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Gaucher disease and the clinical experience with substrate reduction therapy

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Gaucher disease is caused by an enzymatic defect with consequent accumulation of glucocerebroside. Type I, the non-neuronopathic form, is rather common and panethnic. Patients may present with hepatosplenomegaly, anaemia, thrombocytopenia and skeletal or lung involvement. Enzyme replacement therapy ameliorates disease symptoms and signs; however, it involves lifelong intravenous therapy, is costly and is incapable of crossing the blood–brain barrier. Substrate reduction with *N*-butyldeoxynojirimycin (OGT 918) is a harbinger of oral iminosugars for glycolipid storage disorders. Long-term data in the seminal trial (100 mg three times per day), demonstrate safety and efficacy in adult type I patients naive to enzyme therapy, and suggest its application in patients unwilling or unable to receive enzyme replacement and tolerating side effects, including diarrhoea, weight loss, tremor and peripheral neuropathy (mostly reversible with dose reduction or withdrawal). Dose dependency was demonstrated with 50 mg three times per day. In patients stabilized on enzyme therapy switched from or in combination with enzyme, no deterioration in disease parameters was seen but side effects were as above. Although efficacy is less dramatic than enzyme treatment, it may be that plateaux are achieved asymptotically so therapeutic outcomes with OGT 918 may ultimately be comparable. Yet, given the above side effects and the lack of long-term experience, patients with very mild manifestations would probably not be appropriate candidates.

Keywords: Gaucher disease; enzyme replacement therapy; substrate reduction therapy; miglustat

1. INTRODUCTION

Gaucher disease was first described in a 32-year-old woman in 1882 by a French medical student Philippe Gaucher, who actually assumed that the large splenic cells which today bear his name were a manifestation of a primary neoplasm of the spleen. More than a century later, we now know that Gaucher disease is the most prevalent lysosomal storage disorder, caused by an inherited enzymatic defect with consequent accumulation of undegraded glucocerebroside in monocyte-macrophage cells, the 'Gaucher cells' (Beutler & Grabowski 2001). Diagnosis of the disease is via assay of decreased β-glucocerebrosidase activity in peripheral blood in conjunction with DNA mutation analysis. None the less, neither quantity of residual activity nor specific genetic make-up (genotype) can accurately predict type or degree of severity of the disease (phenotype) except in a broad sense. Thus, the clinical heterogeneity that marks all forms of Gaucher disease is attributable only in part to the more than 200 mutations within the glucocerebrosidase gene (Grabowski & Horowitz 1997); other genetic and environmental factors undoubtedly also influence phenotype.

2. ERT

Before the advent of ERT (Barton *et al.* 1991), medical management was confined to symptomatic relief and surgical interventions such as splenectomy and orthopaedic operations. Enzyme therapy with placental-derived preparation, alglucerase (Ceredase, Genzyme, Inc.), or the recombinant form, imiglucerase (Cerezyme, Genzyme Therapeutics Inc., Cambridge, MA), has proven to be safe and effective in more than 3000 patients worldwide (Aerts *et al.* 2003; Brady 2003). Reduction in organ volumes, improvement in haematological parameters, and prevention of skeletal complications when given to at-risk patients, have dramatically improved quality of life of treated patients.

The good clinical results have been noted despite the wide range of dosages and frequencies employed (Grabowski *et al.* 1998). However, the administration of enzyme therapy poses a significant hardship to the patient as it involves intravenous infusions, usually once every two weeks, for life. In addition, the high cost of enzyme treatment limits the number of patients that can avail themselves of this treatment, particularly in third world countries. Finally, the current formulation of enzyme replacement is incapable of crossing the blood–brain barrier, thereby circumscribing its value in patients with significant neurological manifestations.

