every 2 weeks, their doses of administration are different. Both enzymes are available in Europe and in many other countries [31]. There is no solid evidence in superiority of either one in the treatment of FD [32-34].

Using mutated enzymes with greater therapeutic effect on a per milligram basis, and therefore reducing the likelihood of adverse infusion related reactions, has been proposed as a potential improved alternative by some recent studies [35].

ERT EFFECTS

After ERT became available more than a decade ago, many studies (randomized clinical trials, open-label trials, and systematic reviews) have evaluated agalsidasealfa and beta in FD treatment. However, the quality, population, duration, measured outcomes, and results of these studies differ significantly. Although controversy still remains on certain topics, the overall results suggest some beneficial effects of ERT on measures of pain and cardiovascular function, stabilization of renal function, and quality of life with no convincing evidence for an effect on neurological events [36-38].

GL-3 Clearance in Different Tissues

ERT clears GL-3 in plasma, urine, and endothelial cells in various organs including the skin, heart, and kidneys [26,27]. However, GL-3 clearance is not equal in all tissues. It is much better in endothelial cells than kidney podocytes, other epithelial cells, smooth muscle cells, and cardiac myocytes. Additionally, ERT agents generally do not pass the blood brain barrier, suggesting no effects on GL-3 levels in the central nervous system [39].

Proteinuria and Kidney dysfunction

Renal dysfunction is a major complication of FD. Initial presentation is typically with proteinuria starting at an early age. Kidney function most rapidly declines in men with the highest proteinuria levels [40]. End stage renal disease (ESRD) most commonly occurs in affected males before the fourth decade of life [41,42]. Females typically display mild renal involvement but may also develop ESRD [43,44].

Proteinuria is an independent risk factor for progression of renal disease [45]. Studies have shown different effects of ERT on proteinuria. Stabilization of proteinuriais reported in most studies of agalsidasealfa and beta ERT [46-49]. Even though not all of these studies adjusted for the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), a reduction in the risk of proteinuria have nonetheless been reported in the studies that did [50,51].

Some studies have reported stabilization and slowing of the progression of renal dysfunction with ERT, especially in patients with higher glomerular filtration rates (GFR) and lower proteinuria levels at baseline [47,50,52-54]. However, few studies have shown that long term ERT has only limited effects on renal function, suggesting that some of the previously observed positive results are possibly attributable to concomitant anti-proteinuric therapies [55-57]. It has been suggested that dose [58], frequency [59], and duration [50] of ERT may be associated with its effectiveness on renal function.

Cardiomyopathy

The cardiovascular manifestations of FD can include left ventricular hypertrophy (LVH), arrhythmias, heart block, valvular dysfunction, angina, and atrial wall thickening. The hypertrophy becomes more severe with disease progression, which may progress to serious cardiac events including cardiac related death [13,60,61].

In both male and female patients with or without LVH at baseline, beneficial effects on left ventricular mass (LVmass) have been reported with either agalsidasealfa or beta therapy. Heterogeneity has been noted in different studies. While some have shown stabilization or improvement of LV mass others have shown a slight increase in LVmass despite treatment. However, this increase was still significantly slower than inuntreated patients [56]. Better results have been reported when treatment was initiated during the early stages of cardiomyopathy [61-64].

Transient Ischemic Attacks (TIA)/Stroke

Studies have not shown a significant change in the risk of having TIA or stroke with ERT. Whether on or off ERT, patients with FD are at a high risk for TIA or stroke after the age of 40 [45,50,51,65]

Gastrointestinal (GI)Involvement

Gastrointestinal disturbances include mainly abdominal pain and diarrhea, and are common in men and women with FD [66,67]. Some studies have shown that ERT might decrease the frequency and severity of abdominal pain and also improve baseline diarrhea in some patients [68,69].

Neuropathy and Pain

With ERT, pain outcomes in FD are highly variable, ranging from no changes to significant improvements in pain scores. Some patients reported discontinuation of pain medications, while others reported no changes in the dose or freq uency of pain medication intake [45,47,50,51,70-73]

Measures of neuropathy, including detection thresholds of vibration, heat-pain onset, and coldness, could improve. Patients who experience no change or even a worsening of thresholds during treatment, might have reached irreversible stages of nerve damage before starting ERT [27,53,74].

