Lysosomal Storage Disease 1

Phenotype, diagnosis, and treatment of Gaucher’s disease

Gregory A Grabowski

Gaucher’s disease continues to be a model for applications of molecular medicine to clinical delineation, diagnosis, and treatment. Analyses of several thousand affected individuals have broadened the range of the pan-ethnic disease variants, provided initial genotype and phenotype correlations, and established the effectiveness of enzyme therapy. Large numbers of affected individuals worldwide have provided insight into the effect of disease variation related to ethnic origin, prognosis, and outcome. The ability to safely and effectively use enzyme therapy to inhibit or reverse visceral-disease progression and involvement has provided impetus for design of new enzyme therapies, and creation of substrate depletion and pharmacological chaperone strategies. Such innovations could provide interventions that are effective for neuropathic variants and, potentially, could be more cost effective than other treatments. These developments are novel, clinically important, advancements for patients with other lysosomal storage diseases and genetic diseases.

Introduction

Gaucher’s disease, the most common lysosomal storage disease, is an autosomal recessive trait, and has three classic variants (table 1). It was the first lysosomal storage disease to be described and has served as a model for the development of specific therapies for monogenic traits.1 Gaucher’s disease is caused by the insufficient activity of the lysosomal enzyme α-glucosidase (glucocerebrosidase, Enzyme Commission number 4.2.1.25), and has resulted in the lysosomal accumulation of its main substrate, glucosylcerebrosides. This insufficient activity results from the detrimental effects of more than 300 mutations in the GBA gene on glucocerebrosidase’s catalytic function, intracellular stability or subcellular trafficking, or both.2–7

The excess accumulation of glucocerebrosides in macrophages is the main manifestation in the visceral organs of affected individuals.8 This accumulation leads to hepatosplenomegaly, anaemia and thrombocytopenia, bone involvement, and, less commonly, lung features, and many inconsistent clinical manifestations,9 by poorly understood mechanisms. These visceral manifestations are common to all variants of Gaucher’s disease, but categorical differentiation into neuronopathic (types 2 and 3) and non-neuronopathic (type 1) variants serves useful clinical purposes. Because of the primary visceral macrophage involvement in type-1 disease, this variant has become a focus for the development of enzyme therapy by targeting intravenous administration of enzyme to the macrophage.7 Patients with such disease can have secondary neurological involvement.9 This review will focus on new developments in clinical classification, pathophysiology, diagnosis, and management of Gaucher’s disease to elucidate areas of unmet medical need. Comprehensive reviews of all aspects of Gaucher’s disease are available.3,10–14

Epidemiology and clinical classification

Gaucher’s disease is a pan-ethnic disorder that has had major focus in developed countries with populations of European origin. In particular, the high frequency of Gaucher’s disease type 1 in the Ashkenazi Jews (about one in 800 livebirths) has led to characterization of disease phenotypes mainly on the basis of that population.9 However, the growing recognition of substantial populations with type 1 disease in Asia, South America, the Indian subcontinent, and other demographic areas is broadening our appreciation of the range of phenotypes in this variant. Similarly, with the broader recognition of types 2 and 3, widespread variation and range of involvement from early onset has become increasingly evident.15,16 The overall frequency of Gaucher’s disease variants is about one in 40 000 to one in 50 000 livebirths. The only comprehensive population analysis was done in Australia in a predominantly white population of European origin, with a frequency of about one in 40 000.17 The general frequencies of any of the variants in large populations of China, India, Indonesia, the Middle East, or Africa are unknown.

The availability of a large comprehensive database from the International Collaborative Gaucher Group (ICGG) has helped in the analyses of large numbers of patients at baseline—ie, before they begin enzyme therapy. The ICGG database is a registry that mainly focuses on type 1 disease, and thus, the most extensive analyses can target that variant, with lesser contributions to types 2 and 3. This database contains entries of more than 5000 affected individuals submitted by more than 700 physicians. Most patients have sufficiently severe disease to have been treated with enzyme replacement therapy at least once. This is the first in a Series of three papers about lysosomal storage disease.