In a recent summary of the database provided by the International Gaucher Registry, the excellent efficacy and safety profiles of enzyme replacement in over 1000 patients with 2–5 years of treatment were recorded (Weinreb *et al.* 2002). In anaemic patients, haemoglobin concentration increased to normal or near normal within a year with sustained response lasting 5 years. In thrombocytopenic patients with intact spleens, the most rapid response occurred during the first 2 years, with sub-

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sequent slower improvement. The likelihood of achieving a normal platelet count decreased with increasing severity of baseline thrombocytopenia and degree of splenomegaly at baseline. In patients with prior splenectomy, platelet counts normalized within 1 year. Hepatomegaly decreased by 30-40% over 2–5 years as a function of baseline liver volume. Splenomegaly decreased by 50–60% over 2–5 years, but rarely to volumes less than five multiples of normal. In patients with bone pain or bone crises, 52% were pain-free after 2 years and 94% reported no additional crises.

Thus, ERT prevents progressive manifestations of Gaucher disease, and completely or partly ameliorates Gaucher disease-associated anaemia, thrombocytopenia, organomegaly, bone pain and bone crises. It is important to note, however, that most children who begin enzyme therapy in childhood do not suffer skeletal complications to the same extent as patients of prior decades (Dweck *et al.* 2002). This indeed may prove to be among the greatest advantages of early diagnosis: early onset of treatment in children at risk of severe disease will lead to a significant decrease in bone involvement and hence one can hope for an improved quality of life among treated children (Dweck *et al.* 2002).

The effect on bone density may still be preliminary and is further complicated by the impact of other genetic and environmental factors. Thus an option for clinical management of skeletal disease in patients with Gaucher disease, as in the normal population, is bisphosphonates, which combat both bone loss and secondary bone pain. In a prospective, double-blind, placebo-controlled study, an oral bisphosphonate was given to adult patients who had undergone at least 2 years of enzyme therapy and was shown to improve the mineral bone density (Wenstrup *et al.* 2001). A similar new clinical trial is underway for children above the age of 12 years (G. A. Grabowski, personal communication).

Infiltrative lung disease that is secondary to severe Gaucher disease in both children and adults (Lee 1982; Goitein *et al.* 2001), possibly as a consequence of hepatopulmonary syndrome (Dawson *et al.* 1996), may benefit from enzyme therapy. However, pulmonary hypertension has been noted in some patients on enzyme therapy (Harats *et al.* 1997). Although a causal relationship with enzyme replacement has been difficult to prove, treatment withdrawal may be considered in those patients who evince a primary-like pulmonary hypertension and show a progressive increase in tricuspid insufficiency gradient (greater than 30 mmHg) with therapy during routine echocardiographic monitoring (Elstein *et al.* 1998). A recent study has concluded that there was a remarkable predisposition for pulmonary hypertension in type 1 Gaucher disease. Progression to severe, life-threatening pulmonary hypertension was correlated with genetic factors such as a non-N3 705 mutation, positive family history, and the ACE I gene polymorphism as well as epigenetic modifiers such as splenectomy and female gender.

With reference to very mildly affected adults, it should not be assumed that there is never any progression in disease severity, and hence, although one cannot recommend the institution of enzyme therapy without reservations to all mildly affected patients, particularly in less wealthy countries, routine evaluations in centres experienced in the treatment of Gaucher disease are invaluable and should be encouraged at regular intervals to follow the trajectory of each individual's disease course.

3. MAINTENANCE REGIMENS

Despite the success of enzyme treatment for symptomatic patients, one must ask whether, in individual patients who have had up to 10 years of this therapy, dose adjustments and/or circumscribed 'drug vacations' may be suggested, particularly to patients who have achieved near-normalization of the major parameters of the disease. This argument is particularly cogent in light of a paper that documents the fate of adult patients and one child who, after varying periods on (low-dose) enzyme therapy, withdrew from treatment for personal reasons. Unexpectedly, for most of the adults there was a continuation of the beneficial effects of enzyme on disease parameters, with none showing abrupt deterioration (Elstein *et al.* 2000). None the less, drug vacations should not be considered for children. Regular and frequent intervals for evaluation of status are critical for patients who do stop enzyme therapy, particularly with reference to platelet counts and chitotriosidase levels. Similarly, for patients unable to receive enzyme infusions because of adverse reactions or who are unwilling to do so for an open-ended period, new treatment options need to be explored.

