Therapy of adult Gaucher disease

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Gaucher disease, the most common lysosomal storage disease, is caused by an autosomal-recessively inherited deficiency of glucocerebrosidase. The inability to cleave glucosylceramide into glucose and ceramide leads to a slow transformation of macrophages into storage cells, evident as *Gaucher cells* in bone marrow aspirates. Long-term accumulation of Gaucher cells in liver, spleen and bone marrow and other parenchymal organs leads to hepatosplenomegaly, anemia, low platelet counts and devastating bone disease. The standard therapy for adult visceral Gaucher disease is enzyme replacement therapy (ERT). After being introduced in 1991, currently more than 4500 patients world-wide are receiving macrophage-targeted glucocerebrosidase for treatment. The focus of this article is a summary of established, probable and anecdotal effects of therapy in type I Gaucher disease, the most frequent adult visceral form of the disease. Safety and failures of ERT and economic problems of this therapy are considered. Ways to provide reasonable management of ERT, as indicated in an article by de Fost *et al*. published in this issue of the journal,[1] are outlined. Other therapeutic approaches, such as substrate deprivation therapy are discussed and the most burning scientific issues in Gaucher disease are briefly indicated. The current article might help clinicians to be alert to atypical manifestations of the disease and help establish sound clinical use of the expensive and effective molecular-based therapy.

Principles of ERT and safety of imiglucerase

Following the identification of a deficiency of glucocerebrosidase as being the pathogenetic basis of Gaucher disease,[2] the proof of principle for ERT was made in 1990 by Brady and colleagues[3] and confirmed in a series of 12 Gaucher patients.[4] After the native purified glucocerebrosidase[5] had been shown to fail to produce a sustained clinical response in Gaucher patients,[6] the native enzyme was digested by sialidases leading to a mannose-terminated form of the enzyme which was recognized by macrophages. In the end, this approach was found to be clinically effective. After initial purification of the enzyme from human placenta, in 1997 the mannose-terminated enzyme was synthesized by recombinant gene technology. The recombinant enzyme has the same efficacy as the original enzyme, but has the advantage of being free of potential pathogenic contaminants.[7] Today, about 4500 patients world-wide are treated with ERT (*J. Yee, Genzyme corporation, personal communication*). Usually, the enzyme is given intravenously over a period of 1-2 h every other week at doses varying between 10-120 U/kg body weight, depending on the severity of the disease, the stage of treatment and economic considerations in the country of use, as discussed later. The therapy is well tolerated, with side effects usually being both rare and mild.[8] Local reactions can occur, and ERT may be associated with inadequate weight gain in some patients. The exact reason for this is not known, but it is known that the untreated disease is associated with increased resting energy expenditure[9] and that the therapeutic decrease of spleen size is associated with a loss of early satiety. Between 1994 and 2005, IgG antibodies to imiglucerase were detected in approximately 15% of treatment-naive patients, although these usually did not affect efficacy of the infused enzyme.[8] Still today, one unit of the enzyme costs an equivalent of about €6, making Gaucher disease one of the very expensive treatable orphan diseases, with annual costs averaging €75,000 to 300,000 or more per patient.

In view of this, therapeutic goals, based on realistic expectations, must be defined in each individual patient.[10] Ways to provide reasonable management of enzyme supplementation therapy must be defined. What can be expected when a patient is put on therapy? This perspective article is based on a review of the approximately 400 papers on ERT published to date. It has subjective bias with the expressed purpose of incorporating some studies on rare manifestations of the disease. The complicated field of progressive neuronopathic forms of the disease, i.e. type II and type III, is largely excluded, but it should be highlighted that neurologic manifestations are frequent also in so-called type I patients, even in the absence of the L444P mutation, and can, in the end, determine the severity of the disease in the single patient.[11]

Established effects of ERT

ERT leads to improvement of subjective symptoms, prevents progressive manifestations of Gaucher disease and alleviates Gaucher disease-associated anemia, thrombocytopenia, organomegaly, bone pain and bone crises. An overview of the established effects of ERT is given in Table 1. The documented outcome of therapy has been investigated in a few controlled studies, some retrospective analyses of extensive patient cohorts, some large-scale studies drawing on the International Gaucher Registry (ICGG) and many case reports. A representative cross-section of the essence of research on ERT is given in Tables 1[3,4,7,12-23] and 2.

Other documented effects and failures of ERT

Besides the frequent and clearly established effects of ERT, some additional effects can be expected, in Gaucher patients who present with unusual manifestations of the disease. In brief, many systemic manifestations seem to

Table 1. Established effects of enzyme replacement therapy.