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Search strategy and selection criteria

Medline (from 1963 to 2006) and the American Society for Human Genetics Abstract Series presentations (2006) were searched for “Gaucher’s disease”, “Gaucher disease”, “glucocerebrosidase”, “glucosylceramide”, “glucosyl-ceramide glucosidase”, “enzyme therapy”, “enzyme replacement therapy”, “lysosomal storage disease”, “chaperone”, “pharmacologic chaperone”, “substrate reduction therapy”, “deoxynojirimycin”, and “imino sugar”. Additionally, relevant books were also used. Only articles in English were read completely. Abstracts in French and German were read.

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prescribed specific treatments, but more than 1000 type 1 patients in the database are not on enzyme or substrate-reduction therapy. Data for many mildly symptomatic individuals would not be in this database, and most longitudinal data for such patients would indicate a slower or minimum progression than might be expected from those who have sufficiently severe disease to be placed on specific treatments.

Phenotype conclusions that rely on these data are based on all patients who have type 1 disease with intact livers and spleens. Comprehensive analyses of this database are also skewed to the populations of patients in Europe, the USA, and Israel who are predominantly Ashkenazi Jews.4 With these caveats, the following conclusions are evident. First, about 55–60% of type 1 patients are diagnosed before 20 years of age. Although type 1 disease had been designated as adult Gaucher’s disease, this classification is clearly not the case, since most symptomatic patients are diagnosed before they reach adulthood. Indeed, about 30% of such patients are diagnosed before 10 years of age.4–8 Second, greater degree of involvement of visceral organs, especially liver and splenic enlargement, occurs in the youngest patients; lesser degrees of organ enlargement occur in adults. Third, anaemia or thrombocytopenia, or both, are present in less than 50% of affected patients in the registry. Consequently, the notion that type 1 disease is a mainly haematological disorder needs re-examination. Last, about 80–90% of patients at any age have some degree of bone manifestations including distal femoral deformities (Erlenmeyer’s flask deformities), lytic lesions, osteopenia or osteoporosis, or bone pain or crises. Additionally, about 35% of children with type 1 disease had significant growth retardation.8

Thus, on the basis of such data, a range of symptomatic Gaucher’s disease type 1 has evolved from adult-onset disorders with major haematological and bony manifestations to childhood disorders, with mainly visceral and bony involvement.9 This recognition of the phenotype variation, even in European-based populations, has important implications for the development of health-care systems and for treatment. As larger groups of patients with type 1 disease are characterised in populations that are non-European in origin, the range of phenotypes will increase in scope and variation—e.g., types 2 and 3 are the neuronopathic variants that represent various CNS diseases, ranging from onset in the neonatal period to the first overt manifestations in the second to third decades.24–26 Clinically, retention of the terms types 2 and 3 helps in prognosis and counselling of families about longevity and potential disability, but might well represent variations of a similar pathobiological process or processes.21

The most severe end of the range is type 2, which presents in the first few days to months of life with substantial CNS involvement, especially with bulbar signs and oculomotor paresis. A perinatal and lethal variant of type 2 disease presents in the newborn baby or with fetal hydrops, and is lethal within the first weeks of life.11,22 The classic type 2 disease has rapid progression of CNS disease with a median age of death at 9 months.25–27 By comparison, type 3 disorder can arise in the first year of life with isolated saccadic initiation deficits, but usually without bulbar signs. One variant, termed type 3b, can have severe visceral findings with mild progression of the CNS involvement for 10–20 years.28 Another variant, termed 3a, presents with mild visceral involvement, but with severe progressive myoclonic seizures leading to death within the first two decades.29

A unique variant of Gaucher’s disease type 3 is associated with the genotype D409H/D409H, and such patients have hydrocephalus, corneal opacities, and characteristic aortic valvular and ascending aortic calcifications.30 Thus, the range of neuronopathic variants in Gaucher’s disease has broadened substantially from that in table 1. The characterisation of populations in Asia, particularly the Indian subcontinent, and Africa will continue to broaden this range, as it has in type 1 disease. Our appreciation of a broad range of abnormalities will determine both public policy and decision making about treatments. Furthermore, the development of well characterised phenotypes will allow direct comparisons of treatment outcomes in populations, so that the assessments of any interventions can be based on similar phenotypes.