4. FUTURE IMPROVEMENT OF ERT

Despite the obvious advantages of efficacy and safety that have made enzyme replacement the gold standard for treatment of Gaucher disease and a model aspired to for treatment of other lysosomal storage disorders, there is always room for improvement. Poor delivery to the lungs, bones and brain, and increased convenience for the patient are two areas that are currently being explored by Genzyme Therapeutics Inc., the manufacturer (Barranger 2002). Increased delivery to the storage cells, possibly by altering mannose residues on the enzyme or by increasing the receptors on the storage cells, are potential avenues. Another approach that is being explored is blocking the enzyme from being diverted to other cells such as the hepatocytes and thereby dissipating its effectiveness. Improved deglycosylation of the enzyme offers another modality. Finally, increased longevity of the enzyme may be attempted.

5. SUBSTRATE REDUCTION THERAPY

Unlike enzyme replacement, which has a direct effect on breakdown of the glycolipid, the concept of substrate reduction involves an indirect action on storage material within the macrophages. In 1996, Radin referred to enzyme therapy as this 'spectacularly expensive mode of treatment should be replaceable with a suitable enzyme inhibitor that simply slows formation of the lipid, and matches the rate of synthesis with the rate of the defective, slowly working beta-glucosidase' (Radin 1996, p. 153).

Substrate reduction with the iminosugar *N*-butyldeoxynojirimycin (miglustat; OGT 918), an inhibitor of ceram-

ide glucosyltransferase, the first committed step in the biosynthesis of glycolipids, is a harbinger of a new class of drugs for many glycolipid storage disorders. The basic concept of this approach is to attenuate the rate of synthesis to achieve a balance with the reduced activity of endogenous glucocerebrosidase in patients with Gaucher disease. This biological rationale of substrate inhibition (Platt *et al.* 1994), the successful outcome in animal models (Platt *et al.* 1997) and the safety data from a clinical trial involving 130 patients with HIV (Tierney *et al.* 1995) had suggested OGT 918 as a suitable candidate for oral treatment of glycolipid storage disorders (Butters *et al.* 2003; Platt *et al.* 2003).

A similar concept to the above is to develop small molecules that are inhibitors of the ceramide moiety rather than via the (imino-) sugar moiety as above, and that are structurally based on the parent compound D-*threo*-1-phenyl-2-decanoylamino-3-morpholino-1-propanol. These inhibitors provide useful tools for manipulating glycosphingolipid levels in cells and have also been applied in Fabry disease models (Abe *et al.* 2001).

6. THE SEMINAL TRIAL OF OGT 918 FOR TYPE 1 GAUCHER DISEASE

The pivotal clinical trial of OGT 918 was a non-comparative phase I/II study carried out in 28 adult patients from four centres (Cambridge, UK; Amsterdam; Prague; Jerusalem) mostly naive to ERT, with mild to moderate type 1 Gaucher disease, who were unable or unwilling to receive enzyme treatment. Twenty-two patients completed 12 months of treatment with 100 mg TID OGT 918 and achieved a mean reduction in liver volume of 12.1% and a mean reduction in spleen volume of 19%. A mean increase (not statistically significant) in haemoglobin concentration of 0.26 g dL^{-1} and a mean platelet count increase of 8.3×10^9 l^{-1} were observed (Cox *et al.* 2000; Moyses 2003).

7. THE EXTENSION OF THE SEMINAL TRIAL OF OGT 918

Patients in this study were given the option of continuing into a study extension. Eighteen patients were enrolled into the extension study and received 100 mg daily to 200 mg TID OGT 918. Fourteen subjects were evaluated after 24 months and, after 3 years of continuous OGT 918 treatment, results from 13 patients were available.

Baseline mean liver volume was 2.5 (range of 1.76–3.48) or 1.1–2.5 times normal size. The mean reduction in liver volume was 14.5% after 24 months and 17.5% after 36 months. Mean spleen organ volume at baseline was 1.7 (range of 0.91–3.36) or 5.1–24.8 times normal size. The mean reduction in spleen volume from baseline was 26.4% after 24 months and 29.6% after 36 months.

