J Inherit Metab Dis (2008) 31:319–336
DOI 10.1007/s10545-008-0779-z

REVIEW

Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring

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Received: 24 September 2007 / Submitted in revised form: 28 January 2008 / Accepted: 19 February 2008 /
Published online: 23 May 2008

Summary Enzyme replacement was introduced as treatment for non-neuronopathic Gaucher disease more than 15 years ago. To ensure the best use of this costly ultra-orphan agent, a systematic disease management approach has been proposed by an international panel; this includes the development, by consensus, of achievable treatment goals. Here we critically review these goals and monitoring guidelines and incorporate emerging experience of the disease in the therapeutic era, as well as contemporary clinical research. This review makes recommendations related specifically to the management of pregnancy; the appropriate use of splenectomy and bisphosphonate treatment; the relevance of biochemical markers to disease monitoring; and the use of semi-quantitative methods for assessing bone marrow infiltration. In addition, we identify key areas for development, including the requirement for a validated index of disease severity; the need to correlate widely used biomarkers with long-term disease outcomes, and the desirability of establishing agreed standards for moni-

Communicating editor: Bruce Barshop

Competing interests: None (see Acknowledgements)

References to electronic databases: Non-neuronopathic Gaucher disease, type I: OMIM 230800. Acute neuronopathic Gaucher disease, type 2: OMIM 230900. Chronic neuronopathic Gaucher disease, type 3: OMIM 231000. Glucocerebrosidase: EC 3.2.1.45.

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toring of bone disease particularly in infants and children with Gaucher disease.

Abbreviations

BMB	bone marrow burden
CCL18/PARC	chemokine (C-C motif) ligand 18/pulmonary and activation-regulated chemokine
DXA	dual-energy X-ray absorptiometry
RANKL	receptor activator of NF-κB ligand
QCSI	quantitative chemical shift imaging

Introduction

Lysosomal storage disorders are a group of rare inherited metabolic diseases characterized by the appearance of undegraded macromolecular substrates derived from impaired recycling of cellular components within the lysosomal compartment.

Gaucher disease is the most common lysosomal disorder (Meikle et al 1999; Poorthuis et al 1999) and was the first in its class for which a rationally based corrective treatment (macrophage-targeted enzyme replacement therapy) has been developed (Barton et al 1991). Gaucher disease is a multisystem disorder principally caused by mutations in the gene encoding lysosomal acid beta-glucosidase (glucocerebrosidase, EC 3.2.1.45) and is inherited as an autosomal recessive trait. More than 300 mutations have been identified (Beutler et al 2005; Grabowski 1997; Hruska et al 2006; Koprivica et al 2000). Deficiency in the activity of glucocerebrosidase leads to accumulation of the major substrate, glucocerebroside, principally in the lysosomal compartment of macrophages. The pathogenetic link between the presence of the 'storage' material and disturbed cellular physiology is, however, far from clear (Cox 2001; Futerman 2006).

The lipid-laden cells assume the characteristics of alternatively activated phagocytes and are known as Gaucher cells (Boven et al 2004). Gaucher cells occur in several major organs, especially the liver, spleen, bone marrow and lung and are accompanied by tissue injury and fibrosis. The presence of Gaucher cells is associated with numerous abnormalities of plasma proteins and the pathological release of cytokines and enzymes (including acid hydrolases) implicated in the inflammatory features, increased basal metabolism and tissue changes that characterize the disease (Aerts and Hollak 1997; Boot et al 2004; Cox 2001; Moran et al 2000).

Nervous tissue can also be affected, but the role of Gaucher cells in the pathogenesis of brain disease is unclear (Schueler et al 2003). Besides the direct effects of Gaucher cells *in situ*, it has been proposed that excess glucocerebroside and cognate glycosphingolipids (which are present in non-macrophage cells, and occur in compartments other than the lysosome) interfere with tissue function. Disturbances in cellular calcium homeostasis, for example, are common to several glycolipid storage diseases affecting the brain (Futerman and van Meer 2004). Raised cytosolic calcium concentrations (observed in brain microsomes prepared from patients with overt neuronopathic Gaucher disease (Pelled et al 2005) and in a murine model of Gaucher disease (Kortotian et al 1999) will enhance neuronal sensitivity to injurious agents, including neurotransmitters (Berridge et al 1998).

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The course and extent of Gaucher disease is highly variable but it has been classified operationally into three clinical subgroups: non-neuronopathic disease, also known as type I disease (OMIM 230800); acute neuronopathic disease (type II: OMIM 230900); and chronic neuronopathic disease (type III: OMIM 231000) (Beutler and Grabowski 2001). Neuronopathic forms of the disease may be accompanied by extensive visceral disease and cause death in infancy (type II) or in childhood or early adult life (type III). Since enzyme therapy has been introduced, the experience of Gaucher disease has intensified at many centres, and it is now clear that type I disease does not necessarily exclude neurological manifestations (Capablo et al 2008; Chérin et al 2006). Understanding all the manifestations of Gaucher disease and their pathogenesis is an ongoing field of research.

Type I disease affects 1 in 50 000–100 000 in the population worldwide and 1 in 400–600 in the Ashkenazi Jewish population (Cox and Schofield 1997; Grabowski 1997; Pinto et al 2004; Poorthuis et al 1999). It is a clinically heterogeneous disorder although early onset is associated with more severe disease (Zimran et al 1992), more rapid rates of disease progression, and reduced life expectancy (Grabowski et al 2006; Maaswinkel-Mooij et al 2000). Even patients of the same genotype, including siblings and monozygotic twins, may show distinct patterns of disease (Amato et al 2004; Lachmann et al 2004). Different organs may also be affected to differing extents within an individual patient (Beutler and Grabowski 2001) and the degree of visceral disease may not correlate with the degree of bone involvement (Charrow et al 2007; Kaplan et al 2006).

Presentation usually involves one or a combination of the following: splenomegaly with associated anaemia; a tendency to bleed because of thrombocytopenia (or more rarely, platelet malfunction) or coagulation factor deficiency; an enlarged liver (which may be accompanied by mild elevation of transaminases and, occasionally, by more severe hepatic disease such as cirrhosis and portal hypertension); and skeletal disease with bone pain, deformation and pathological fractures (Cox and Schofield 1997; Wenstrup et al 2002). Rarely, pulmonary arterial hypertension or lung infiltration by pathological macrophages may occur. Untreated patients may experience progressive deterioration in health and premature death related to complications such as; bleeding, infection, lung disease, skeletal disease and liver failure (Lee 1982). The incidence of multiple myeloma and hepatocellular carcinoma is also increased in adult type I Gaucher patients (de Fost et al 2006b; Rosenbloom et al 2005; Zimran et al 2005). B-cell proliferation may also be associated with lymphomas or amyloidosis (Cox and Schofield 1997; Kaloterakis et al 1999; Shiran et al 1993).

