REVIEW

Profile of eliglustat tartrate in the management of Gaucher disease

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Abstract: Gaucher disease (GD) is a lysosomal storage disorder caused by the deficient activity of acid beta glucosidase, with consequent accumulation of glucosylceramide in the spleen, liver, bone marrow, and various organs and tissues. Currently, the gold standard for GD treatment is enzyme replacement therapy (ERT). The efficacy of ERT in improving or stabilizing the visceral and hematological symptoms of GD is well-proven. However, since ERT has to be administered by frequent intravenous infusions, this therapeutic approach has an important impact on the patient's quality of life. Eliglustat tartrate is a new substrate reduction therapy for GD, which acts as a specific and potent inhibitor of glucosylceramide synthase and can be administered orally. This review summarizes the results of the preclinical and clinical trials, which experimented with eliglustat, and discusses its possible role in the management of GD, when compared to the currently available treatments and the new experimental approaches.

Keywords: Gaucher disease, enzyme replacement therapy, substrate reduction therapy, eliglustat tartrate

Introduction

Gaucher disease (GD; OMIM: 230,800, 230,900, and 231,000) is the most common autosomal recessive lysosomal disorder, first described by Philippe Gaucher in 1882. GD is caused by the deficiency of the lysosomal hydrolase acid – β-glucosidase (GCase). This enzyme is present in the lysosomes of all nucleated cells and cleaves the β-glucosidic linkage of glucosylceramide (GlcCer) yielding glucose and ceramide. GCase deficiency leads to the progressive lysosomal accumulation of GlcCer and other glycosphingolipids and subsequent multiorgan dysfunction. The storage predominantly occurs in cells of the monocyte–macrophage lineage, but an increase in GlcCer concentration is detectable in most of the body tissues.[1]

GD is a rare panethnic disease, presenting an estimated prevalence in the general population of 1:30,000–40,000 people. However, it is the most frequent genetic disease in the Ashkenazi Jewish population, where it shows a prevalence of 1:1,000.[2]

Clinically, based on the presence and progression of the central nervous system involvement, the disease has been traditionally classified into three different phenotypes: chronic non-neuronopathic (GD1), acute neuronophatic (GD2), and chronic neuronopathic (GD3) forms. GD1, the most common phenotype (accounting for 90%–95% of GD patients), is characterized by visceral symptoms that include hepatosplenomegaly, bone marrow infiltration causing thrombocytopenia and anemia, and skeletal involvement with osteoporosis, bone lesions, and bone pain. Patients affected by GD2 manifest visceral symptoms with early and severe neurological impairment, involving the brainstem, leading to death in the first 2–3 years of life. In patients affected by GD3, symptoms are associated with neurological alterations,

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presenting an onset that might range from childhood to early adulthood, and include abnormal eye movements, seizures, and mental retardation.[3] Although the classification of GD in these three main phenotypes is still widely accepted, and will also be used in this review, the clinical presentation of GD is currently considered as a continuum spectrum of phenotypes, ranging from very mild to extremely severe forms.[4] Moreover, patients affected by GD1 cannot be considered free of neurological complications anymore, since an increased risk of parkinsonism has been widely documented in these patients, and a high prevalence of peripheral neuropathy has been recently demonstrated.[5,6]

The β-glucosidase gene, *GBA1* (GenBank accession no J03059.1), is located on chromosome *1q21* and contains 11 exons spread out in ~7.5 kb of the genomic sequence. A highly homologous 5.7 kb pseudogene (GenBank accession no J03060.1) is located 16 kb downstream from the active gene.[7] To date, >430 mutations have been described (http://www.hgmd.org).

