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The Managing of Gaucher Disease Type 1(GD)

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Abstract:
Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder that results from loss of function of acid β- glucosidase and there are about 200 mutations in acid- β -glucosidase (GlcCerase) have been described, to manage this disease there are two treatments are available the enzyme replacement therapy (ERT) and the substrate reduction therapy.
There are nearly about 3 types of this disease that has different outcomes:
In type 1 GD massive painless splenomegaly weighing from300 gm to about 10 kg is present. Hepatomegaly may be seen in about 50% of patients on the other hand cirrhosis and portal hypertension is uncommon also patients may develop anemia with thrombocytopenia with bleeding manifestation, skeletal involvement may manifest as bone pains pathological fractures and lytic lesions in long bones with premature osteopenia.
Type 2 GD patients might have hypertonia, seizures with strabismus and progressive psychomotor degeneration leading to early death.
Type 3 GD may present as myoclonic epilepsy and learning disability and dementia.

Introduction

Gaucher disease, the most common lysosomal storage disorder, is caused by the defective activity of the lysosomal enzyme, acid-β-glucosidase (GlcCerase), leading to accumulation of glucosylceramide (GlcCer), particularly in cells of the macrophage lineage. Nearly 200 mutations in GlcCerase have been described, but for the most part, genotype-phenotype correlations are weak, and little is known about the down-stream biochemical changes that occur upon GlcCer accumulation that result in cell and tissue dysfunction. In contrast, the clinical course of Gaucher disease has been well described, and at least one treatment is available, namely enzyme replacement therapy. One other treatment, substrate reduction therapy.[1,2,3]

Discussion:

Three main phenotypes are conventionally distinguished:

_ Chronic non-neuronopathic, type I: this accounts for 95% of cases. The main signs and symptoms are hepatosplenomegaly, bone lesions (painful crises caused by bone infarcts or osteonecrosis) and thrombocytopenia;

_ Acute neuronopathic type II: early involvement (before the age of 1 year) of the brain stem and rapidly progressive (death before the age of 2 years), associated with organomegaly;

_ Subacute neuronopathic type III: Progressive encephalopathy (oculomotor apraxia - epilepsy – ataxia) associated with the signs of type I disease in the child or adolescent. This brain involvement may be present from the beginning or occur later.

*Definitive diagnosis is established by the demonstration of a deficiency of glucocerebrosidase activity by a specialized laboratory. This test is usually carried out on the patient's blood or during prenatal diagnosis.[1,4,5]

General treatment goals

• Correct anemia and low platelets within 1-2 years
• Changes as early as 3-6 months
• Prevent post surgical, obstetrical and spontaneous bleeding
• Reduce liver and spleen size: 2 -5 years
• Spleen can decrease by 30% to 50% in 12 months, 50% to 60% over 2 to 5 years
• Avoid need for splenectomy
• Improve bone pain
• 50% improve within 1-2 years
• Prevent bone crises and irreversible bone damage
• Maximize bone density: >2 years
• Pediatric: attain normal skeletal mass
• Adult: prevent loss of bone density, prevent fracture
• Improve fatigue, dyspnea[6]

Specific GD medication

There are currently 2 specific medications for GD:

_ Enzyme replacement therapy (imiglucerase) is the reference treatment;

_ Substrate-reduction therapy (miglustat).

specific GD medication must generally be administered for life. Certain complications of GD may cause irreversible lesions: fibrous splenomegaly, secondary osteoarthritis, osteonecrosis, deformities due to vertebral compression, hepatic fibrosis, lung fibrosis. Once these lesions are established they do not respond to specific treatments. Treatment must therefore be instituted before they occur.[2,3,7]

