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Review Article

A Review on: Enzyme Replacement Therapy

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Enzyme replacement therapy is known as one of the most important therapy, and studies on its effectiveness were initiated over 30 years ago. In 1964, Christian de Duve first suggested that enzyme replacement might prove therapeutic for lysosomal storage diseases (LSDs).Early efforts identified the major obstacles, including the inability to produce large quantities of the normal enzymes, the lack of animal models for proof-of-concept studies, and the potentially harmful immune responses to the "foreign" normal enzymes. Subsequently, the identification of receptor-mediated targeting of lysosomal enzymes, the cloning and over expression of human lysosomal genes, and the generation of murine models markedly facilitated the development of enzyme replacement therapy (ERT). However, ERT did not become a reality until the early 1990s, when its safety and effectiveness were demonstrated for the treatment of type 1 Gaucher disease. Today, ERT is approved for six LSDs, and clinical trials with recombinant human enzymes are ongoing in several others. Several diseases can, at least in theory, be treated by the administration of an enzyme, the deficiency of which is the cause of the disease. The aim of this review is to determine the clinical effectiveness, importance and cost-effectiveness of enzyme replacement therapy (ERT) in the treatment of different diseases as well as the administration of ERT, common side effects, management of the side effects drug costs and insurance concerns will be highlighted. Further studies are required to confirm the long-term clinical benefits of enzyme replacement therapy.

Keywords: Enzyme replacement therapy, lysosomal storage diseases, Gaucher disease.

INTRODUCTION

Enzyme replacement therapy is a medical treatment replacing an enzyme in patients in whom that particular enzyme is deficient or absent. *Enzyme replacement therapy does not correct the underlying genetic defect, but* increases the concentration of enzyme in which the patient is deficient.Enzyme replacement therapy is usually administered through intravenous (IV) infusion. It is currently available for lysosomal diseases, such as Gaucher disease and Fabry disease.

Enzyme replacement therapy usually introduces approximately the same enzyme that is lacking in the body from the outside. For example, Gaucher's disease is caused by a deficiency of glucocerebrosidase, an enzyme which plays an important role in the body's metabolism. The disease can be treated with injections of imiglucerase, a synthetic analog produced by Genzyme.

A second type of enzyme replacement therapy introduces enzymes that have become deficient for some other reason. Cystic fibrosis is caused by the body's failure to produce a particular protein that is crucial to the function of cell membranes. The disease cannot be cured simply by injecting this protein into the body; it would not function correctly.

Enzyme replacement therapy, however, can correct a symptom of cystic fibrosis. The disease causes problems with pancreatic ducts, which prevent enzymes from entering the gastrointestinal tract in order to digest food. Enzyme replacement therapy

can introduce a variety of digestive enzymes in order to correct this secondary problem.[1]

Enzyme replacement therapy is a relatively new type of treatment. As more is discovered about the genome and about the cellular function of proteins, new forms of enzyme replacement therapy are likely to emerge. This treatment is expensive, however, since it requires the external synthesis of proteins and is necessarily ongoing. In the natural course of operations, proteins degrade and are reproduced. Normally this degradation helps the organism to regulate itself, but for enzyme replacement therapy, the implication is that fresh injections of the enzyme are needed almost every week. Enzyme replacement therapy is currently available for some lysosomal diseases like Gaucher disease, Fabry disease, MPS I, MPS II (Hunter syndrome), MPS VI and Glycogen storage disease type II. Usually this is done by giving the patient an intravenous (IV) infusion containing the enzyme. [2]

Mechanism of action in ERT

Enzyme replacement therapy is an established means of treating lysosomal storage diseases. Infused enzymes are normally targeted to the lysosomes of affected cells by interactions with cell-surface receptors that recognize carbohydrate moieties such as mannose and mannose 6-phosphate on the enzymes. Therefore, alternative strategies to deliver the lysosomal enzyme β-glucuronidase in the enzyme-deficient mucopolysaccharidosis type VII mouse model. Here we summarize our recent efforts to use nontraditional ways to deliver β-glucuronidase.