Mutations *N370S*, *84GG*, *L444P*, and *IVS2+1G>A* account for 90% of mutant alleles in the Jewish population, while they represent fewer than 75% of alleles among non-Jewish Caucasian patients, with some differences in defined subpopulations. In any case, *N370S* and *L444P* alleles are the most prevalent alterations throughout most populations. Although, no consistent correlation between the genotype and phenotype has been found, some general conclusions can be drawn regarding the neuroprotective nature of the *N370S* mutation and the association between the *L444P* allele and the severe phenotype.[8,9]

With regard to GD pathophysiology, all cells of the mononuclear phagocyte system, in particular macrophages of the liver (Kupffer cells), spleen, bone (osteoclasts), bone marrow, central nervous system (microglia), lungs, and others, can be altered by lipid accumulation.[1] Nevertheless, the levels of GlcCer and other glycophingolipids in these cells are increased, but are not high enough to completely justify the tissue damage. Thus, other mechanisms have been hypothesized to be involved in GD pathogenesis. Abnormal macrophage activation is considered as one of the key GD pathways. In fact, chitotriosidase, a product of the macrophage activation, is usually elevated in GD plasma, and since its levels correlate with disease severity, it is commonly used to monitor the disease response on treatment.[10] Moreover, proinflammatory cytokines secreted by macrophages, such as interleukin-1β, interleukin-6, and tumor necrosis factor-α (TNFα), and chemokines like CCL18 are elevated in GD plasma.[11] Modified macrophages also change their surface molecules, dysregulating the immune system, in fact, it is common in patients with GD to detect a monoclonal gammopathy, and there is also an increased risk of hematological malignancies (especially multiple myeloma).[12]

With regard to therapy, until the 1990s, the therapeutic approach for GD was mainly palliative. Then, the first specific treatment for GD, enzyme replacement therapy (ERT), aimed to correct the metabolic defect by intravenous infusion of a purified or a recombinant human GCase enzyme, was developed and it is still considered the standard of care for GD.[13,14]

More recently, an alternative therapeutic approach, substrate reduction therapy (SRT), which can be administered orally, has been introduced. SRT inhibits the synthetic pathway of GlcCer. Miglustat was the first SRT approved for GD, but because its tolerability profile was licensed only for patients who are not suitable for ERT.[15] Eliglustat tartrate is a new promising SRT, which acts as a specific and potent inhibitor of glucosylceramide synthase (GCS).[16]

In this review, we illustrate the rationale for the currently approved therapeutic approaches for GD, summarize the results of the preclinical studies and clinical trials, which experimented with eliglustat, and finally discuss the possible role of this new drug in the management of GD, when compared to the already available therapies and the new experimental approaches.

The development of ERT and SRT for GD

The rationale of ERT for lysosomal storage disease treatment is based on the observation that most cell types release small amounts of lysosomal enzymes and that these secreted forms could be internalized by other cells. Therefore, the periodically infused recombinant enzyme can be internalized by the cells, trafficked to the lysosomes, where it can metabolize the accumulated substrate.[17] The first experimented enzyme for GD treatment, called alglucerase (Ceredase®), was placenta-derived. Its introduction in the early 1990s changed the approach to lysosomal storage disorders, paving the way to the development of ERT for the treatment of many disorders. Alglucerase was soon replaced by imiglucerasi (Cerezyme®), the first human recombinant enzyme produced in Chinese hamster ovary cells, which was approved by the US Food and Drug Administration in 1994. More recently, other two preparations have been licensed in some countries: velaglucerase alfa (Vpriv®), produced in human fibroblast cell lines, and taliglucerase alfa (Elelyso®), produced in modified carrot cells. Many studies have demonstrated the efficacy of

ERT in reducing mortality, improving/normalizing hematological parameters and organ volumes, and improving or stabilizing bone pathology in GD.[13,18–20] However, due to its high molecular weight, the enzyme does not cross the blood–brain barrier; therefore, patients with neurological features only benefit from the effect of ERT on visceral, hematological, and skeletal features.[21] ERT is usually well-tolerated and except for possible anaphylactic reactions, side effects are usually mild and include nausea, abdominal pain, rash, fatigue, and headache.[22]