Pathophysiology

The insufficient catabolism of glucosylceramide and the engorgement of macrophages by this substrate lead to visceral manifestations of Gaucher’s disease, but the mechanisms by which systemic and organ-specific involvement are propagated or initiated remain unclear. Two major pathophysiological mechanisms that account for macrophage activation are under investigation. The most obvious candidate for a pathological initiator is the excess accumulation of glucosylceramide. Sphingolipids have been implicated in inflammatory and apoptotic processes,26–29 and glucosylceramide might have direct activating or enhancing effects on macrophage function,30 possibly mediated through selective calcium-channel dysregulation.31

Indeed, several indicators of macrophage activation—including chitotriosidase, CCL18, angiotensin-converting enzyme,23–25 and cathepsin S—have been identified in

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
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<tbody>
<tr>
<td>Age at onset</td>
<td>Childhood or adulthood</td>
<td>Infant</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>– – – –</td>
<td>– – – –</td>
</tr>
<tr>
<td>Bone disease</td>
<td>– – – –</td>
<td>– – – –</td>
</tr>
<tr>
<td>Neurodegeneration</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Age at death</td>
<td>Childhood or adulthood</td>
<td>Median 9 months</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td>Pan-ethnic or Ashkenazi Jews</td>
<td>Pan-ethnic</td>
</tr>
</tbody>
</table>

Table 1: Classic nosology for Gaucher’s disease

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excess in plasma of patients with Gaucher’s disease. Histological assessment showed that such pro-inflammatory molecules, including tumour necrosis factor α, are variably increased in some splenic Gaucher cells. However, the absence of tissues from these patients has restricted such investigations. Work with mouse models of Gaucher’s disease has shown a signature pathway that is associated with the interferon γ and interleukin 4 pathways—ie, the classic and alternative activation of macrophage pathways are both altered in this disease. Although additional investigation is needed, the association of these pathways in the propagation of and tissue damage in Gaucher’s disease provides the theoretical basis for alternative or additional adjunctive treatments.

An alternative mechanism by which these pro-inflammatory and anti-inflammatory pathways could be activated is through abnormal folding of mutant proteins in the endoplasmic reticulum. Such abnormal folding initiates an unfolded protein response that can trigger apoptotic or inflammatory pathways in various tissues. Evidence suggests that some mutations in Gaucher’s disease might lead to proteins that are abnormally folded or are maltrafficked, or both. Although direct evidence of unfolded protein response involvement is not available for Gaucher’s disease, this pathway seems to be active in GM1 gangliosidosis. These pathways are of notable interest in many disorders, including Parkinson’s disease, Alzheimer’s disease, and other neurodegenerative disorders. Thus, the potential for development of alternative agents to alter the unfolded protein response could be on the horizon for patients with Gaucher’s disease in whom this mechanism is activated.

By comparison with visceral tissues, the pathogenesis of the brain disease is completely different. As opposed to massive glucosylceramide storage in visceral macrophages, neuronal death is the major pathogenic pathway for CNS variants. The exact CNS pathogenesis is unclear, but massive glucosylceramide accumulation does not seem to be critical. A toxic reaction to a low-level substrate, glucosylphingosine, might be the inciting mechanism. This mechanism has come under question, since glucosylceramide seems more important than glucosylceramide or an abnormal folding of specific-mutant proteins in specific regions of the brain and an unfolded protein response is not known. This association of Gaucher’s disease alleles (homozygotes or heterozygotes) and Parkinsonism is weak and quite controversial, but the apparent over-representation of these alleles in the brains of patients with Parkinson’s disease suggests a stronger association than might have been appreciated from epidemiological data. The epidemiological association could be seriously questioned because of population bias, and additional data are needed. If such associations continue to become stronger, alternative approaches to treatment will need to be considered not only for neuronopathic variants, but also for type-1 variants.