Sweat Function

Fabry patients have a decreased sweat function. ERT has been shown to increase the patient's ability to sweat in subjective and objective methods of measurement [26,70,71,73]. However, the effects of the frequency and dose of ERT on improving sweat function remain controversial [70,73].

SAFETY PROFILE OF ERT

Mild to moderate infusion reactions are the most common adverse events with ERT and occur mostly in the form of rigor and fever [50,51,74]. These reactions are generally mild and tolerable, and are managed by reducing infusion rate and, if needed, use of additional medications [74].

Positive antibody testing has been also reported in some Fabry patients with ERT [50,53]. The significance of these antibodies is not well known [75].

ERT IN CHILDREN

Evidence of ERT efficacy in FD children is limited. Some open-label trials of ERT in children have shown encouraging results in reducing plasma and tissue GL-3 levels, controlling pain and GI symptoms, increasing sweat volume, improving heart rate variability, and maintaining kidney function and LV mass [50,57,76-78]. It is possible that early treatment starting in childhood can prevent disease progression. However, as most ERT studies have initiated treatment in adults, this has not been proven. Overall, ERT has been well tolerated in pediatric populations, but there have been reports of allergic reactions to the medications and anti-drug antibody production [76-78].

CHAPERONES

While some of the larger mutations in the gene for a-Gal A lead to no protein or catalytically inactive proteins, missense mutations may only result in misfolding of the aberrant protein and not a complete loss in catalytic activity. These misfolded proteins are recognized by the quality control systems of the endoplasmic reticulum (ER) and may be degraded, retained in the ER, or abnormally glycosylated and mistrafficked [79,80].

Pharmacological chaperones (PC), also known as small-molecule ligands, substrate analog competitive inhibitors, or chemical chaperones, can bind and stabilize some mutant forms of a-Gal A in the endoplasmic reticulum. This binding and stabilization favors the native conformation of a-Gal A, facilitates proper protein folding, and allows for correct trafficking [81]. As a result, the stable complex of mutant enzyme-chaperone can be transported to the lysosome, where the complex dissociates spontaneously under the acidic condition and the enzymatic activity of the mutant protein is partially rescued. The majority of PCs that have been identified bind to the catalytic site of enzyme, thus this interaction is a paradoxical phenomenon in which an enzyme inhibitor *in vitro* serves as an enzyme stabilizer *in situ* [82]. Chaperone therapy has been proposed as a feasible strategy for treating some lysosomal storage diseases (LSDs). Potential chaperone agents are under evaluations for diseases like Pompe, Gaucher, GM1-gangliosidosis, and Fabry [81,83-85].

Migalastat hydrochloride (1-deoxygalactonojirimycin HCl, AT1001, GR181413A) is an analog of the terminal galactose of GL-3 that selectively and reversibly binds and stabilizes wild type and mutant forms of a-Gal A [86,87]. It is currently undergoing clinical trials and has become a new oral candidate for treating FD.

In pre-clinical studies, migalastat HCl has been shown to reduce the storage of GL-3 *in vitro* and *in vivo* (Fabry transgenic mice) [88-90]. Furthermore, phase 2 clinical studies of migalastat HCl have demonstrated increases in a-Gal A activity and reductions of GL3 in the blood, skin, and kidneys of patients with amenable a-Gal A mutations. Migalastat HCl was well tolerated in these studies [91,92]. Migalastat HCl is currently being studied under phase 3 trials to evaluate its safety and efficacy as a potential treatment for FD. The results of these phase 3 trials will be available soon (see ClinicalTrials.gov: NCT00925301 and NCT01218659).

In contrast to ERT, pharmacological chaperones have the advantage of being non-invasive, orally available, and having broad tissue distribution, including access to the central nervous system [93]. However, chaperone therapy is genotype-specific treatment. More than 630 gene mutations coding for a-Gal A have been recorded in Fabry patients. (HGMD) [94,95]. It is estimated that one-third to one-half of mutations may be amenable to currently available chaperones [83].