An effective macrophage-targeted form of enzyme therapy was developed after identification of mannose receptors on macrophages (Sly et al 1978). This human placental glucocerebrosidase (alglucerase [Ceredase®], Genzyme Corporation, Cambridge, MA, USA) was shown to be safe and effective in clinical trials (Barton et al 1991) and gained marketing approval in 1991. Recombinant glucocerebrosidase, supplied after enzymatic modification as a mannose-terminated protein, has subsequently been introduced (imiglucerase, [Cerezyme®], Genzyme Corporation). Imiglucerase reverses or ameliorates many of the manifestations of type I Gaucher disease (Weinreb et al 2002) and is considered the standard care for the treatment of patients with type I Gaucher disease (Cox et al 2003; Weinreb et al 2005). Substrate reduction therapy with miglustat (Zavesca®; Actelion Pharmaceuticals, Allschwil, Switzerland) has also been investigated (Cox et al 2000; Elstein D et al 2004; Pastores et al 2005). It is indicated for the oral treatment of mild to moderate type *1* Gaucher disease and may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable (EMEA 2002) or for the treatment of adult patients with mild to moderate type I Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (for example, owing to constraints such as allergy, hypersensitivity or poor venous access). Miglustat is also not approved for use in children (EMEA 2002; FDA 2003). Several other enzyme preparations, a substrate-reducing agent and a pharmacological chaperone, are in advanced stages of clinical development.

Clinical heterogeneity in Gaucher disease, its variable pattern of progression in those affected, and the high cost of treatment mandate an individualized approach to management so that outcomes can be optimized for efficacy and efficiency (Altarescu et al 2000; Hollak et al 1995; Weinreb et al 2002). In 2003, a set of therapeutic goals in Gaucher disease, as well as guidelines for monitoring, were proposed by an international panel with extensive experience in the management of the disorder (Pastores et al 2004; Weinreb et al 2004). Using these guidelines, an individualized treatment plan to reduce the risk of disease progression can be established. If the goals are not achieved within the expected period, therapeutic adjustments may be required until all endpoints are met. Once the therapeutic goals have been attained, the emphasis of treatment shifts to maintenance of the relevant parameters in the long term (Andersson et al

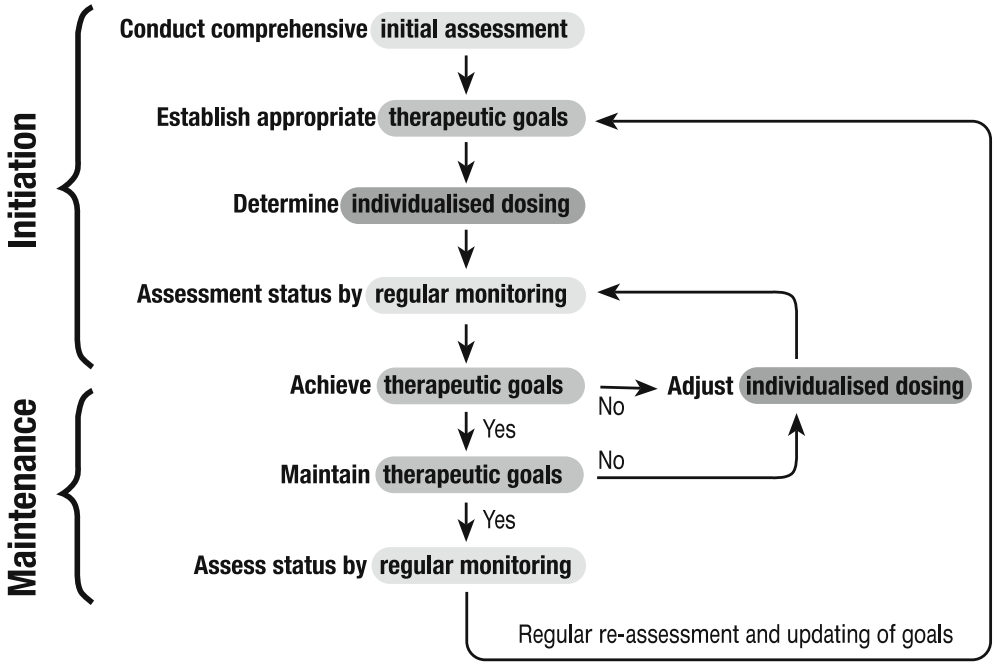

Fig. 1 Scheme outlining a strategy for the management of Gaucher disease

2005). Any proposed goals should be applicable to all treatments for Gaucher patients and should be regularly updated to accommodate burgeoning experience and knowledge of the therapeutic response. The overriding aim is to ensure that current treatment is used to optimal effect (Fig. 1).

Aims and methods

Therapeutic goals for Gaucher type I disease have been proposed (Pastores et al 2004). Here, these therapeutic goals and monitoring guidelines are reviewed to identify priorities for advancing disease management, based on their use by practising clinicians. We also critically re-evaluated the goals in the light of emerging experience of the disease in the mature phase of the therapeutic era with enzyme treatment to introduce any key additions or adjustments to the published principles of disease management.

A group of international experts in Gaucher disease (The Second International Gaucher Disease Management Board) was asked to review and present evidence from peer-reviewed literature, the ICGG Gaucher Registry (described in Charrow et al 2000), from other unpublished data, and from their own clinical experience to support the recommendations for disease management and treatment guidelines. These related specifically to the management of pregnant patients, the appropriate use of splenectomy, the use of bisphosphonates, the clinical use of biochemical markers, and semi-quantitative methods for assessing bone marrow infiltration (based upon the recent consensus of a panel of clinical experts in Gaucher bone disease (vom Dahl et al 2006). Additional unmet needs in the management of Gaucher patients were identified by discussion and consensus between all the contributors. Relevant peer-reviewed medical literature (not restricted by language or date of publication) was supported by online search tools, including PubMed.

Results and discussion

Pregnancy

Pregnancy can exacerbate Gaucher disease, especially for women who have not received enzyme therapy or whose manifestations have yet to be controlled by treatment (Clarkson et al 1998; Granovsky-Grisaru et al 1995; Holtkamp et al 1998; Houlton and Jackson 1978). Some women are first diagnosed with Gaucher disease during pregnancy or soon after delivery (Zlotogora et al 1989). Reported complications include increased visceromegaly (Holtkamp et al 1998; Landyshev and Tochilin 1989; Young and Payne 1986; Zlotogora et al 1989); worsening anaemia and thrombocytopenia, which may lead to postpartum bleeding (Clarkson et al 1998; Granovsky-Grisaru et al 1995;

Holtkamp et al 1998; Houlton and Jackson 1978); possible increases in spontaneous abortion; postpartum infections and associated fever; and bone crises (Granovsky-Grisaru et al 1995). Previous reports, however, have suggested that serious complications resulting from pregnancy are uncommon in Gaucher patients (Goldblatt and Beighton 1985).