SRT is an alternative treatment strategy, based on the administration of small molecules that are able to reduce the biosynthesis of the substances that accumulate in the disease-affected organs, restoring the balance between the rate of production and the rate of degradation.[23] The first compound approved for SRT in GD1 patients was miglustat (Zavesca®), an imino sugar (N-butyldeoxynojirimycin) that inhibits the ceramide – glucosyltransferase, which catalyzes the first step in glycosphingolipid biosynthesis. The drug showed its efficacy on peripheral GD symptoms.[24] Moreover, since the molecule is able to cross the blood–brain barrier, its role in the management of the neuronopathic forms has been hypothesized. A clinical trial was conducted in GD3 patients; however, this study did not demonstrate any beneficial effect of this approach on the neurological symptoms.[25] The main advantage of miglustat treatment in GD patients is its oral administration. The main disadvantages are the side effects that include gastrointestinal dysfunction, tremors, and peripheral neuropathy, which is probably due to its nonspecific inhibitory effect on other enzymes, including the intestinal disaccharidases.[26] Therefore, its indication was limited only to adult GD1 patients with mild-to-moderate phenotype, in whom ERT is unsuitable (eg, hypersensitivity or poor venous access).[15]

Eliglustat tartrate is a newly developed SRT for GD, which is created to specifically inhibit GCS, with the aim to reduce substrate accumulation with limited side effects.

Eliglustat tartrate, preclinical studies

Genz-112638, lately called eliglustat is a synthetic analog of 1-phenyl-2-decanoylamino-3-morpholino-1-propanol formulated as a tartrate salt.[27,28] Its inhibitor activity toward GCS was detected in vitro by measuring the cell surface levels of glycolipids, showing high inhibition potency at nanomolar concentrations. Its specificity toward GCS was determined by testing its inhibiting activity on several different enzymes. Of note, even at low micromolar concentrations,

the compound did not display an inhibitory action on intestinal disaccharidase activities or lysosomal GCase.[29]

The safety and efficacy of eliglustat were first tested in a murine model of GD (gbaD409V/null mouse). Young presymptomatic mice were treated with 75 mg/kg/d or 150 mg/kg/d of Genz-112638, for 10 weeks, and then the measurement of GlcCer in mice tissues evidenced a significant dose-dependent substrate reduction in liver, spleen, and lung tissues and prevention of the Gaucher cell formation, when compared to untreated mice. Moreover, older symptomatic mice were treated with 150 mg/kg/d of the drug for 10 weeks, showing an inhibition of further accumulation of GlcCer, without gastrointestinal issues or other important side effects.[29] These important findings paved the way for the following human studies.

Eliglustat tartrate, clinical trials

Three Phase I trials on eliglustat tartrate, involving 99 healthy volunteers were published in 2011. With regard to safety, the drug was generally well-tolerated at single doses <20 mg/kg and multiple doses <200 mg twice daily. However, there was a warning for doses >10 mg/kg, because mild electrocardiogram modifications (with increase in PR, QRS, and QT/QTc intervals) were observed. Side effects included nausea, dizziness, and vomiting, which were exhibited in increased frequencies with the dosage. Considering pharmacokinetics, maximum plasma concentrations were achieved after 2 hours, with a half-life of around 6 hours. No changes in pharmacokinetics were observed with food ingestion. Notably, higher drug exposure was seen in slower CYP2D6 metabolizers, CYP2D6 being the main hepatic cytochrome involved in eliglustat catabolism.[16]

Following these results, a Phase II trial was initiated involving 26 naïve GD1 patients, 20 of whom completed the 2-year assessment and 19 completed the extended study with 4-year evaluation. Patients were treated with a dosage of 50 mg or 100 mg twice a day. After 2 years of treatment, significant improvement in four target parameters (platelet count, hemoglobin levels, spleen volume, and liver volume) was obtained. Considering the therapeutic goals for these four parameters established for ERT by Pastores et al in 2004, 90%–95% of patients met the criteria for hemoglobin, liver, and spleen and 60% patients for platelets.[30,31] After 4 years, an improvement was seen, with 100% of the patients meeting the therapeutic goals for hemoglobin level and spleen volume, 94% for liver volume, but only 47% for platelets. This minor therapeutic effect on thrombocytopenia is still unexplained, since there was no correlation with baseline

platelet level or splenomegaly. Remarkably, the most evident effect of eliglustat treatment was on spleen size (63% reduction after 4 years). With regard to bone pathology, the mean T-score for the lumbar spine increased after 4 years from the osteopenia range to the normal range, and femur MRI resulted in being stable. Results were also good for GD biomarkers, in fact chitotriosidase levels significantly decreased by 75% and 82% after 2 years and 4 years, respectively. One hundred and ninety-one adverse events were reported after 4 years, of which 74% were considered mild, and 95% were not drug related. Among those considered as being related to treatment, none was classified as serious.[32,33]