Other than rescuing the endogenous, misfolded proteins, chaperones may also be able to enhance the physical stability, and possibly the efficacy, of the recombinant enzymes that are used for ERT. Pre-clinical studies have suggested that combination therapy of pharmacological chaperones and ERT may be beneficial in management of FD [96]. The potential combinations of ERT and chaperones have been developed and studied in other LSDs like Pompe disease [97,98]. However, such combinations have not yet been developed for FD.

In addition to inhibitory chaperones, the development of non-competitive chaperones and molecular chaperones utilizing the heat shock protein are under evaluation as new approaches for lysosomal and other genetic or non-genetic diseases [83].

SUBSTRATE REDUCTION THERAPY (SRT)

Substrate reduction therapy (SRT) is a new therapeutic approach aiming at decreasing synthesis of the substrate GL-3, a glycosphingolipid, by targeting the enzymes involved in the production ofGL-3 in the cell [99,100].

One such agent, Miglustat, is approved for treatment of type 1 Gaucher and Niemann-Pick type C (not approved in US [101-103]. Miglustat(n-butyldeoxynojirimycin (nb-dnj)/ Zavesca) is an inhibitor of glucosylceramide synthase(GCS), which would reduce the biosynthesis of glycosphingolipids by inhibiting the enzyme which catalyzes the first step in the synthesis of glycosphingolipids (GL-1) and therefore subsequent molecules including GL-3 [104].

Table 1: Summary of the current and future potential therapies for FD.

Treatment	Mechanism of Action	Current Examples	Benefits	Disadvantages	Route
ERT	Recombinant human a-Gal A	Agalsidasealfa (Replagal, approved in Europe, not FDA approved), agalsidase beta (Fabrazyme, FDA approved)	Reported beneficial effects on: measures of pain, cardiovascular function, stabilization of renal function, and quality of life	Mild to moderate immunogenic reactions, does not cross blood-brain barrier, and it can be only administered as a slow intravenous (IV) infusion.	Intravenous (IV)
Chaperones	Facilitation of proper protein folding and allowing for correct trafficking of the mutant enzyme	Migalastat hydrochloride (phase 3)	Non-invasive, orally available, broad tissue distribution (crosses Blood-Brain Barrier), potential use as a combination therapy with ERT	Genotype-specific treatment (only one-third to one-half of mutations may be amenable)	Oral
SRT	Decreasing synthesis of the substrate GL-3	Miglustat (not considered for the treatment of FD clinically) Genz-682452 (phase 1)	Non-invasive, orally available, pre-clinical studies showed positive outcomes, potential use as a combination therapy with ERT	Side effects that may compound FD symptoms	Oral
Gene Therapy	Genetically modifying autologous stem cells/somatic cells to induce intrinsic production of the missing enzyme	Gene therapy using viral vectors (pre-clinical studies)	Non-immunogenic, sustained and balanced supply of the deficient enzyme, and production of engineered cells capable of overexpressing the missing enzyme	Limitations with viral vectors: carcinogenesis, immunogenicity, broad tropism, limited DNA packaging capacity and difficulty of vector production.	N/A

Abbreviations: **F**D: Fabry Disease; ERT: Enzyme Replacement Therapy; A-Gal A: Alpha-Galactosidase A; SRT: Substrate Reduction Therapy; GL-3: Globotriaosylceramide

Miglustat has been evaluated with positive outcomes in Fabry mice [105]. However, since the inhibitory effect of Miglustat is not very specific for glucosylceramide synthase (GCS), side effects that may compound FD symptoms have been observed, including gastrointestinal complaints and peripheral neuropathy [106,107]. Therefore, Miglustat has not been considered for treatment of FD clinically.

Another investigational product that is under clinical trials is the glucosylceramide synthase (GCS) inhibitor Genz-682452. Genz-682452 has shown more specificity to GCS than Miglustat. In pre-clinical studies, GCS inhibition by Genz-682452 lowered the tissue level of GL-3 in mice. Since the majority of Fabry patients are null for a-Gal A activity, SRT as a monotherapy is unlikely to be as effective as it has been shown for type 1 Gaucher patients. However, it has been demonstrated that combining ERT with SRT is a more effective alternative to ERT alone in reducing GL-3 levels, especially in the liver, kidneys, and urine [108].