Several case reports confirm that pregnancies usually proceed to term in Gaucher patients, despite disease manifestations such as hepatosplenomegaly (Ayhan et al 1996) and portal hypertension (Mazor et al 1986), and even with rare complications such as myocardial involvement (Torloni et al 2002) and disseminated intravascular coagulation (Clarkson et al 1998). Hepatosplenomegaly rarely restricts fetal growth, although abdominal discomfort, bloating, early satiety, heartburn, and low back pain are likely to be aggravated in untreated pregnant Gaucher patients (Tordjeman et al 1991). Premature delivery in a woman with an anticoagulant factor has occurred (Jimenez Saenz et al 1991). Pregnancy exacerbates symptomatic pulmonary hypertension in women with this relatively rare complication of Gaucher disease and has been associated with fatal cardiopulmonary decompensation (Mistry et al 2002).

The question of pregnancy and its possible outcomes should be discussed with women of childbearing age. Clearly, the risk of radiation exposure to the fetus means that pregnancy should be excluded before radiography. Ideally, therapeutic goals should be achieved before considering a pregnancy to help ensure that women are in optimal health throughout pregnancy and the postpartum period. Bone involvement should be assessed before pregnancy, as pregnancy may exacerbate bone crises. Although uncommon in most developed countries, pelvic and hip deformities associated with severe, untreated Gaucher disease may interfere with a normal vaginal delivery. Successful hip replacement, however, does not preclude a normal delivery. After delivery, women with Gaucher disease should be monitored for infection, bleeding, appearance of bone crises, and bone rarefaction.

Any significant decrease in the platelet count during pregnancy should raise suspicion about co-existent immune thrombocytopenia, which may occur in non-pregnant patients with Gaucher disease (Lester et al 1984). Establishing this diagnosis is important because of potential danger not only to the mother but also to the newborn infant. Other causes of thrombocytopenia include folate deficiency and increasing spleen size and hypersplenism due to Gaucher disease. In addition to thrombocytopenia, clotting factors may be reduced so that as well as platelet counts, coagulation studies are also recommended (Hollak et al 1997). For a further review of haematological guidelines in pregnancy, see Hughes et al (2007).

Rarely, patients with Gaucher disease give a history of perioperative bleeding despite normal platelet counts; such patients have usually had a splenectomy. The bleeding tendency is due to an acquired defect of platelet membrane glycoprotein Ib function, the acquired so-called pseudo-pseudo-Bernard–Soulier defect (Kelsey et al 1994). Ristocetin-induced aggregation is severely impaired in platelets from these patients—an abnormality that may be corrected experimentally by rendering the platelets free of plasma by washing *in vitro* (Kelsey et al 1994). The platelet abnormality can be overcome pharmacologically in the short term by stimulating platelet degranulation with the vasopressin analogue desmopressin. Such patients have a significant risk of severe peripartum or operative haemorrhage and may require treatment with platelet transfusions and parenteral desmopressin acetate in the emergent situation. Desmopressin 0.3 μg/kg is given in 50 ml 0.9% saline solution intravenously over 15 to 30 min; the duration of action is 8–10 hours. Desmopressin given as nasal spray can also be administered for this purpose but systemic absorption by this route is less reliable and thus parenteral administration is preferable when bleeding is brisk or where there is a high risk of haemorrhage. In the medium-to-long term, this platelet defect appears to be at least partially corrected by enzyme replacement therapy (Kelsey et al 1994). Expert assistance from a haematologist with expertise in the management of haemorrhagic disorders should be sought if this abnormality is suspected.

Ferritin concentrations are often elevated in the serum of Gaucher patients as part of the sustained acute inflammatory response (Laine et al 1996). This usually does not indicate iron overload but may mask the presence of iron deficiency especially in pregnancy. Iron supplementation is advisable in pregnant Gaucher patients with hypochromic microcytic anaemia who do not have evidence of a haemoglobinopathy (e.g. β-thalassaemia trait), reduced concentrations of serum iron and decreased serum transferrin saturation.

There is no definitive evidence whether enzyme therapy should be continued during pregnancy. In the United States, imiglucerase currently has a pregnancy category C rating from the Food and Drug Administration (FDA 2002), that is, it 'is not known whether it is harmful to an unborn baby' and patient information states that it should be given to pregnant women only if clearly needed (FDA 2002). Similar statements are also expressed in the EMEA summary of product

characteristics (EMEA 2005). The safety of enzyme therapy for mothers or the fetus has not been tested in a randomized prospective clinical trial. Evidence on the effects of treatment on pregnancy and childbirth come from retrospective studies and case studies (Aporta Rodriguez et al 1998; Cleary et al 2001; Elstein Y et al 2004; Elstein et al 1997). Miglustat is contraindicated in pregnancy and has a pregnancy category X rating from the FDA, that is, it 'may cause fetal harm when given to a pregnant woman' (FDA 2003). The EMEA states that miglustat 'should not be used during pregnancy' (EMEA 2002). Patients who receive treatment with miglustat should thus avoid pregnancy and those of either sex in the reproductive age group are advised to use appropriate contraceptive methods (Cox et al 2003). Alkylated iminosugars have been associated with reversible male infertility in experimental animals (Suganuma et al 2005; van der Spoel et al 2002). However, a recent report suggests that miglustat does not affect spermatogenesis in normal men (Amory et al 2007).

Enzyme replacement therapy has been continued without interruption throughout pregnancy with successful delivery at term (Aporta Rodriguez et al 1998). Enzyme therapy has been initiated in pregnancy to prevent bone deterioration (Cleary et al 2001) and continued in pregnancy in a patient with antiphospholipid syndrome (Sherer et al 2002) with successful outcomes. One study comparing outcomes in 23 enzyme-treated and 43 untreated patients demonstrated no significant difference in the live birth rate between the two groups (Elstein Y et al 2004). All but two of the enzyme-treated women continued treatment before and during their pregnancies (including the first trimester, which is critical for organogenesis). Most untreated women (with milder Gaucher disease), had uncomplicated pregnancies and deliveries. Treated patients (with more severe disease) had more bleeding and postpartum infections. Neonatal outcomes were comparable in treated and untreated groups and no adverse effects were attributable to enzyme treatment; spontaneous abortion rates in this study were not detectably increased in either group of patients. However, it is worth noting that five women in the group who received enzyme therapy had experienced a total of 13 abortions before treatment was started (Granovsky-Grisaru et al 1995); subsequently they each had had one or two uneventful pregnancies after starting enzyme replacement therapy. It has been suggested that enzyme treatment should not be interrupted during pregnancy because its continuing administration is likely to reduce complications during pregnancy, delivery, and postpartum bleeding (Elstein et al 1997). For women diagnosed during childhood and adolescence and in whom disease manifestations remit with enzyme treatment, pregnancy appears to be substantially less hazardous than was the case before the advent of effective treatment. When enzyme infusions are continued during pregnancy, the consensus of clinical experience is that the risk of complications is decreased; indeed, in a small series of pregnant women with Gaucher disease, bone crises or bleeding were observed principally in those who were naive to enzyme therapy or in the few cases in whom treatment had been discontinued (Guffon 2006).