First, we used a chimeric protein of the insulin-like growth factor II (IGF-II) fused to β-glucuronidase to deliver enzyme via the IGF-II binding site on the bifunctional IGF-II/mannose 6-phosphate receptor.

Second, we used the 11-amino-acid human immunodeficiency virus (HIV) Tat domain fused to β-glucuronidase to mediate uptake by absorptive endocytosis. Interaction with heparan sulfate on the cell surface internalizes and delivers the Tat-tagged enzyme to the lysosome via plasma membrane recycling.

Third, we created a chimeric β-glucuronidase fused to the Fc portion of human immunoglobulin G (IgG) Fc, which was transported by the neonatal Fc receptor from the maternal circulation across the placenta to sites of storage in fetal tissues.

Finally, periodate treatment was used to eliminate interaction with carbohydrate receptors, creating an enzyme with increased plasma half-life, resulting in transport across the blood–brain barrier and clearance of storage in neurons. These strategies for delivering lysosomal enzymes could also be used to target nonlysosomal proteins or enzymes identified for bioremediation of other conditions. [3]

The classical example is the means by which the enzyme glucocerebrosidase, which is deficient in Gaucher disease, is delivered to macrophages.[4, 5] Delivery of this enzyme is dependent on the binding of terminal mannose residues located on the carbohydrate chains of the enzyme. These residues bind to mannose receptors (MRs) on the cell surface of macrophages and other cells of the reticuloendothelial system. After endocytic

internalization, the enzyme is transported by endosomes to the lysosome, resulting in the breakdown of accumulated storage material.

In contrast to Gaucher disease, most other LSDs contain storage in other cell types that lack the MR. Delivery to these cell types employs a different receptor, the insulin-like growth factor II/cation-independent mannose 6-phosphate receptor (IGF-II/MPR). This receptor recognizes mannose 6-phosphate (M6P) moieties present on the carbohydrate chains of lysosomal enzymes synthesized in mammalian cells. Enzymes such as β-glucuronidase (GUS), α-iduronidase, and α-galactosidase, which are deficient in mucopolysaccharidosis VII (MPS VII), MPS I, and Fabry disease, respectively, rely on this delivery system to deliver infused enzyme by the IGF-II/MPR present on the cell surface. In addition, these enzymes usually have carbohydrate chains containing terminal mannose residues, which allow uptake by the MR.

In many cases, lysosomal enzymes used for ERT produce less than ideal results. In some cases, enzymes such as α-glucosidase, which is deficient in Pompe disease, are very poorly phosphorylated when the recombinant enzyme is produced in mammalian cell systems. This condition requires the use of very high doses of enzyme to obtain even modest clearance of storage in these patients.[6] In other cases, rapid clearance of infused enzyme from the circulation by IGF-II/MPR and MR in the liver and spleen lead to inadequate delivery to other tissues. Another problem is the lack of delivery of enzyme across the blood–brain barrier (BBB). This is due to the natural function of the BBB to limit access by unwanted substances and to the lack of both the MR and IGF-II/MPR transport systems at that location.

To improve delivery to resistant sites, we have investigated alternative strategies for delivery of lysosomal enzymes using the lysosomal enzyme GUS in the murine model of β-glucuronidase deficiency. For these studies, we used the enzyme-deficient MPS VII/E540A^{tg} mouse model that we previously made tolerant to human GUS. This tolerance allows multiple infusions of the human enzyme to be used without complications arising due to immunological reaction.[7,8,9]

Application of enzymes replacment therapy

1. LYSOSOMAL STORAGE DISEASES (LSD)

The lysosomal storage diseases (LSDs) are a group of disorders heralding in a new era in the treatment of genetic diseases. Enzyme replacement therapy (ERT) moves the treatment of these disorders from symptomatic management to therapeutic interventions. ERT is not a cure for these disorders, but it can greatly modify or attenuate the phenotype. Treatment for LSDs is lifelong and the diseases affect multiple organ systems. It is possible that nurses in almost every specialty will encounter a patient with one of these conditions.