The response of haematological parameters was assessed as an increase from the baseline value. Baseline mean haemoglobin concentration was 11.56 g dL^{-1} (range of 0.93–1.51 g cm^{-3}). Overall, there were steady increases in mean haemoglobin concentration throughout the study with increases of 0.09 g cm^{-3} at 24 months and 0.095 g cm^{-3} at 36 months. Patients with a baseline haemoglobin of less than 1.15 g cm^{-3} (anaemic subjects) had a larger mean increase at 24 months (0.13 g cm^{-3}).

Baseline mean platelet count was 75.3×10^9 l^{-1} (range of $33–262 \times 10^9$ l^{-1}). Throughout the first 24 months there was a small gradual increase in platelet count from baseline. At 18 months the increase was 11.2×10^9 l^{-1}, at 24 months it was 13.6×10^9 l^{-1} and at 36 months, the mean increase in patients remaining on therapy was 22.2×10^9 l^{-1}.

Elevated chitotriosidase activity is characteristic of Gaucher disease and appears to reflect the burden of abnormal storage cells. Reductions in the level of chitotriosidase are therefore specifically indicative of improvement in disease severity. From the mean baseline of 16 877 nmol ml^{-1} h^{-1} there was a reduction of 15% at 12 months and a reduction of 21.9% at 24 months.

Quantitative chemical shift imaging was performed on two subjects to image three vertebrae of the spine. The results showed an improvement in bone marrow fat fraction at 12 months and a further improvement at 24 and 36 months.

The most common adverse event during the first year of the study was diarrhoea, which occurred in 16 (89%) patients principally during the first 12 months of treatment with OGT 918, and declined during the extension phase. Some patients did find the symptoms intolerable and gastrointestinal symptoms were a major cause of withdrawal. However, the symptoms disappeared promptly on cessation of treatment. The proportion of patients with weight loss declined from 9 patients (50%) after 12 months to only two patients (29%) at 36 months.

Two patients were withdrawn as reported in the seminal trial paper because of peripheral neuropathy; therefore, neurological assessments including electromyography and nerve conduction velocity studies were conducted in all patients. Tremor and paraesthesia were noted in the extension in three patients (17%), with the third patient discontinuing the trial.

(a) *In summary*

These long-term data presented on safety and efficacy in type 1 patients who were essentially naive to enzyme therapy but had measurable disease suggest future applications of oral substrate reduction therapy with OGT 918 in those unwilling or unable to receive intravenous enzyme replacement and who tolerate the side effects.

8. THE LOW-DOSE TRIAL OF OGT 918 FOR TYPE 1 GAUCHER DISEASE

The objective of this study was to evaluate the efficacy and safety of low-dose substrate balance therapy with OGT 918 for the treatment of adults with Gaucher disease. Since the haematological parameters in the original trial of OGT 918 at a dosage of 100 mg TID did not appear to respond as well as the reduction in spleen and liver volume, it had been suggested that a degree of marrow suppression might have been engendered by treatment with OGT 918. It was therefore considered important to assess the response to a lower dose, and secondarily, whether 50 mg TID would result in fewer or milder side effects than those seen with 100 mg TID. Eighteen patients with Gaucher disease from two centres