**Diagnosis**

DNA testing has improved diagnostic accuracy in Gaucher’s disease not only for affected individuals, but also for the detection of carriers. Detection of insufficient enzyme activity is the gold standard for the diagnosis of patients with all variants of Gaucher’s disease. This diagnosis can be done in any nucleated cell source, but peripheral blood leucocytes or cultured skin fibroblasts are the most common sources. Although DNA sequencing can identify sequence variants in GBA, enzyme diagnosis is still needed to show the association of new nucleotide variants with enzymatic deficiency. Many of the more than 300 GBA mutations are restricted to single families. By comparison, enzyme testing for carrier status with peripheral blood leucocytes has substantial (20–30%) false negatives and false positives, which are not useful clinically. DNA diagnosis, by whole gene sequencing or selective sequencing within families, provides improved accuracy for carrier detection, and is therefore recommended for family testing.

The identification of causal mutations for Gaucher’s disease provides the opportunity to develop genotype and phenotype correlations for prognostication. So far, use of genotype information for clinical outcome in Gaucher’s disease has become useful in two circumstances. The first is correlation with Gaucher’s disease type 1—ie, non-neuronopathic disease. The N370S allele in affected individuals, even in combination with a different GBA mutant allele, is predictive of non-neuronopathic (type 1) Gaucher’s disease. The second circumstance is correlation with neuronopathic Gaucher’s disease. Various alleles containing the L444P substitution are strongly, although not exclusively, associated with the development of neuronopathic disease. Many of these GBA alleles contain additional mutations and are termed complex alleles, with serious clinical implications. Indeed, the combination of two complex alleles, or a complex allele and the L444P allele, are strongly associated with type 2 disease. By comparison, L444P homozygosity is strongly associated with type 3 variants. Because of the presence of these complex alleles, and the much rarer finding of additional nucleotide substitutions on the N370S alleles, full gene sequencing of GBA is now the standard for mutation analysis in Gaucher’s disease. Once mutations and alleles are characterised in a family, further direct tests can be developed at reduced cost.
The figure and table 2 provide age at diagnosis and recognition correlations with the disease or recognition are more uniformly spread, and in combination with other mutant alleles. Clearly, homozygote individuals with the N370S allele are diagnosed or recognised one to three decades later than are affected individuals with the other genotypes. Diagnosis is by a laboratory test verifying or proving the presence of a disease, but diagnosis is not confirmed until proven by laboratory testing. The figure clearly shows a broad distribution of ages at diagnosis or medical recognition of these patients. The N370S/N370S patients’ ages at diagnosis or recognition are more uniformly spread, whereas the remaining genotypes show substantial clustering and skewing at younger ages. However, the broad ranges of involvement, as seen in age at diagnosis, make individual prognostication difficult for all genotypes. This prognostication is most difficult for the N370S/N370S genotype, since at least half of such patients never come to medical attention.

Other phenotypical manifestations, including liver and splenic volumes and degree of bony involvement, show similar correlations with the genotypes. The implication is that early onset disease is more severe and more progressive than late onset disease, and probably needs early intervention to prevent later disease manifestations. As noted previously, about 50% of N370S/N370S homozygote individuals are symptomatic and inappropriately represented in this assessment. Continued analyses of such data will be needed for additional patient populations from different demographic regions. Data from Brazil and Poland show differential degrees of involvement in patients from those populations compared with those from other demographic or ethnic groups. Such broad-based and demographic-specific data can provide clinical guidance for the initiation of treatment and for preventive measures of affected patients. Such data also show the confusion of limited genotype or phenotype correlations and their limited application to prenatal testing in families whose only exposure to Gaucher’s disease is through screening programmes. As noted previously, D409H homozygote individuals have a unique phenotype whose full range of involvement awaits description. Certainly, a broad range of involvement would be expected within this genotype.

**Management and treatment**

Since 1992, enzyme therapy has become the standard of care for the treatment of individuals with severe Gaucher’s disease. Additionally, this disease has become a model for the development of substrate reduction, pharmacological chaperone, and gene therapies. During the past one and a half decades, regular infusions of mannose-terminated glucocerebrosidase have proved to provide clinical guidance for the initiation of treatment and for preventive measures of affected patients. Such data also show the confusion of limited genotype or phenotype correlations and their limited application to prenatal testing in families whose only exposure to Gaucher’s disease is through screening programmes. As noted previously, D409H homozygote individuals have a unique phenotype whose full range of involvement awaiting description. Certainly, a broad range of involvement would be expected within this genotype.