- ***Enzyme replacement therapy***: Three commercially available ERT products for treatment of GD type 1 (GD1) include imiglucerase, velaglucerase Alfa, and taliglucerase alfa.
- Imiglucerase and velaglucerase alfa are produced in different mammalian cell systems from Chinese Hamster Ovary Cells and human respectively they need to be modified Such modifications add to production costs.
- **Imiglucerase**(Cerezyme) that alleviates many disease symptoms although not dealing with the underlying cause،which would require gene therapy.
- ***Approved by FDA in 1995***
- The goal of all treatment strategies for GD is to reduce the GlcCer storage burden, thus diminishing the deleterious effects caused by its accumulation.
- supplementing defective enzyme with active enzyme using Cerezyme a recombinant form of GlcCerase.
- ERT has proved to be safe and effective over a period of >12 years.
- is always administered by intravenous infusion sometimes by a central venous access. Treatment is generally well tolerated. A few non-serious systemic signs may occur. More serious adverse effects are exceptional (anaphylactic shock).[2,3,4,5,7]
- Symptoms suggesting hypersensitivity (urticaria, angioedema, pruritis, rash, respiratory discomfort etc). These signs mainly occur at the start of treatment, justifying administration in a hospital setting during the first 2 years. If the patient has a history of adverse effects suggesting hypersensitivity, an adrenaline kit must be available at home.
- Imiglucerase should only be administered to pregnant woman when it is formally indicated and after careful assessment and ensuring that the benefits outweigh the risks both for the mother and foetus.
- **Taliglucerase alfa**(Elelyso)is a plant cell-expressed acid β-glucosidase approved in the United States and other countries for ERT in adults with GD1. A plant-based expression system, using carrot root cell cultures, was developed for production of taliglucerase alfa and does not require additional processing for postproduction glycosidic modifications. [2,3,4,5,7]
- **It approved for adult by FDA in 2012 and for children in 2014.**
- these included significant improvements in organomegaly and hematologic parameters as early as 6months, and maintenance of achieved therapeutic values in previously treated patients.
- The use of ERT during pregnancy in symptomatic patients with GD (versus untreated patients) has been associated with:
  – Reduced risk of spontaneous abortions
  – Reduced risk of GD-related complications during delivery and the postpartum period
  • **Imiglucerase** and **velaglucerase alfa** may be used during pregnancy in patients with GD and both have been associated with favourable maternal and neonatal outcomes For patients with GD of childbearing age for whom obstetric complications are an important symptom of disease, pregnancy is not contraindicated and ERT should not be interrupted.[4,5,7]

Substrate reduction therapy:

- using N-butyldeoxynojirimycin (NB-DNJ: Zavesca.
- NB-DNJ is an inhibitor of GlcCer synthase, the enzyme responsible for GlcCer synthesis and hence synthesis of all GlcCer-based glycolipids
- Was originally shown to delay neurological deterioration in Sandhoff mice.
- Since GlcCer synthesis is reduced, levels of its accumulation are lowered. A study in adult patients with mild to moderate type 1 GD who were unable or unwilling to receive ERT demonstrated the clinical feasibility of SRT.
- **Eliglustat** is an oral inhibitor of glucosylceramide synthase which is used in the therapy of type 1 Gaucher disease and is small molecule inhibitor of glucosylceramide synthase, the first and rate controlling step in the pathway of glycolipid synthesis
- Eliglustat was shown to decrease the intracellular accumulation of glycosylceramide in animal models of Gaucher disease. In several randomized controlled trials, eliglustat was shown to decrease spleen and liver volume and increase hemoglobin and platelet counts in patients with type 1 Gaucher disease(1st Line).

- **Approved as oral therapy of type 1 Gaucher Disease in the United States in 2015 and by FDA in 2014**. [2,3,4,5,7]

Surgical and other procedures

If symptoms are severe

- **Bone marrow transplant.** In this procedure, blood-forming cells that have been damaged by Gaucher disease are removed and replaced, which can reverse many of Gaucher signs and symptoms. Because this is a high-risk approach, it's performed less often than is enzyme replacement therapy.
- **Spleen removal.** Before enzyme replacement therapy became available, removing the spleen was a common treatment for Gaucher disease. Now this procedure typically is used as a last resort.[7]

Conclusion:

To conclude there are no curable treatment for GD, all available drugs are used to alleviate symptoms

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