ERT is not a cure for these disorders, but it can greatly modify or attenuate the phenotype (the signs and symptoms and severity of the condition) and disease progression. The success of ERT has proven that development of pharmacologic treatments for the LSDs is economically feasible and that development

of better treatment options is worthwhile.[10]

ERT IN GAUCHER'S DISEASE

- **1st developed ERT**
- Most common of the lysosomal storage diseases
- Deficient enzyme: Glucocerebrodase (catabolyzes glucoceramide)
- Affects spleen, liver & bone marrow

Enzyme replacement therapy is a treatment of Gaucher disease. People with Gaucher disease have a deficiency of the enzyme called glucocerebrosidase. This enzyme helps break down fatty substances in the body, and when the enzyme is deficient, fatty substances build up in parts of the body and cause damage. These replacement enzymes are typically given IV (intravenously), in high doses every two weeks.Current available synthetic enzymes are Cerezyme® (imiglucerase), VPRIV® (velaglucerase) and Ceredase® (alglucerase). In many individuals with Gaucher disease. [11]

ERT IN FABRY DISEASE

Also known as Fabry's disease, Anderson-Fabry disease, angiokeratoma corporis diffusum, and alpha-galactosidase -A deficiency associated with rare genetic lysosomal storage disease, inherited by X-linked manner. Fabry diseases can cause a wide range of systemic symptoms· It is a form of sphingolipidosis, as it involves dysfunctional metabolism of sphingolipids. The disease is named after one of its discoverers, Johannes Fabry (June 1, 1860 – June 29, 1930)[33].

Bbilateral, whorl-like corneal pattern of cream - colored lines in a patient with Fabry disease.

The first treatment for Fabry's disease was approved by the US FDA on April 24, 2003. Fabrazyme (agalsidase beta, or Alpha-galactosidase) was licensed to the Genzyme Corporation. It is an enzyme replacement therapy (ERT) designed to provide the enzyme the patient is missing as a result of a genetic malfunction. The drug is expensive — in 2012, Fabrazyme's annual cost was about US$200,000 per patient, which is unaffordable to many patients around the world without enough insurance. ERT is not a cure, but can allow improved metabolism and partially prevent disease progression, as well as potentially reverse some symptoms. The pharmaceutical company Shire manufactures agalsidase alpha (which differs in the structure of its oligosaccharide side chains) under the brand name Replagal as a treatment for Fabry's disease, and was granted marketing approval in the EU in 2001. FDA approval was applied for the United States. However, Shire withdrew their application for approval in the United States in 2012, citing that the agency will require additional clinical trials before approval. Clinically the two products are generally perceived to be similar in effectiveness. Both are available in Europe and in many other parts of the world, but treatment costs remain very high. Pain associated with Fabry disease may be partially alleviated by ERT in some patients, but pain management regimens may also include analgesics, anticonvulsants, and nonsteroidal anti-inflammatory drugs, though the latter are usually best avoided in renal disease.[12]

ERT IN POMPE DISEASE

Pompe disease is a rare inherited neuromuscular

disorder that causes progressive muscle weakness in people of all ages. Pompe disease is caused by a defective gene that results in a deficiency of an enzyme acid alpha-glucosidase (pronounced "AL-fa glue-CO-sih-days" and often abbreviated GAA). The absence of this enzyme results in excessive buildup of a substance called glycogen, a form of sugar, in a specialized compartment of muscle cells throughout the body. Although the effects of Pompe disease vary from patient to patient, some generalizations can be made. Most patients experience muscle weakness in the arms and legs, usually most prominently in the legs, making walking or climbing stairs difficult. Muscles used for breathing may frequently be affected, making it difficult to breathe, especially when lying down. In infants, the heart is usually affected, resulting in greatly enlarged heart and other heart problems. [13] **Myozyme** (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for use in patients with Pompe disease (GAA deficiency). has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use of Myozyme in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy. [14,15]