Symptomatic
Decreased epistaxis and easy bruising
Alleviation of abdominal distension and early satiety
Decreased exertional dyspnea and fatigue
Decreased need of analgesics
Hematologic
Increased hemoglobin and platelet levels
Visceral
Decreased liver and spleen volume
Avoidance of new splenic infarctions
Partial decrease of Gaucheromas (pseudo-Gaucher tumors)
Skeletal
Decreased bone pain
Decreased probability of new pathologic fractures
Prevention of bone crises
Improvement of bone mineral density in adult and pediatric patients
Improvement of bone marrow involvement
Increase in cortical bone thickness
Children
Normalization of growth
Functional health
Improvement of quality of life
Improvement (or restoration) of physical function for carrying out normal daily activities
Surrogate parameters and biomarkers
Decreased serum tartrate-resistant acid phosphatase (TRAP)
Decreased serum angiotensin-converting enzyme (ACE)
Decreased serum ferritin
Decreased plasma chitotriosidase
Decreased hepatic glucocerebroside
Decreased plasma glucocerebroside
Increase of signal intensity in magnetic resonance images of bone marrow

respond quite well to infusional therapy, with two exceptions: first, neurologic manifestations do not usually improve during ERT and second, if the level of fibrosis/inflammation has led to irreversible destruction of tissue, there will be no response to ERT. Examples are bone infarctions, a completely fibrous spleen, established pulmonary hypertension or liver cirrhosis. If any of these conditions is present or a deterioration of the disease occurs, investigations for amyloidosis, as a secondary complication of Gaucher disease, must be made.[24] A list of documented failures of ERT is given in Table 3. Some of the documented failures in the past might have resulted from inadequate dosages. It must be emphasized that, in contrast to other systemic manifestations of the disease, the neurological signs of Gaucher disease, especially type II and type III, do not respond adequately to enzyme supplementation therapy. This reflects a lack of understanding of the molecular basis of neurological Gaucher disease. As glucosylceramide-storing macrophages are not present in most parts of the central nervous system, direct effects of Gaucher-associated neurotoxins, such as glutamate[25] and psychosine, or other excitotoxic mechanisms predisposing nerve cells to glucocerebroside toxicity are discussed.[26]

Table 2. Documented additional effects of enzyme replacement therapy.

Category	*Effect*	*Reference*
Lung	Improvement of pulmonary involvement	49
	Resolution of ground-glass appearance in high resolution computed tomography of the lung	50
Blood	Improvement of monoclonal and polyclonal gammopathy	51,52
	Resolution of antiphospholipid syndrome	53
	Improvement of coagulation abnormalities	54
	Improvement of platelet dysfunction	54
Pregnancy	Uneventful pregnancy during ERT	55,56
Infectious	Decrease in number and severity of bacterial infections in children	57
	Resolution of multiple foci of osteomyelitis and soft tissue abscesses	58
	Correction of neutrophil chemotaxis defect and tendency to infections	59
Bone	Improved outcome of total hip arthroplasty	60
	Improvement of thoracic kyphosis	61
	Resolution of metaphyseal deformity	62
	Decrease of Gaucher cell burden in bone marrow	63
	Resolution of erosive changes in proximal humerus	64
Liver	Clearance of Gaucher cells from liver	65
	Delayed progression of hepatic fibrosis and cessation of variceal hemorrhage	66
	Decrease of elevated aminotransferases in adults	67
Kidney	Resolution of nephrotic syndome	68
Heart	Resolution of impaired cardiac function	69
Eyes	Reversal of loss of vision by ocular Gaucher pseudotumor	70
Biomarkers	Decrease of serum neopterin, adenosine deaminase and ß-hexosaminidase	71
	Decrease of serum pulmonary and activation-regulated chemokine (PARC/CCL 18)	72,73
	Correction of eosinophilia, if present	74
	Decrease of total plasma lipid, apolipoprotein (APO) A- and HDL-C	75
	Decrease of urinary oligosaccharide excretion	76
	Increase of calcium/creatinine urinary ratio	77
	Increase of functional activity and decrease of O2- generation of monocytes and macrophages	78
	Decrease of serum cathepsin activities	79
	Increase of total serum IGF-I, free IGF-I and IGFBP-3	80
	Improvement in antioxidant capacity of red blood cells	81
	Correction of decreased plasma taurine	82

The list includes some further probable ERT effects on Gaucher manifestations with a limited database in the literature. Although being reflected only by a smaller number of observations, the named manifestations are more likely to respond than to fail upon administration of ERT. At least one representative publication is given for each individual item.

Management of patients on ERT

Treatment of Gaucher disease by ERT differs from that of type 1 diabetes mellitus with insulin. As the pathophysiology of Gaucher disease is thought to result mainly from lipid accumulation, the initial therapeutic strategy aims to decrease the amount of Gaucher cell burden as

Table 3. Some documented failures of enzyme replacement therapy.