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produce regression in many or most of the visceral manifestations in Gaucher’s disease. The safety and effectiveness in the reduction or elimination of anaemia, thrombocytopenia, and hepatosplenomegaly have been shown in a large case series. Such treatment data provide the basis for therapeutic goals to aid physicians in the management of these patients. These goals have quantitative endpoints and timelines for achievement. Existing guidelines and goals will be revised on the basis of additional new data as they become available, but are summarised in table 3. These goals or guidelines were developed by clinicians with extensive and broad-based experience in the care of patients with Gaucher’s disease after a comprehensive review of the published work on enzyme therapy outcome and personal experience. Although these goals are based on results of enzyme therapy, they are clearly applicable to other agents that are or will be used for the treatment of Gaucher’s disease. Additionally, these guidelines provide methods for assessment of various disease manifestations as patients respond to treatment.

The expense of available enzyme and substrate-reduction therapies for Gaucher’s disease (US$100 000 to >$200 000 per year) makes judicious use a necessity. The rarity of Gaucher’s disease has inhibited large-scale randomised dose-finding studies and, therefore, much controversy has developed about the appropriate dose and dosing schedules for effective treatment. Studies with larger numbers of patients have begun to address this issue scientifically, but additional data will be needed.

Groups of treated patients from Amsterdam (Netherlands) and Düsseldorf (Germany) were compared as low-dose and high-dose populations, respectively, for enzyme therapy. The high-dose group had a somewhat better response of the bone marrow burden scores and reductions in bone marrow and the biomarker chitotriosidase than did the low-dose group. Efforts to match patient characteristics in this study were only partly successful, but they provided an initial approach to assess comparisons between dosage groups. A larger study of 366 patients in three dosing groups (122 patients per matched group) from the ICGG database who were matched more rigorously for degrees of involvement, were compared for dose-response characteristics of anaemia, thrombocytopenia, and hepatosplenomegaly. Patient matching was achieved with propensity scores in an effort to simulate a randomised controlled trial, and the matched groups were modelled with non-linear mixed methods. The goal of propensity scoring methods is to reduce bias in the analyses of observational data for treatment effect by matching different groups that have similar distributions of initial disease characteristics. In this study, robust incremental differences in responses to enzyme therapy were seen between each group at 15, 30, and 60 U/kg over 2 weeks. The responses were directly related to dose. The initial response was more rapid in the higher-dose group (60 U/kg) than in the other groups, and the final (after 60 months) increases in haemoglobin and platelet concentrations or decreases in hepatic and splenic volumes were greater in the group given 60 U/kg.

A similar dose-response trend was detected in less rigorously matched patient groups for improvements in bone-mineral density as assessed by dual-energy X-ray absorptiometry. These improvements need much greater treatment times of 4–8 years. Such quasi-controlled large studies might be the only option to simulate true-controlled studies for rare diseases, and could provide some guidance for the treatment of patients with varying degrees of involvement. It should be noted that the effect of enzyme therapy on Gaucher’s disease of the lung (pulmonary hypertension or interstitial or alveolar disease) has not been rigorously demonstrated. The CNS and lymph nodes seem to be inaccessible to intravenously administered enzyme that is mannose terminated. With the use of such data and improved stratification of doses, more effective and perhaps more cost-effective treatment strategies and clinical recommendations can be developed for severely affected individuals. The completion of an improved severity scoring system that is sensitive to clinical effects of treatments would help additional analyses and