Decisions as to whether enzyme therapy should be continued during pregnancy are best made after informed discussion with the patient, recognizing that the true risks and benefits are, as yet, uncertain. Irrespective of the decision about treatment, specific monitoring should be available throughout pregnancy to ascertain or pre-empt complications related to the disease. Many women and their physicians choose to stop enzyme therapy during the first trimester of pregnancy to protect the fetus from any theoretical risk of teratogenicity, although there have been no reports of congenital defects specifically associated with enzyme replacement therapy. Severe anaemia and/or thrombocytopenia significantly increase the risks associated with anaesthesia (epidural anaesthesia is contraindicated) and delivery; these manifestations pose a risk to the fetus, and increase the likelihood of postpartum complications. Ideally, to compensate for the additional physiological burden of pregnancy, blood counts should be kept in the normal range, for most patients, in effect, mandating continued enzyme replacement during pregnancy. This does not apply to other treatments. Substrate reduction therapy with miglustat is contraindicated in both men and women wishing to start a family, as stated by the manufacturer. Bisphosphonates are also contraindicated during pregnancy and are not recommended for mothers who are breastfeeding. In summary, for the reasons stated, the authors take the view that unless there are specific contra-indications, enzyme replacement therapy after the first trimester is advised for all pregnant women with Gaucher disease.

If a patient is trying to conceive or is not using contraception but wishes to discontinue treatment in the event of pregnancy, a pregnancy test should be offered before each infusion. If treatment is discontinued, the patient should be monitored closely. Resumption of enzyme therapy is advised if the platelets are less than 80 000/μl (80×10^9/L) or are falling rapidly, the haemoglobin concentration is less than 8 g/dl, and/or a bone infarction crisis occurs. A

report describing the outcome of four pregnant Gaucher patients has suggested that a rapid rise chitotriosidase activity may be an indication of deteriorating disease and the need to re-institute enzyme therapy (Guffon 2006). Although there are no definitive studies on this aspect, there is no scientific basis for any risk to the infant (or mother) from the continuation of enzyme therapy during breastfeeding. After infusion the protein is cleared from the circulation within minutes and is rapidly taken up by tissue macrophages and hepatocytes (Mistry et al 1996). Enzyme has been detected in breast milk (Esplin et al 1993) but is unlikely to have any untoward effects since it is inactivated at neutral pH and likely to be degraded in the intestine. On the other hand, there maybe a health risk for mothers who interrupt treatment while breastfeeding, especially if they breast-feed for several months. Mothers should be reassured and encouraged to continue enzyme therapy during breastfeeding, even in the absence of studies that definitively validate the safety of this consensus recommendation.

Ideally a multidisciplinary approach should be adopted for the management of pregnant Gaucher patients (Ioscovich et al 2004; Tordjeman et al 1991). According to the patient's needs this will include cooperation between an obstetrician, anaesthesiologist and haematologist. A clinical geneticist and orthopaedic specialist with experience of Gaucher disease may also be required. Every child born to a woman with Gaucher disease is, at least, an obligate carrier. The parents, and, at a later appropriate time, the child, should be offered information and genetic counselling about the meaning of carrier status. It is noteworthy that in affected members of communities with a high frequency of the disease, or in consanguineous unions, there is an appreciable risk of pseudo-dominant transmission of the disease from parent to offspring.

Splenectomy

Therapeutic goals for splenomegaly were described in 2004 (Pastores et al 2004), without guidance as to any circumstances in which splenectomy might be needed. Splenomegaly is a manifestation in all but the most mildly affected Gaucher patients and is the most common presenting manifestation (Kolodny et al 1982; Beutler and Grabowski 2001). In severe cases, the spleen may weigh more than 10 kg (Shiloni et al 1983). Before the advent of enzyme replacement therapy, splenectomy was carried out in frequently in Gaucher patients for severe cytopenias due to functional hypersplenism and the mechanical pressure on other viscera (Salky et al 1979). Enzyme therapy effectively reduces splenomegaly and hepatomegaly in almost all patients (Patlas et al 2002; Weinreb et al 2002) and thus, where enzyme treatment is available, splenectomy is only very rarely indicated. Nonetheless, despite the associated risks, splenectomy may be life-saving for patients who, for various reasons, do not have access to enzyme therapy to treat severe life-threatening cytopenias and other complications of splenic enlargement.

Very occasionally, and even when enzyme replacement therapy is available, splenectomy is indicated in the treatment of patients with Gaucher disease. Splenectomy may be the only means of controlling life-threatening thrombocytopenia or pressure effects (for example, hydronephrosis), or severe cachexia due to massive splenomegaly in patients with rapidly progressive and advanced disease—despite the introduction of appropriate enzyme treatment. Moreover, splenectomy is essential in patients with pathological splenic rupture, which may complicate minor trauma. In rare patients with autoimmune haemolytic anaemia occurring on a background of Gaucher disease, or where all other measures have failed in idiopathic thrombocytopenic purpura, splenectomy may be the sole means available to arrest the vicious cycle of transfusion-related glycolipid loading and worsening hypersplenism. Another rare indication for splenectomy is when a lymphoma is suspected. A growing mass in the spleen, especially in patients receiving imiglucerase therapy, may necessitate splenectomy to exclude lymphoma or another tumour (Hughes et al 2007).

Splenectomy may have a significant impact on the course of Gaucher disease. The spleen has been proposed to be a reservoir for undegraded substrate and thus its removal may result in this material accumulating preferentially in other macrophage-rich organs (Fleshner et al 1991; Rodrigue et al 1999; Shiloni et al 1983). The distribution of Gaucher cells may be uneven and concentrate, for example, in the bone marrow, liver or lungs (Kyllerman et al 1990). Consequently, there may a skewed distribution of disease in these compartments. Replacement of the bone marrow by Gaucher cells may eventually result in the development of pancytopenia due to marrow failure (de Fost et al 2003). Pancytopenia in splenectomized patients is a clear indication of severe and widespread disease of the bone marrow compartment.