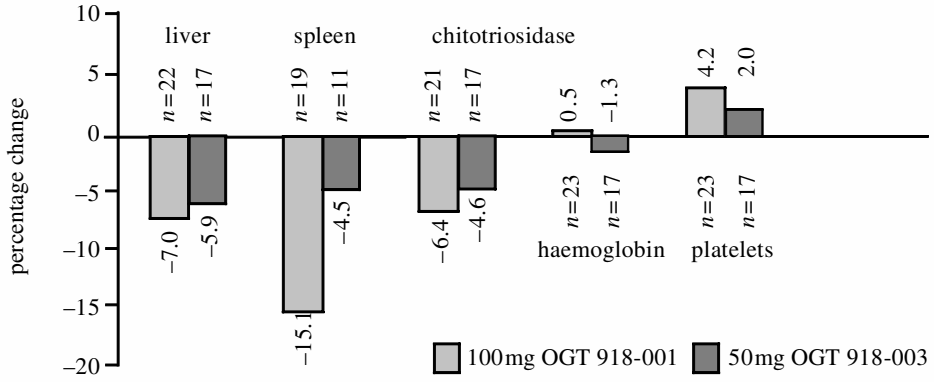

Figure 1. Comparison of percentage changes at six months with OGT 918 at 100 mg TID and 50 mg TID in patients naive to ERT.

(Johannesburg and Jerusalem) were enrolled in an open-label six-month study of OGT 918, 50 mg TID. Apart from the lower dose of 50 mg TID, the study was similar to the main efficacy trial in terms of entry criteria, assessments and clinical endpoints (Heitner *et al.* 2002).

In comparison with the results of the first study, at six months subjects who received 50 mg OGT 918 TID showed smaller reductions in liver organ volumes (mean of 5.9%) and spleen organ volumes (mean of 4.5%) than those who received 100 mg OGT 918 TID (figure 1). Only small mean changes in haemoglobin concentration from baseline were seen. There was no reduction in the severity or frequency of gastrointestinal side effects relative to the incidence seen in the seminal trial; in addition there was an increased incidence of tremor. The exact mechanism of the tremor remains unexplained although it could not be distinguished from an exaggerated physiological tremor and disappeared with withdrawal. Seventeen subjects completed the six-month phase.

Quality of life measures were also assessed in this study, and subjective amelioration was reported from baseline to month six in physical function (mean of 9.4%, $p = 0.052$), enhanced role limitations due to physical problems, general health perceptions, vitality (mean of 16.5%, $p = 0.004$) and social function.

9. THE EXTENSION OF THE LOW-DOSE TRIAL OF OGT 918

Sixteen subjects continued into the extended treatment phase where treatment was increased up to a maximum of 100 mg TID in the majority of patients. Data up to 12 months were available for 13 patients.

(a) *In summary*

Although this study highlights the dose dependency of OGT 918 in naive patients with measurable type 1 Gaucher disease, there was no inherent value in this regimen as an alternative starting regimen since there was no improvement in the haematological parameters and there was an unchanged profile of gastrointestinal side effects. The patients who continued in the extension showed further statistically significant improvements in organ reduction and in chitotriosidase levels, whereas haematological parameters of haemoglobin concentration and platelet counts showed a trend towards improvement.

Gastrointestinal complaints including diarrhoea and weight loss showed the same trajectory as in the high-dose trial. EMG/nerve conduction assessments revealed one patient with mild asymptomatic Charcot–Marie–Tooth syndrome; no drug-related changes in these tests were identified. Two additional patients with peripheral neuropathy were reported, but both also suffered from vitamin B_{12} deficiency (Heitner *et al.* 2002).

10. OGT 918 AS ORAL MAINTENANCE REGIMEN FOR TYPE 1 GAUCHER DISEASE: SWITCH FROM OR COMBINATION WITH INTRAVENOUS ENZYME REPLACEMENT

This study was designed to assess the tolerability and pharmacokinetic profile of OGT 918 when given to patients who had been previously treated with enzyme replacement, and to compare the results with either medication taken alone or in combination.

Thirty-six patients from a single centre (Jerusalem) who had been stabilized after a minimum of 2 years on enzyme replacement therapy were randomized to three treatment groups:

(i) switch to OGT 918 (100 mg TID),
(ii) continue with enzyme therapy (Cerezyme) at current regimen, and
(iii) combination of OGT 918 and the current enzyme (Cerezyme) regimen

for a period of six months. The randomization was carried out according to a minimization procedure, which included a random component and was balanced across gender, age, splenectomy, avascular necrosis and length of time on ERT. The entry criteria and assessments were similar to those for the other studies with the exception of the requirement of enzyme therapy.