### Table 3: Treatment goals for Gaucher’s disease type 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Time to achieve</th>
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<tbody>
<tr>
<td><strong>Anaemia</strong></td>
<td></td>
</tr>
<tr>
<td>Improve and maintain haemoglobin at normal values (age, sex-dependent levels)</td>
<td>12–24 months</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
</tr>
<tr>
<td>Increase and maintain platelet count sufficient to avoid bleeding difficulties</td>
<td>12 months</td>
</tr>
<tr>
<td>(1) Splenectomised patients—normalise</td>
<td>12 months</td>
</tr>
<tr>
<td>(2) Intact spleen— increase 1.5–2 fold, and then to low normal</td>
<td>12–24 months</td>
</tr>
<tr>
<td>(3) Avoid splenectomy</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatomegaly</strong></td>
<td></td>
</tr>
<tr>
<td>Decrease and maintain liver volumes at 1·0–1·25 normal volumes</td>
<td>12–25 months</td>
</tr>
<tr>
<td>(1) Decrease by 20–30%</td>
<td>About 36 months</td>
</tr>
<tr>
<td>(2) Decrease by 30–40%</td>
<td></td>
</tr>
<tr>
<td><strong>Splenomegaly</strong></td>
<td></td>
</tr>
<tr>
<td>Decrease and maintain spleen volume &lt;2–8 times normal volumes</td>
<td>12 months</td>
</tr>
<tr>
<td>(1) Decrease by 30–50%</td>
<td>About 24–36 months</td>
</tr>
<tr>
<td>(2) Decrease by 50–60%</td>
<td></td>
</tr>
<tr>
<td><strong>Bone involvement</strong></td>
<td></td>
</tr>
<tr>
<td>(1) Lessen or eliminate bone pain</td>
<td>12–24 months</td>
</tr>
<tr>
<td>(2) Prevent bone crises</td>
<td>12–24 months</td>
</tr>
<tr>
<td>(3) Attain ideal peak bone mass in children</td>
<td>By puberty</td>
</tr>
<tr>
<td><strong>Paediatric growth</strong></td>
<td></td>
</tr>
<tr>
<td>(1) Achieve normal growth rate</td>
<td>By 36 months</td>
</tr>
<tr>
<td>(2) Achieve normal puberty</td>
<td>Family adjusted</td>
</tr>
<tr>
<td><strong>Pulmonary involvement</strong></td>
<td></td>
</tr>
<tr>
<td>Reverse hepatopulmonary syndrome, decrease or eliminate pulmonary hypertension, prevent pulmonary failure</td>
<td>Needs development</td>
</tr>
<tr>
<td><strong>Quality of life</strong></td>
<td></td>
</tr>
<tr>
<td>(1) Restore daily activities</td>
<td>Patient adjusted</td>
</tr>
<tr>
<td>(2) Improve quality-of-life scores on validated tests</td>
<td>24–36 months</td>
</tr>
</tbody>
</table>

potentially improve therapeutic regimens that can be tailored to individuals.

The profile of adverse events for enzyme therapy at any dose is very good. About 15% of treated patients develop IgG antibodies to the enzyme given, and about three or four patients have developed IgE antibodies and anaphylaxis. Most IgG-positive patients become antibody negative by 24–36 months of continuous enzyme therapy. Only four patients have developed clinically significant inhibitory IgG antibodies and were given very high doses of enzyme, which made them tolerant to the therapy. Few adverse events have necessitated discontinuation of treatment.

Enzyme therapy attempts to reduce the amount of accumulated substrate by supplying sufficient supplemental amounts of an exogenous enzyme to re-establish the glucosylceramide flux. This process is the same as increasing the drain size in a bathtub to increase the outflow of water from the tub, and thereby reducing the amount of water within the tub. By analogy, an alternative approach, first developed by Shukla and others, would be to reduce the inflow of water into the tub—ie, decrease the amount of substrate produced by inhibiting its synthesis or by giving substrate-reduction therapy.

Glucosylceramide synthase is the first committed step in the synthesis of gloco-based glycosphingolipids, including glucosylceramide and gangliosides. Consequently, inhibitors of glucosylceramide synthase would decrease the amount of glucosylceramide and gangliosides presented to the lysosomes for degradation. In the presence of small amounts of residual or mutant enzyme activity, a diminished amount of substrate would be presented to the residual enzyme in lysosomes, and would reduce the excess accumulation of the specific substrate. For Gaucher’s disease, inhibitors of glucosylceramide synthase have been developed to mimic either the glucon head group or ceramide lipid moiety. The objective is not to reduce the synthesis of glucosylceramide completely. Smaller amounts of this lipid synthesised could be used to process essential glycosphingolipids, but residual enzyme activity would hydrolyse a greater amount of presented lipid than with normal synthetic rates. Theoretically, this process should work, since all individuals with Gaucher’s disease have some residual enzyme activity.