Symptom	*Reference*
Fibromyalgia	83
Xerostomia and low salivary output	84
Uveitis	85
Amyloidosis	24
Osteonecrosis	86
Avascular necrosis of the femoral head	87
Hepatomegaly, hepatic fibrosis and elevation of liver enzymes in a child	88
Bone infarcts	89
Pathologic fractures	90
Diffuse reticular nodular lung pattern	91

Therapeutic failures can occur in any of the categories listed in Tables 1-3, but likelihood is low or moderate for those listed in Tables 1 and 2.

fast as possible. After stabilization of the disease, the enzyme dose that is capable of controlling symptoms and preventing further reaccumulation of glucocerebroside should be sufficient. The enzyme dose must, therefore, not only to be adapted to the severity of the disease in the individual,[27] but also to the stage of disease treatment. The treatment phases are: *initiation*, followed within 6-12 months by an *adaptation* phase in which dose adjustments are made to reach optimal symptom relief, therapeutic progress and surrogate parameter control. After *stabilization* of the disease process, which usually takes a couple of years, the enzyme dosage can be decreased (*tapering*), to reach a stable dose that the patient receives for the rest of his or her life (*maintenance*).

The most effective dosing regimen of ERT is still a matter of debate. Advocates of low dose regimens draw attention to the extremely high costs of the enzyme, in the absence of convincing evidence for clinical superiority of high doses.[28] Others argue that high doses are required for optimal effect in severe disease, especially bone disease or in children.[29] Different approaches have been used to manage ERT, comparable to the medical management of Crohn's disease.[30] One strategy could be called *top-down*, with the dose being relatively high at the beginning and then subsequently tapered down to reach a maintenance phase. The other strategy could be called *step-up*, with the dose being relatively low at the beginning, and then being increased, if necessary, during the course of the disease. Both approaches have been compared in a recent study.[22] Although showing similar results for hematologic and visceral parameters, a higher dose was more effective in improving surrogate parameters such as chitotriosidase and bone marrow involvement. There are very few data on tapering, but there is some evidence that sudden cessation of therapy is generally not advisable, since rebound phenomena can occur.[31,32] In a paper published in this issue of the Journal,[1] de Fost *et al*. show that, in stable patients, the simple sudden reduction of the frequency of administration of the enzyme from weekly/biweekly infusions to a single monthly infusion, with a stable cumulative dose per month, can result in therapeutic failure in a subset of patients. The determinants of treatment failure in these patients are not known. In a different study from Spain, after 2-3 years of initial biweekly ERT treatment, infusion intervals were prolonged to 3 weeks with a 33% reduction of the monthly average dose.[33] Within a couple of years, all patients had to resume the original ERT schedule, due to symptomatic relapse of the disease.

Substrate deprivation therapy

Miglustat (Zavesca, N-butyldeoxynojirimycin, OGT 918) was introduced 6 years ago. This compound inhibits glucosylceramide synthase, preventing new synthesis of glucosylceramide on top of accumulated lipid. This therapeutic approach is called substrate reduction therapy. There are currently fewer than ten original clinical studies on miglustat published in the literature. These studies show that miglustat is effective in most patients with mild and stable disease at controlling at least hematologic and visceral parameters.[34-39] Miglustat is less well tolerated than ERT, mostly due to diarrhea and weight loss by drug-induced inhibition of intestinal lactases, which resulted in a significant drop-out rate from trials. Concerns about miglustat-induced cognitive impairment have been laid to rest recently.[40] The impact of miglustat, which crosses the blood-brain barrier, on neurological types of Gaucher disease is still under investigation. In Europe, miglustat is licensed for patients who cannot receive standard ERT.

Future issues in the therapy of Gaucher disease

Nearly 200 mutations in glucocerebrosidase have been described, but for the most part, genotype-phenotype correlations are weak, and little is known about the downstream biochemical changes that occur upon glucosylceramide accumulation and that result in cell and tissue dysfunction.[41] There is now consensus that the presence of the L444P mutation, at least on one allele, is required in patients with a progressive neuronopathic form of the disease: type II (acute neuronopathic) and type III (chronic-neuronopathic). To improve delivery of glucocerebrosidase to cells without mannose-specific endocytic receptors on the plasma membranes, recombinant glucocerebrosidase containing an in-frame fusion to the HIV-1 trans-activator protein transduction domain (TAT) was expressed in eukaryotic cells. There was a significant expression of enzyme within these cells and TAT-modified forms of glucocerebrosidase could represent a novel strategy for a new generation of therapeutic enzymes.[42] Another novel therapeutic option is the use of more specific small molecules that either inhibit substrate synthesis (substrate deprivation) or act as a chaperone to increase the residual activity of the lysosomal enzyme (enzyme enhancing therapy) as reviewed by Sawkar *et al*.[43] Although various gene therapies have been developed for administration of the defective gene to the bloodstream or directly to the brain, as reviewed by Beck *et al*.,[44]

the near-future perspective remains life-long ERT or, for some patients, oral substrate deprivation therapy. Gaucher disease has been shown to be associated with a higher risk of cancer[45-48] and it will be interesting to see whether this risk can be reduced by ERT. It will also be challenging to determine, from studies based on the Gaucher registry, whether type I Gaucher patients have a decreased life expectancy and whether this can be significantly affected by therapy.

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