Subsequently, two Phase III studies[34,35] were conducted: the first (called ENGAGE) was a placebo-controlled trial involving 40 naïve GD1 patients in 12 different countries; the second was a noninferiority study (called ENCORE), comparing eliglustat to the standard treatment with imiglucerasi, which involved 160 patients belonging to 39 centers in the four continents. The latter was the largest prospective trial of any treatment for GD1. At the end of the ENGAGE study, after 9 months, comparing the eliglustat group with the placebo group: the mean spleen volume (the primary end-point) decreased by 30.3%, liver volume decreased by 6.64%, Hb level increased by 1.22 g/dL, and platelet count increased by 41.06%, with the largest improvement seen in the most severely affected patients. These results suggested a possible role of eliglustat as first-line treatment for GD1 patients, without prior amelioration of target parameters with ERT. No serious adverse events were reported, the main adverse events in the eliglustat group being arthralgia, nasopharyngitis, and headache. As expected, in the eliglustat group, substrate levels (glucosylceramide and GM3 ganglioside) decreased. Of note, an increase in sphingomyelin levels was detected, probably due to increased bioavailability of ceremide with treatment. However, its levels remained in the normal range.[34]

The results of the ENCORE study were recently published, and these demonstrated the noninferiority of eliglustat toward standard ERT (imiglucerase) in maintaining stable hematological parameters and organ volumes, after 1 year of treatment, in patients who had already achieved the therapeutic goals after being on ERT for at least 3 years. The noninferiority margin chosen by design was 25%. Interestingly, 94% of all patients expressed their preference for oral treatment when asked. The number of adverse events reported in the eliglustat cohort was higher than that in the imiglucerase group (656 vs 141), involving, respectively, 92% of patients compared to 79%. The authors explained

these differences by the fact that expected adverse events of imiglucerase typically occur in the first year of treatment, and the patients of this study were already on ERT for at least 3 years. The most common side effects deemed related to eliglustat were diarrhea (5% of patients), followed by arthralgia, fatigue, and headache. No significant effect of eliglustat on electrocardiogram was found. Given the results of this study, the authors suggested that eliglustat might be proposed as a maintenance treatment in patients who switched from ERT.[35]

Considering the above trials, eliglustat received the US Food and Drug Administration approval in August 2014, and more recently the European Union approval.

Discussion
The advent of the ERT for GD in 1990s changed the natural history of the disease, and this therapeutic approach is still considered as the standard of care for GD. ERT is effective in counteracting the peripheral symptoms, especially hepatosplenomegaly and hematological disturbances, with generally poor side effects. However, ERT has several limitations that prompted the development of new therapeutic strategies. First, ERT must be administered intravenously and, since it cures the symptoms but not the disease, it is required as a lifelong therapy. Regular frequent intravenous infusions for a lifetime can understandably affect patients' quality of life. Second, although ERT is usually well tolerated, some patients develop allergic reactions during infusions, which can contraindicate further treatment, or produce autoantibodies, which can decrease the efficacy of ERT in the long term. Third, it has no effect on central neurological symptoms, especially in type 2 and 3 forms, since the recombinant enzyme is a macromolecule, which is not able to cross the blood–brain barrier.[36] Furthermore, long-term complications of GD1, like an increased risk of malignancy, especially multiple myeloma, and association with parkinsonism, are emerging despite the classical therapy.[37]

SRT has the main advantage of being administered orally, increasing therefore the patients' quality of life. The first attempt of an SRT for GD with miglustat treatment did not achieve the expected results due to its low benefit–risk profile. The second available SRT, eliglustat tartrate, recently approved by USA and European regulatory agencies, seems to be more promising for GD1 treatment.