An imino sugar that is an analogue of glucose with a short hydrophobic chain attached, N-butyl-deoxyojirimycin (miglustat), was the first such agent to be approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for use in the treatment of Gaucher’s disease type 1. Miglustat is an oral agent that, in clinical trials, has shown decreases in hepatic and splenic volumes, and increases in platelet counts during 1–3 years in affected adults. Improvements in quantitative measures of fat fractions in bone marrow have also been shown in two patients. The reported side-effects included diarrhoea (85–90%), paraesthesias, and fine tremor (about 10%). Neither of the last two side-effects were well controlled, and their validity is questionable. The diarrhoea resolves within 8–12 months, and, anecdotally, can be controlled by modification of diet. Miglustat was approved by the FDA for use in adults with Gaucher’s disease type 1, who have medical contraindications to enzyme therapy. EMEA has a somewhat lesser restriction than FDA—ie, patients should be unable or unwilling to take enzyme therapy. Studies of attainment of treatment goals and, thus, direct comparisons to enzyme therapy have not been done, but seem similar to results with low-dose enzyme therapy.

Alternatives to the deoxynojirimycin derivatives are ceramide analogues as originally developed by Shukla and co-workers. Short-chain-ceramide analogues are being tested preclinically in mouse models of Gaucher’s disease and are in phase I trials. The initial results show that excess glucosylceramide storage and Gaucher cells can be eliminated from visceral organs by oral administration of such compounds in mouse models. Furthermore, phase I trials revealed no unexpected safety hazards.

Such compounds have two inherent advantages over available intravenous enzyme therapy: (1) oral administration and therefore convenience, and (2) potential penetration across the blood-brain barrier for the treatment of CNS variants of Gaucher’s disease and other lysosomal disorders involving glucosylglycosphingolipids (eg, Sandhoff’s disease). A persistent disadvantage might be the high cost, which is based on small incremental treatment effects.

An alternative approach to enzyme or substrate-reduction therapy would be to modify in situ the endogenous mutant enzyme, with the use of specific agents that interact with these dysfunctional enzymes. For lysosomal storage disorders in general and Gaucher’s disease in particular, the counter-intuitive approach has been to use competitive inhibitors of the enzyme to improve lysosomal activity. Such treatment could result in redirecting malfolded enzymes away from the endoplasmic reticulum for trafficking to the lysosomes or by enhancing the stability or active conformation of the enzyme in the lysosome to improve substrate flux through this organelle. The competitive inhibitor is envisioned to provide a scaffold for the active site or global conformational changes to improve the previously mentioned properties. This approach was first proposed by Fan, and ex-vivo studies have shown the ability to re-traffick or improve stability of the mutant lysosomal enzymes. Such studies are rapidly progressing towards clinical trials, but, importantly, the range of mutations that might be responsive to one chaperone needs investigation. All potential mutations in a specific disease are unlikely to be responsive to one pharmacological chaperone, and thus, a range of designer chaperones might need to be developed for broad-based treatment. Furthermore, these agents are potent inhibitors and their dose-dependency will need to be defined for therapeutic effect or potentiation of disease.

Pharmacological chaperones avoid the potential for antibody responses to exogenous proteins, the need for
intravenous infusions since they are oral agents, and if well designed with high specificity, could avoid potential adverse events. Additionally, pharmacological chaperones have the potential to cross the blood–brain barrier and affect treatment of lysosomal storage diseases, including variants of Gaucher’s disease affecting the brain. An absolute requirement for a protein, albeit mutant, to be synthesised is that it can be refolded to have substantial stability in the lysosome so as to exceed the activity threshold needed for treatment. This domain of research is providing compounds for ongoing clinical trials.

With the development of new enzyme agents, substrate-reduction therapies and pharmacological chaperones for the treatment of Gaucher’s disease and combined therapy with enzyme might provide enhanced treatment benefit to affected individuals. With such combined therapies, effects in various organs—including CNS, lung, and bone—that show no or partial effects so far might be improved. Potentially, these alternative therapies could provide long-term primary treatment after the induction phase with enzyme, or as primary agents themselves. Carefully designed clinical trials will be needed to assess the usefulness of combined versus primary therapies, by obtaining information about treated patients from large databases. Because of the rarity of Gaucher’s disease of type 1 and its other variants, these studies will need to be done internationally.