Aggressive bone disease has long been associated with splenectomy in Gaucher patients (Fleshner et al 1991; Ida et al 1999; Rose et al 1982; Schiffmann et al 2002) but it is only latterly that evidence for a cause-and-effect

relationship has emerged. Osteolytic lesions have been reported to appear within just a few months of splenectomy (Ashkenazi et al 1986), splenectomy has been described as an independent risk factor for osteonecrosis (Rodrigue et al 1999), and bone mineral densities have been found to be significantly lower in asplenic patients compared with those with an intact spleen (Pastores et al 1996). Others report no evidence of accelerated bone disease following splenectomy (Goldblatt et al 1978; Zimran et al 1992) and considered that this could be an ascertainment bias as those undergoing splenectomy at younger ages might be expected to have more severe Gaucher disease with a greater risk of subsequent skeletal complications. Re-analysis of data from the University of Pittsburgh Gaucher Registry (Lee 1982) is consistent with reports that splenectomy is associated with bone disease. In the study, 58 of 114 patients with a history of splenectomy had bone disease reported (50.9%), but only 39 of 125 patients with intact spleens had bone disease judged by the same criteria (31.2%), ($p < 0.01$, by the χ^2 test).

Any need for orthopaedic intervention in splenectomized patients carries with it a greater operative risk largely due to increased susceptibility to infection (Diamond 1969; Ein et al 1977; Finkelstein et al 1992; Margalit et al 2002). There is likely to be an increased risk of vascular events in patients with high platelet counts after splenectomy and especially in the splanchnic circulation in the immediate perioperative period.

Splenectomy has been suggested to predispose Gaucher patients to malignancy (Fleshner et al 1991) and portal hypertension. Lachmann et al (2000) reported four Gaucher patients aged between 18 and 45 years, all of whom developed portal hypertension after splenectomy; the portal hypertension was associated with massive hepatomegaly. Severe sepsis contributed to the deaths of three of these asplenic patients, which in two was related to infection of orthopaedic prostheses. Pulmonary hypertension in Gaucher disease occurs principally in splenectomized individuals (Elstein et al 1998; Mistry et al 2002) and is likely to be related to changes associated with the asplenic state (Hoeper et al 1999).

As well as the consequences of splenectomy related to underlying Gaucher disease, functional hypersplenism has important general implications. The spleen is a major organ of the immune system with a particular role in innate defence against encapsulated bacteria such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, as well as other pathogens including protozoa. Splenectomized patients are at increased risk of overwhelming sepsis and must receive specific initial and booster vaccinations and take prophylactic antibiotics as indicated based on age and risk of exposure (Davies et al 2002; Price et al 2006). Measures to avoid malarial and other protozoan parasites, such as *Babesia* spp., are strongly recommended. The risk of bacterial sepsis in splenectomized patients is greatest during the first three years after surgery (Kyaw et al 2006). Patients who have undergone splenectomy should wear an identifier that notifies healthcare personnel of their susceptibility to overwhelming bacterial infection and the need for prompt introduction of parenteral antimicrobial therapy, should this be suspected. Any Gaucher patient with anaemia and/or thrombocytopenia, even with an intact spleen, and those with splenomegaly should carry a notification in case of accident.

Although splenomegaly in Gaucher patients responds well to enzyme therapy (Patlas et al 2002), even in so-called developed countries unfortunate instances of 'diagnostic' splenectomy continue to occur in patients with unsuspected Gaucher disease. Since Gaucher disease is readily diagnosed by measuring acid β-glucosidase activity in peripheral blood leukocytes or skin fibroblasts obtained after facile biopsy, there is clearly a continuing need for greater awareness of the disease. The risks of splenectomy in Gaucher patients and the response of the condition to enzyme-replacement therapy make it mandatory to consider this diagnosis in any patient who presents with unexplained splenic enlargement or thrombocytopenia (Goldblatt et al 1978).

Elimination of the need for splenectomy in Gaucher disease should be a therapeutic goal since it is predicted to reduce the incidence of pulmonary hypertension and hepatic fibrosis. Splenectomy should only be considered in exceptional circumstances after assessment by a physician experienced in the management of Gaucher disease. These circumstances may include, for example, when unexplained masses are present in the spleen (Hughes et al 2007; Krasnewich et al 1998) and/or in cases of refractory severe thrombocytopenia associated with spontaneous bleeding in vital organs.

Biomarkers

Several molecules have been found to be elevated in the plasma or tissues of Gaucher patients (Aerts and Hollak 1997), but hitherto no single 'gold standard' biomarker that accurately reflects overall disease burden, disease activity, organ-specific complications or the response to therapy has been developed. A

highly specific and sensitive biomarker that accurately reflects the notional concept of 'disease activity' and clinical behaviour would be a great advantage in Gaucher disease. Nonetheless, biomarkers have the potential to indicate disease in sanctuary sites, as for example, persistently elevated plasma chitotriosidase activity in Gaucher disease patients who have been treated either by bone marrow transplantation or by enzyme replacement therapy with alglucerase (Young et al 1997). Ultimately, biomarkers may allow a distinction between active disease and fibrosis and between insufficient treatment and residual disease that is relatively refractory to treatment. The ideal biomarker for Gaucher disease would be one that:

- Accurately reflects the presence and activity of disease
- Predicts clinically meaningful outcomes
- Changes rapidly in response to therapy
- Is easily measured and stable in accessible clinical samples
- Is specific and sensitive
- Is subject to little or no genetic variation
- Is reproducible (based on agreed standards of measurement)
- Is inexpensive to measure

Angiotensin-converting enzyme (ACE), tartrate-resistant acid phosphate (TRAP) and chitotriosidase have been recommended as useful biomarkers for monitoring disease activity in Gaucher patients (Weinreb et al 2004) and have been found to be useful indicators of disease progress and the response to treatment (Cabrera-Salazar et al 2004). A subsequent survey in children concluded that chitotriosidase was the most reliable of the three markers and that acid phosphatase can be dropped from routine clinical practice (Vellodi et al 2005).

Chitotriosidase is, perhaps, the marker that most closely meets the above requirements in Gaucher disease. A dose–response relationship has been reported for plasma chitotriosidase activity and abnormal bone marrow infiltration in Gaucher patients (de Fost et al 2006a). The measurement of plasma chitotriosidase immediately before and after splenectomy has been carried out in only a few patients. Relatively modest reductions in chitotriosidase activity (less than 50%) have been observed (personal observation J.M.F.G.A.). Although chitotriosidase is strikingly elevated in treatment-naive patients with Gaucher disease (Aerts and Hollak 1997; Hollak et al 1994) up to 6% of the European and North American population do not have any chitotriosidase activity and about 30% are heterozygous for an inactivating intragenic duplication in the chitotriosidase gene, which halves plasma chitotriosidase activity compared with patients with two intact chitotriosidase genes (Aerts and Hollak 1997). Other chitotriosidase polymorphisms and patient age may also influence the measured activity in plasma or serum (Grace et al 2007).