There are important structural differences between eliglustat and miglustat: the first resembles the ceramide moiety of glucosylceramide, while the second resembles the glucose moiety and, therefore, is less-specific as a GCS inhibitor.

Indeed, its inhibitory activity on different enzymes is considered responsible for its main side effects. The trials on eliglustat showed its effectiveness, both in naïve GD1 patients and in patients who switched over from ERT, in reaching and maintaining the therapeutic goals for visceral symptoms, with good safety. In fact, the reported side effects were generally mild, diarrhea being the most frequent, but was notably less frequent than what was experienced with miglustat (5% vs 80%).[26,31,34,35] Nevertheless, concerns exist about the use of eliglustat in patients with heart disease or arrhythmias, since a single dose ≥10 mg/kg (more than five times higher than the suggested therapeutic dose) caused electrocardiogram abnormalities in Phase I studies.[16] Although no cardiac events considered related to treatment were reported in clinical studies, it must be taken into account that patients with previously known cardiac diseases were excluded from clinical trials. Of note, both the USA and European Union regulatory bodies prescribing information includes warnings and precautions for eliglustat use in cardiopathic patients. To avoid high blood concentration of the drug, the dosage should be personalized on individual capacity to metabolize eliglustat (predictably analyzing the cytochrome CYP2D6 genotype), and patients who result in poor metabolizers should not be treated with this drug. Moreover, several medicines that can interfere with eliglustat metabolism must be avoided. Further safety concerns due to the poor data available on children and the unknown effects of the drug in the long term will be probably be clarified in the near future.

Besides the advantage of being administered orally, eliglustat may have other positive effects, when compared to ERT. Considering that eliglustat is a diffusible small molecule that can reach different organs and tissues, it has been hypothesized to play a possible role in addressing skeletal, pulmonary, and other systemic manifestations that are refractory to ERT, which selectively targets macrophages.[33,35] Eliglustat seems, in fact, to be promising in preventing the development of monoclonal gammopathy and multiple myeloma, with a proven effect on controlling clonal B cell expansion in GD mice; although studies on humans are needed to confirm this potential effect.[38]

Since eliglustat does not inhibit glucosylceramidase activity, it is also possible to hypothesize a combined therapy, ERT with SRT, for those cases who do not respond properly to ERT alone or in poorly compliant patients, to try to reduce the frequency of ERT infusions. However, a combined effect has not been studied.

Considering that eliglustat inhibits the first limiting step in the glycosphingolipid biosynthetic pathway, other lysosomal disorders associated with the accumulation of complex glycosphingolipids could benefit from eliglustat treatment. Unfortunately, since it does not cross the blood–brain barrier, its potential effect would be limited in glycosphingolipid disorders, such as Tay Sachs or Sandhoff disease, whose pathology is mainly neurologic. Other analogs of 1-phenyl-2-decanoylamino-3-morpholino-1-propanol, which are able to reach the central nervous system, are under evaluation for these disorders, and could potentially be helpful also for GD2 and GD3.[39]

The main limitation for both ERT and SRT is their effect only on the consequence of the disease and not on the disease itself. To completely counteract the disease, other approaches have been tried, such as bone marrow transplantation, or are under study, such as gene therapy or combined gene therapy and stem cell transplantation. Bone marrow transplantation has been performed in severe affected GD patients. However, it requires human leukocyte antigen-matched donors and its correlated morbidity and mortality are still high.[40] Gene therapy has the advantage of being a one-off procedure, curing the origin of the disease. Unfortunately, several attempts in the past failed to find safe gene vectors. However, the use of self-inactivating lentiviral vectors carrying the *GBA1* gene under the control of human promoters has recently been successfully experimented with in mice and a study on humans is required to confirm the safety of this approach.[41]

Finally, it must be considered that all therapies available for GD until now (both ERT and SRT) are costly and difficult to be performed, and so their availability is limited worldwide.

Conclusion

SRT is an alternative treatment strategy for GD, with the main advantage being that it is administered orally. Eliglustat tartrate seems to be a promising SRT for GD, although its long-term efficacy and safety need to be further defined.

Disclosure

The authors report no conflicts of interest in this work.

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