Gene therapy has been a long-term promise for curative approaches for Gaucher’s disease on the basis of early successes in bone marrow or stem-cell transplantation. However, progress in gene therapy has slowed because of issues of gene delivery and expression, especially in stem cells derived from bone marrow. Concerns about toxic effects are related to insertional mutagenesis and malignant-cell transformation. The ability to use adeno-associated virus or retrovirus to deliver genes to cells for stable expression has been the focus of attention, especially in animals. In particular, this approach has proved effective in expressing wild-type enzyme for the lifetime of the mouse with mutant glucocerebrosidase, a Gaucher’s-disease analogue. In such studies, one intravenous injection of adeno-associated virus containing the glucocerebrosidase gene was expressed in the liver and the enzyme was secreted into the circulation, which corrected the macrophage storage of glucosylceramide in other tissues. The optimum approach for gene therapy continues to need assessment, but gene delivery for stable expression and antibody sensitisation are obstacles to clinical use.

Conclusions
Cost continues to be an important concern for treatments of all rare diseases. For Gaucher’s disease, the cost of either enzyme therapy or available agents with substrate-reduction therapies ranges from US$100 000 to more than $250 000 per year. Although the number of patients is small relative to other more common disorders and the total relative cost to health-care systems is not great, the individual cost, both economically and emotionally, can be staggering. Thus, prudent and appropriate use of these expensive agents that clearly improve the health status of affected individuals is essential for their long-term health. The development of treatment goals and objectives, improved staging systems, and expert guidance in the use of these agents are essential in the care of patients affected with Gaucher’s disease.

Conflict of interest statement
GAG received travel expenses, honoraria, and speaker’s fees in the past 3 years from Genzyme (consultant, basic research grant.), Amicus (basic research grant), TKF/Shire (member of advisory board for Hunter disease, basic research grant), National Gaucher Foundation (member of the Medical Advisory Board), and Project Hope/Genzyme Gaucher Initiative (member of the expert committee, Chairman, Expert Committee, 1999–2008). GAG continues to receive research support from the National Institutes of Health, USA for basic research in Gaucher’s disease and other glycosphingolipidoses (DK56729 and NS36681) and epilepsy (NS45911), and a grant from the State of Ohio to support clinical services and a computational medicine centre.

References
Lysosomal storage diseases are inherited metabolic diseases that are characterized by an abnormal build-up of various toxic materials in the body's cells as a result of enzyme deficiencies. There are nearly 50 of these disorders altogether, and they may affect different parts of the body, including the skeleton, brain, skin, heart, and central nervous system. New lysosomal storage disorders continue to be identified. While clinical trials are in progress on possible treatments for some of these diseases, there is currently no approved treatment for many lysosomal storage diseases. Signs &...Â Gaucher Disease Types I, II, and III: Gaucher disease is the most common type of lysosomal storage disorder. The lysosomal storage diseases are inborn errors of metabolism, so that the person affected with one of these diseases carries evidence of the disorder from the time of conception. Histologic signs of lipid accumulation have been found in spinal cord neurons of fetuses with the GM1- and GM2-gangliosidoses as early as 20 weeks of gestation. Similarly, Gaucher's disease has been detected in a fetus with hydrops in whom lipid-filled histiocytes were present in the lungs, liver, and other organs. Although histologic, biochemical, and molecular DNA evidence of a lysosomal storage disease can b Gaucher's disease continues to be a model for applications of molecular medicine to clinical delineation, diagnosis, and treatment. Analyses of several thousand affected individuals have broadened the range of the pan-ethnic disease variants, provided initial genotype and phenotype correlations, and established the effectiveness of enzyme therapy. Large numbers of affected individuals worldwide have provided insight into the effect of disease variation related to ethnic origin, prognosis, and outcome.Â These developments are novel, clinically important, advancements for patients with other lysosomal storage diseases and genetic diseases. Download full-text PDF. Source.