STEM CELL TRANSPLANT AND GENE THERAPY

In principle, it is possible to cure LSDs by transplanting stem cells capable of producing the missing enzyme. However, allograft transplant has been reported with long-term but only partial effectiveness [109]. The requirement for a matching donor and possible treatment-related serious side effects (eg. graft-versus-host disease (GvHD)), limit the clinical application of allogeneic stem cell transplant [110]. Additionally, levels of enzyme secreted by non-modified transplanted cells and their progeny do not reach to therapeutic levels that could affect uncorrected cells in other organs [111].

Gene therapy has been explored as an alternative treatment for LSDs including Fabry disease [109,112,113]. Gene therapy is conducted through the delivery of the gene of therapeutic interest using carriers of the gene into targeted cells. Recombinant viruses including retroviral [114] lentiviral [111], adenoviral [115] and adeno-associated viral are the most commonly used vectors [116]. There are limitations with viral vectors, including carcinogenesis, immunogenicity, broad tropism, limited DNA packaging capacity, and difficulty of vector production. Advances in the field of gene therapy like introduction of non-viral vectors and engineered nucleases that allow precise correction of disease-causing genes (e.g. zinc-finger nuclease (ZFN), transcription activator-like effector nuclease (TALEN) or CRISPR–Cas (clustered regularly interspaced short palindromic repeat–CRISPR-associated)) may overcome current limitations [117,118]. Gene therapy can genetically modify autologous stem cells *ex vivo* to over-produce and secrete the therapeutic enzyme. This would alleviate risks involved with post-transplant GvHD and would likely be more effective at systemic correction of LSDs. Alternatively; an *in vivo* strategy may use systemic delivery and a tissue-specific promoter or direct injection into a target organ [81]. No gene therapeutics has so far been approved by the FDA despite many clinical trials worldwide.

Unlike ERT, gene therapy can provide a non-immunogenic, sustained and balanced supply of the deficient enzyme. Also the enzyme secreted from cells engineered by gene therapy to over express, can be taken up by celsinamnannose-6-phosphate(Man-6-P) in a receptor-dependent manner in uncorrected cells of patient affected organs in a process termed 'metabolic

cooperatively' or 'cross-correction'. This enhances prospects of therapeutic application of gene correction in treatment of LSDs including FD [114,119].

For some LSDs including MPS, Pompe disease, neuronal ceroidlipofuscinoses, and Gaucher disease, clinical trials with gene correction are already in progress. Pre-clinical studies of gene therapy in FD have shown promising results, reporting production of functional a-Gal A and reduction of GL-3 in Fabry mice and patient bone marrow mononuclear cells [111,114,116]. A future clinical trial may follow [120].

CONCLUSION

As the only FDA approved treatment for FD, ERT has been shown to be a well-tolerated therapy overall. While ERT can cause immunogenic responses and does not affect the neurological manifestations of FD, it can be beneficial in treatment of proteinuria, renal dysfunction, cardiomyopathy, pain, and gastrointestinal findings in adult and pediatric Fabry patients. Controversy remains on the significance of these effects in long-term treatment.

Small molecule drugs used as chaperones or in SRT have the potential advantage over ERT in that they can be administered orally, have more potential to gain access to most cell types, can cross the blood brain barrier, do not cause autoimmune responses, and have lower manufacturing costs. Combination therapy of ERT and these new treatment strategies may increase the efficacy of ERT, providing healthcare providers with innovative methods to manage Fabry disease. Finally, stem cell transplant and gene therapy are modalities that if fully developed, can potentially provide an intrinsic and sustained source of the deficient enzyme in Fabry patients.

CONFLICT OF INTEREST

Dr. AnjayRastogi has a personal financial interest in the Genzyme Corporation, developer of the Fabrazyme drug. Specifically, Dr. AnjayRastogi is receiving income for speaking at patient educational events. In addition, he is participating in the Genzyme Fabry Registry study.

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