An alternative substrate, 4-methylumbelliferyl-(4-deoxy)chitobiose has been proposed to overcome nonlinearity of the assay due to substrate inhibition related to the presence of transglucosidase activity (Aguilera et al 2003), but this substrate has not yet been universally adopted. Nevertheless, when the patient serves as an internal control and serial measurements are performed at a single laboratory, with the exception of patients with a null genotype, chitotriosidase management is a useful, albeit not stand-alone, procedure for monitoring the response to treatment.

A newly-described chemokine, CCL18/PARC, is a sensitive and responsive measure of total Gaucher cell volume that may prove a useful alternative to plasma chitotriosidase activity as a surrogate biomarker for monitoring the response to therapy, especially in patients who are chitotriosidase deficient (Boot et al 2004). CCL18/PARC is on average 30-fold elevated, without overlap between patient and control values. The initial study reported that CCL18/PARC was independent of spleen status or skeletal disease (Boot et al 2004), while later evaluation of its clinical utility showed that CCL18/PARC concentrations correlated reliably with visceral volumes and with key clinical responses to enzyme therapy (Deegan and Cox 2005; Deegan et al 2005). CCL18/PARC is modestly elevated in several disorders associated with inflammatory processes (Boot et al 2004) and, like chitotriosidase, in patients suffering from iron storage in macrophages due to red cell transfusion in beta-thalassaemia major (Dimitriou et al 2005). Antigenic properties of CCL 18/PARC, upon which measurement depends, withstand multiple freeze–thaw cycles. Unlike chitotriosidase, genetic variation in serum CCL18/PARC does not appear to influence its utility as a biomarker. CCL18/PARC is a small (~8 kDa protein) that is also present in urine. It has been demonstrated that changes in urinary and plasma CCL18/PARC occur proportionally (Boot et al 2006), thus permitting determination of the chemokine in small samples of urine for monitoring Gaucher patients.

Based on present knowledge, decisions about treatment should not be made on evidence from a single biomarker. Clinical decisions should be made by monitoring trends in several biomarkers over time and by scrupulous clinical and laboratory observation.

Caution should also be exercised in the interpretation of biomarker data because concomitant administration of drugs other than substrate-reducing agents and enzyme therapy may sometimes affect results.

Although currently available biomarkers are clinically useful adjunctive measures of disease severity, finding the perfect laboratory marker, either alone or in combination, continues to pose an investigative challenge. Assessing the predictive power of all proposed surrogate markers will require a prospective study and a large cohort of patients, a formidable difficulty for a rare disorder in which most symptomatic patients in countries where the relevant investigations are possible are already receiving treatment. It is recommended that, where possible, physicians maintain an archive of biological samples (with the ethically appropriate permission of individual patients) and other clinical data so that, at the very least, studies of any innovative biomarker can be evaluated using such invaluable retrospective collections.

Monitoring bone disease

Bone disease is a common and often painful and disabling manifestation of Gaucher disease (Beutler and Grabowski 2001; Grabowski et al 2006; Wenstrup et al 2002). Enzyme replacement therapy permits restoration of bone growth in children, reduces the frequency of avascular necrosis and nonspecific bone pain and may also contribute to improved bone mineral density (Bembi et al 2002; Charrow et al 2007; El-Beshlawy et al 2006; Rosenthal et al 1995; Wenstrup et al 2007). Enzyme therapy cannot reverse established osseous injury, including fractures and joint collapse that occur as a result of bone infarction or the effects of local osteolysis.

The pathophysiology of Gaucher disease impacts bone metabolism (turnover, remodelling and mineralization), bone architecture, bone density and bone strength, which are not necessarily synonymous. It is important to consider that the effects of Gaucher disease on bone structure are multicompartmental, involving cortical and trabecular bone, bone marrow organization and composition, and bone vascularity. Adequate evaluation and monitoring of Gaucher skeletal disease must therefore reflect all these aspects.

Monitoring of Gaucher-related bone marrow disease is enhanced by use of quantitative chemical shift imaging (QCSI) (Hollak et al 2001; Johnson et al 1992; Maas et al 2002; Miller et al 1996). This MRI technique provides a sensitive measure of fat fraction, which correlates with clinical bone complications. Changes in fat fraction may occur early to provide a means of monitoring the response to therapy (Hollak et al 2001; Johnson et al 1992; Maas et al 2002). There is, however, limited experience with QCSI worldwide, owing to complex technology, specialized software, and requirement for a dedicated physicist.

As a more practical alternative, several semi-quantitative MRI scoring methods have been introduced (vom Dahl et al 2006; Maas et al 2003), such as the bone marrow burden (BMB) score. This method takes into account the patterns by which infiltration of bone marrow progresses in the lumbar spine (axial marrow) and the femur. A scoring system assigns up to 8 points for femoral involvement and 8 points for lumbar spine involvement to give a maximum score of 16 points. Measurements correlate with other indices of bone complications and with QCSI severity ratings, and there is high inter-observer reliability (Maas et al 2003). BMB provides a sensitive means of monitoring bone marrow changes in response to imiglucerase and can be carried out retrospectively to allow central reading of MR images from different centres (Robertson et al 2007).

The use of MRI techniques to monitor bone marrow infiltration in children is challenging as the variability of normal physiological conversion of red to yellow marrow during maturation may confound interpretation of accumulation of lipid-laden Gaucher cells in the marrow (Babyn et al 1998). The duration of MR imaging in the apparatus may, in addition, require sedation in young children.

Radiographs are useful at baseline to identify gross skeletal pathology and in response to specific situations in Gaucher patients, such as the observation of fractures and the monitoring of patients with femoral head avascular necrosis. Radiographs may also be useful in the detection of lytic lesions, which may be predictive of fracture risk. Many clinicians use radiography in association with the Hermann score (Hermann et al 1986) to describe the severity of bone disease. However, the Hermann score is weighted towards the detection of irreversible bone lesions, and radiographic measurements are generally of little value for detecting therapeutic responses. Radiographic sensitivity and specificity are reported to be 62% and 82%, respectively, when compared with MRI for the detection of bone involvement in a Gaucher paediatric population (El-Beshlawy et al 2006). MRI is, by far, the preferred method for imaging bone disease. When MRI is not available, radiographs are a poor substitute for gauging the severity of disease and/or response to therapy.

Dual energy X-ray absorptiometry (DXA) is used to measure bone mineral density (BMD) in Gaucher

patients (Ciana et al 2003, 2005; Fiore et al 2002; Lebel et al 2004; Pastores et al 1996). However, DXA assessments may produce false normal or even high values in patients with severe skeletal disease and sclerotic areas, avascular necrosis or collapsed vertebrae (Kinoshita et al 1998; Liu et al 1997; Pye et al 2007). Based on studies of non-Gaucher postmenopausal osteoporotic patients (McClung 2006), low bone mineral density (BMD) may indicate an increased risk of fractures, although this relationship has not been formally proven in Gaucher disease. DXA measures of bone mineralization density in children receiving enzyme therapy are useful in ensuring achievement of peak bone mass (Bembi et al 2002). DXA was, however, designed for use in adults and there are no agreed universal standards for paediatric assessments. DXA should be carried out in children only when normal age- and gender-appropriate values are available for comparison (vom Dahl et al 2006). A persistently low DXA score (T-scores of <-2.5 or <-2.0 in patients with a prior history of fracture) may be useful in determining when adjunctive bisphosphonate therapy, reported to improve BMD in Gaucher patients on enzyme therapy (Wenstrup et al 2004), should be considered (see below).