Thirty-three subjects completed the six-month study. Twenty-nine subjects entered the optional extended treatment phase of six months to receive OGT 918 alone. Therefore extension data on those patients switching to OGT 918 from enzyme replacement therapy or combination therapy were available in 19 subjects for six months, and in 10 subjects for 12 months.

After six months, there were few statistically significant differences among groups in all measures (table 1); none

Table 1. Results of percentage changes in key endpoints at six months in the switch-over trial.

	change from baseline in treatment group, at six months			
variable	OGT 918	cerezyme	combination	significance
liver volume (%)	−2.9	3.6	−4.9	$p = 0.047$, cerezyme versus combination
spleen volume (%)	−4.8	−2.1	−8.5	not significant
haemoglobin (g dL^{-1})	−0.31	−0.15	−0.10	not significant
platelet count ($\times 10^9 l^{-1}$)	−21.6	15.3	2.7	$p = 0.028$, OGT 918 versus cerezyme
chitotriosidase activity (%)	33.0	−0.3	−3.9	$p = 0.004$, OGT 918 versus cerezyme; $p = 0.001$, OGT 918 versus combination

had clinical impact. Patients receiving OGT 918 alone reported significantly greater convenience with no deterioration in overall quality of life. Among the 33 patients completing the six-month study, 29 opted to receive OGT 918 alone in an extended protocol. At 18 months, 22 patients remained on therapy and their liver and spleen volumes were essentially unchanged. Haemoglobin values remained stable, whereas platelet counts fluctuated but showed a trend to fall. There was a rise in mean chitotriosidase levels which is unexplained. No subject required re-institution of Cerezyme treatment during the extended treatment period due to deteriorating disease. No subject withdrew due to lack of efficacy and 27 subjects continued on OGT 918 beyond 12 months. The most common adverse events were gastrointestinal and tremor. The tremor, which was more common than in the seminal trial, disappeared with decreased dosage or withdrawal.

There was virtually no effect on the pharmacokinetics of Cerezyme by OGT 918 and there were no adverse drug–drug interactions between Cerezyme and OGT 918.

(a) *In summary*

This clinical trial, the largest randomized study in patients with Gaucher disease, is also the first to investigate maintenance modalities for patients who had been stabilized on ERT. Importantly, it presents an opportunity for these patients to be weaned from what has heretofore been considered a lifetime dependency on intravenous enzyme infusions. Similarly, this modality may be an alternative for patients who have developed serious side effects or who have failed to respond to ERT.

Most side effects associated with OGT 918 were similar to those reported in the seminal study, with the exception of tremor. It is inexplicable why these patients are different than the mostly naive patients, where none developed tremor in the first six months of the trial. In addition, it is unexplainable why there were increased levels of chitotriosidase, a well-accepted marker of disease activity, among these patients whose levels had been stable for years on enzyme therapy.

11. COGNITIVE IMPAIRMENT

Five patients among all the trials had complained of memory loss during or following participation in the OGT 918 trial and cognitive impairment was found in two of these. The aetiology in both patients is unclear but vitamin B_{12} deficiency is a possible diagnosis for one and a putative diagnosis of Alzheimer's disease for the other (66-year-old) patient.

12. CLINICAL APPLICATION OF OGT 918

OGT 918 may play a part in the treatment of type 1 Gaucher disease in patients unwilling or unable to receive ERT. Although the efficacy data are not quite as good as those seen with enzyme treatment within the first 2 years of therapy, it may prove to be the case that plateau values are achieved asymptotically so that the therapeutic outcome with OGT 918 is comparable to ERT. Since the presentation of these data at the October meeting of The Royal Society of Medicine, OGT 918 was approved for marketing in Europe for patients with mild to moderate type 1 Gaucher disease for whom ERT is unsuitable. Yet, given the side effects profile, the authors do not recommend treatment of patients with asymptomatic disease or minimal signs, in whom follow-up and/or ERT should be the preferred option.

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GLOSSARY

ERT: enzyme replacement therapy
TID: three times per day