ERT IN MORQUIO

Morquio A is a rare inherited disease that affects major organ systems in the body. The disease is a form of mucopolysaccharidosis, which is a type of lysosomal storage disorder. People born with Morquio A can't break down glycosaminoglycans (GAGs) molecules because their bodies don't make enough of an enzyme, or protein, called N-acetylgalactosamine-6 sulfatase (GALNS). This enzyme breaks down or recycles materials the body can't use. When the body doesn't produce enough of the enzyme, GAGs build up in tissues, bones, and major organs. GAGs cause serious problems, including heart disease, skeletal abnormalities, vision and hearing loss, difficulty breathing, and early death. Morquio A is a progressive disease, meaning that it will get worse over time. According to the recently published "International Guidelines for the Management and Treatment of Morquio A Syndrome," it's important to get an early diagnosis in order to prevent further damage, and to start treatment with an enzyme replacement therapy (ERT) right away. The chart below shows the two most common to tests to check for Morquio A. [16]

2. ENZYME REPLACEMENT THERAPY FOR CYSTIC FIBROSIS

It is a hereditary disorder affecting the exocrine glands. It causes the production of abnormally thick mucus, leading to the blockage of the pancreatic ducts, intestines, and bronchi and often resulting in respiratory infection. Enzyme supplements can replace natural enzymes so that fat and proteins can be absorbed properly, which improves nutrition and reduces fatty stools. Enzymes help a person who has cystic fibrosis digest food by replacing digestive enzymes that are normally released by the pancreas. Pancrelipase is available in tablet, powder, or capsule form.[17]

Clinical trial of ERT

Xtensive preclinical evaluations of enzyme replacement therapy were performed in α-Gal A–

deficient mice. To date 109 patients with classic Fabry disease have been evaluated in recent clinical trials of enzyme replacement therapy. Human α-Gal A, produced by two companies, has been used in these trials. Recent independent studies comparing specific activity, biochemical composition, and cell uptake of the two preparations—gene-activated human α-Gal A (ga-hαGalA, agalsidase alfa [Replagal, Transkaryotic Therapies, Inc., Cambridge, Massachusetts]) and recombinant human α-Gal A (r-hαGalA, agalsidase β [Fabrazyme, Genzyme Corp., Cambridge, Massachusetts])—found that the proteins were structurally and functionally very similar, with comparable specific activities and glycosylation.[18]

Safety of enzyme replacement therapy

Enzyme Replacement Therapies (ERT) are a class of drugs that provide people with sufficient quantities of an important enzyme that their own body cannot make. In MPS VI, the body is lacking in the ASB (Arylsulfatase B) enzyme needed to break down GAG (Glycosaminoglycans), a substance that builds up inside the body and leads to MPS VI. Naglazyme (galsulfase) provides ASB to break down the GAG buildup that leads to MPS VI symptoms. Naglazyme is a prescription medicine that can help patients with MPS VI. Naglazyme provides an enzyme that is needed to break down and get rid of a GAG that causes symptoms of MPS VI. Severe and life-threatening allergic reactions can occur during NAGLAZYME (galsulfase) infusions and up to 24 hours after infusion. Typical signs of an allergic reaction include shock, difficulty breathing, wheezing, swelling of the throat, and low blood pressure. If a severe allergic reaction occurs during infusion, the infusion should be stopped immediately and should receive medical attention. Contact doctor or get medical help right away if develop any severe symptoms after infusion.[19]

CONCLUSION

ERT is safe and effective; however, it is costly and burdensome to the family. As individuals live longer with these conditions and some aspects of the disease are treated, it is likely that new disease complications will emerge as the disease phenotype changes in response to therapy. Since most disease complications do not appear to be completely reversible, if at all, it is of utmost importance to diagnose LSDs early in life and begin ERT prior to the onset of irreversible damage. ERT is safe and effective; however, it is costly and burdensome to the family. Now that it has been demonstrated that the development of therapies for rare diseases is financially feasible, hopefully further development of more convenient, cost-beneficial therapies will continue so that life-changing therapies are available to prevent the devastating complications of LSDs. ERT is not a cure for any condition; but it does offer a therapy that treats the underlying cause of the disease, namely deficient enzyme activity. It is probably most beneficial for patients with Gaucher disease since ERT can reverse and prevent some complications. It is not effective at treating CNS disease or existing bone disease, so other therapies need to be developed to treat those aspects of the disease. Although most patients anecdotally report improvements in quality of life, it remains to be

determined if both the monetary cost and psychosocial burden of infusions support the benefits derived from ERT.

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