There is currently no biomarker that correlates with, or is predictive of, the osseous complications of Gaucher disease (vom Dahl et al 2006). Although biochemical markers of bone formation (for example, osteocalcin) are generally normal in osteopenic patients with Gaucher disease, and biomarkers for bone resorption are sometimes elevated in untreated patients (Ciana et al 2005) unlike other secondary resorptive bone disorders such as multiple myeloma, there is no evidence for perturbation of RANKL (required for osteoclast differentiation) and/or osteoprotegerin (inhibitor of osteoclast activity) in Gaucher disease (Magal et al 2006). However, the plasma concentrations of the osteoclast-activating cytokines, MIP1-α and MIP1-β, have been reported recently to be abnormally increased in patients with Gaucher disease and skeletal involvement (van Breemen et al 2007). Further work is required to achieve a greater understanding of the pathophysiology of Gaucher bone disease in all its aspects.

Current methods of monitoring bone disease in Gaucher patients have been reviewed recently (vom Dahl et al 2006). Key conclusions and recommendations included the following.

- MRI is the most sensitive method of monitoring bone marrow infiltration by Gaucher cells. The preferred semi-quantitative method for assessing bone marrow infiltration in routine clinical practice should use readily available technology; include both the lumbar spine and femur; be validated for inter-reader reliability at multiple centres; and be shown to correlate with other methods of assessing marrow disease. Methods meeting these criteria include the MRI bone marrow burden (BMB) scoring method (Maas et al 2003) and the ^{99m}Tc-Sestamibi scintigraphic method (Mariani et al 2003). Uptake of ^{99m}Tc-Sestamibi (a synthetic lipophilic radiopharmaceutical) in patients enables imaging of Gaucher cells infiltrating the bone marrow (whether in the lower limbs or other sites such as the humerus). A semi-quantitative scoring method (0–8) based on the extent and intensity of ^{99m}Tc-Sestamibi uptake enables disease monitoring and the response to imiglucerase therapy. The Düsseldorf scoring method (Poll et al 2001) may be used for evaluation and monitoring of bone marrow disease and its complications of the lower bone extremities. A score based on eight anatomical sites is a measure of disease severity. This method also identifies a homogeneous (type A) and non-homogeneous (type B) pattern of bone marrow infiltration. Type B is associated with a higher degree of disease irreversibility.
- If possible, serial plain radiographs should not be routinely used as the *sole* method in assessing the evolution of bone disease in Gaucher patients. Although baseline plain radiography during initial assessment may yield useful information, radiographs are less sensitive for monitoring Gaucher bone disease than MRI and DXA technology.
- MRI assessment in children with Gaucher disease presents a special case (see below). Further research into child-focused monitoring methods is needed.
- Gaucher patients should receive a comprehensive initial radiological evaluation for bone disease and regular, ongoing radiological monitoring, at least every two years. Active bone disease may require more frequent monitoring.

We re-iterate the recommendations made by the Frankfurt panel of bone experts on current monitoring methods (vom Dahl et al 2006). The Bone Marrow Burden (BMB) score is the recommended semi-quantitative scoring method for assessing bone marrow infiltration of Gaucher cells and should be more widely adopted. Although MRI is a powerful technique, it is not available in all centres, and especially in developing countries or in remote locations. In such areas,

despite its limitations, plain radiography should be used to assess and monitor bone disease. Furthermore, many clinicians and even radiologists have little experience in interpreting MRI images from Gaucher patients. Provided proper technique is used, current digital technology offers the possibility of reading and interpreting images by a central panel of specialists to make effective use of available resources and support. This would help to eliminate differences in the interpretation of MRI images, which could have an impact on treatment decisions.

A standard radiological method is needed to detect subtle bone changes in children—the group in whom early intervention can best prevent long-term complications. Although there is some consensus on evaluation and monitoring recommendations for children with type I Gaucher disease (Charrow et al 2004), there is significant and continuing need to refine and validate radiological imaging standards and methods able to monitor skeletal disease in paediatric patients. The natural conversion of red to yellow bone marrow with time in children makes interpretation of MR images problematic (Babyn et al 1998). Use of DXA to assess bone mineralization density may also be challenging. There is a need for agreed standards for calculating values for bone mineralization density in children (Maas et al 2008).

Enzyme therapy is expensive and for its optimal effect should ideally be directed to the prevention of disability rather than palliation—a universal therapeutic principle with explicit relevance to the skeletal manifestations of Gaucher disease. Thus, early introduction of adequate treatment consequent upon rigorous assessment, with regular monitoring, is essential for a satisfactory outcome in Gaucher disease.

Use of bisphosphonates

The effect of enzyme replacement therapy on BMD remains uncertain; although recent evidence suggests that many osteopenic patients improve, a response may take years to become evident (Wenstrup et al 2007). It has been suggested that the effect of enzyme treatment on osteopenia may be age-dependent, although it is also likely that less than optimal results could be related to low-dose regimens (Lebel et al 2004). In addition, osteopenia may transiently worsen after initiation of treatment as normal haematopoietic marrow replaces marrow containing pathological macrophages and accompanying cells (Rudzki et al 2003). Anti-resorptive therapy with oral bisphosphonates in high doses rapidly increases bone density in Gaucher disease patients who are simultaneously treated with enzyme infusions (Wenstrup et al 2004), but the effect of bisphosphonate treatment on bone strength (Mariani G et al 2003) or fracture risk is unknown.

There is anecdotal evidence that parenteral administration of more potent bisphosphonates (for example, pamidronate) may ameliorate Gaucher bone pain in children (Bembi et al 1994; Ciana et al 1997). However, except in children or young adults with vertebral collapse and recurrent pathological fractures due to severe osteoporosis (Ostlere and Gold 1991), there is insufficient evidence to recommend use of adjunctive bisphosphonates for Gaucher disease as standard clinical practice. The achievement of peak BMD in children is an important therapeutic goal that will be accomplished optimally with enzyme replacement therapy, good nutrition, and judicious exercise. In the absence of a systematic controlled clinical trial in Gaucher disease, and relying on safety data from children treated with bisphosphonates for osteogenesis imperfecta, cautious use of adjunctive bisphosphonates in severely osteoporotic children with Gaucher disease by experienced clinicians may be justifiable.

The optimal duration of bisphosphonate treatment has not been defined. There are reports linking the use of bisphosphonates with development of osteonecrosis of the jaw, particularly but not exclusively in cancer patients (Bamias et al 2005; Marx et al 2005; Najm et al 2005; Van Poznak 2006; Zarychanski et al 2006). This complication may occur spontaneously or after dental care and may be related to the length of exposure to bisphosphonates (Junod et al 2005), the bisphosphonate used, previous dental procedures (Bamias et al 2005), the underlying disease process, and concurrent treatments such as radiotherapy or chemotherapy. It is suggested that the condition may be prevented by dose adjustment (Najm et al 2005) combined with scrupulous attention to oral sepsis and gingival disease.

At the time of writing, osteonecrosis of the jaw has not yet been reported in Gaucher patients receiving potent bisphosphonates. The proposed mechanism for this complication, however, which involves bisphosphonate-induced suppression of normal bone turnover resulting in metabolically dead and brittle bone tissue (Whyte 2006), should raise caution about the routine, long-term use of bisphosphonates for Gaucher disease.

There are no formal clinical trials in Gaucher disease for high-potency bisphosphonates such as pamidronate, zolendronate and ibandronate. There are also no reliable data in Gaucher disease for other available treatments for osteoporosis including oestrogens or selective oestrogen receptor modulators, calcitonin or teriparatide, or for new, currently investigational, treatments such as strontium ranelate and

denosumab. Calcitriol (vitamin D) is ineffective in increasing bone mineral density in splenectomized patients with Gaucher disease (Schiffmann et al 2002) and the role, or recommended amount, of calcium supplementation is unknown.

In adults with Gaucher disease with persistent osteoporosis despite enzyme therapy, and particularly in elderly patients with high risk of falling, there is at least worldwide anecdotal evidence that oral bisphosphonates appear relatively safe. Patients should be made aware of, and be observed for, osteonecrosis of the jaw, particularly in association with dental infection and oral surgery. Almost all individuals who have suffered osteonecrosis of the jaw had malignancies being treated with chemotherapy and/or radiation therapy and there are no reported cases in children. Experience with bisphosphonates in patients suffering from malignant disease suggests that zoledronic acid therapy carries the greatest risk of jaw bone necrosis, or painful refractory bone exposures of the jaw, but this complication may also occur with several of the newer nitrogen-containing agents, including also pamidronate and alendronate (Marx et al 2005; Ruggiero et al 2004). Dental procedures, including extractions, and active periodontal disease are a frequent association with the development of these lesions. Since these bisphosphonates bind to bone tissue and have long-lasting effects, the risks of dental surgery, as with the effects of radiation, are also likely to be long-lasting.

The FDA has issued a warning about bisphosphonate therapy in relation to dental procedures, which should be avoided where possible for at least ten years. Although the risks cannot be obviated completely, vigorous preventive measures, including treatment of periodontal disease (enhanced hygiene and chlorhexidine mouthwashes, and where necessary antimicrobial therapy) should be instituted. Here, we now advise that Gaucher patients receiving these agents should have a formal dental review at the start of treatment. Gaucher cell infiltration and mandibular abnormalities are reported in Gaucher patients (Hall et al 1985). It seems reasonable that dental and oral evaluations should be carried out during bisphosphonate therapy as well as for several years after drug discontinuation (Junod et al 2005). It has also been suggested that all patients, regardless of the underlying primary diagnosis, be counselled regarding possible occurrence of osteonecrosis of the jaw before initiation of therapy (Zarychanski et al 2006).

For all patients, before adjunctive bisphosphonate treatment is started, the end-points of therapy should first be determined. Treatment response should be monitored with serial DXA scans so that therapy can be stopped when the desired bone mineralization density (and reduction of fracture risk) has been achieved.

It should also be noted that administration of parenteral bisphosphonates in patients with hypovitaminosis D may cause severe hypocalcaemia with a risk of seizures and arrhythmias. Any use of these agents in patients with Gaucher disease should be justified on the basis of the presence of severe metabolic bone disease and only after investigation of vitamin D status, with appropriate supplementation where necessary. In view of possible complications related to, for example, calcium homeostasis or renal function, initial administration of parenteral bisphosphonates should be done as directed by the manufacturers in a medical setting in which calcium levels (preferably ionized) should be monitored, with emergency treatment available if required.

Unmet needs

Disease severity scoring indices used to describe the extent of disease in Gaucher patients, such as Zimran score (Zimran et al 1992) and Hermann score for bone disease (Hermann et al 1986), were conceived in the pre-treatment era. Despite incorporating quantifiable and potentially modifiable parameters such as organ volumes, serum liver-related tests and subjective pain assessments, these tests give substantial weight to constants such as splenectomy, osteonecrosis, joint replacement and imaging abnormalities, and are, thus, not sufficiently sensitive to define therapeutic changes that evolve slowly over time. An innovative disease severity index is urgently needed that is validated in type I Gaucher disease and able to discern relevant salutary changes in the disease specifically in response to treatment. Such a severity index might also allow the course and prognosis of the disease to be broadly predicted at the time of diagnosis. Thorough clinical validation of one or more biomarkers in this context may also prove to be an invaluable adjunct to operational research in this field. There is also an urgent need for radiological monitoring guidelines for bone disease in children with Gaucher disease, and for agreed paediatric standards for DXA assessment of bone mineral density and MRI assessment of bone marrow infiltration (Maas et al 2008).

Conclusions

Gaucher disease is a chronic and clinically heterogeneous inherited disorder affecting many systems. Therapeutic goals and monitoring guidelines published in 2004 define the response in different tissue compart-

ments that can be expected over time from enzyme replacement treatment. These goals require periodic review to incorporate continually emerging knowledge of the disease and its treatment. Since 2003, new data on biomarkers, the use of bisphosphonates, and methods for monitoring bone disease have mandated a re-examination of published therapeutic objectives. It is also necessary to review the guidelines for pregnancy and for splenectomy. In furthering the best international standards for clinical management of Gaucher disease based on therapeutic goals, we endorse the formation of a working group to develop and validate a new disease severity index which can be applied universally. A second working group will investigate the most widely applied biomarkers to determine the extent to which their use might predict long-term outcomes of the disease. A third working group of experts in bone disease and bone imaging will be established to investigate which standards and technologies can best evaluate clinically relevant aspects of Gaucher bone disease in children.

Acknowledgements The Second International Gaucher Disease Management Board is an independent body supported by an educational grant by Genzyme Corporation, Cambridge, MA. This publication was supported by an unrestricted educational grant from Genzyme Corporation, Cambridge, MA. Editorial support was provided by Conscience Creative LLP, Leatherhead, UK. The opinions or views expressed in this paper are those of the authors and do not necessarily reflect the opinions or recommendations of Genzyme Corporation.

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