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Sustained therapeutic effects of oral miglustat (Zavesca, *N*-butyldeoxynojirimycin, OGT 918) in type I Gaucher disease

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Summary: It has been shown that treatment with miglustat (Zavesca, *N*-butyldeoxynojirimycin, OGT 918) improves key clinical features of type I Gaucher disease after 1 year of treatment. This study reports longer-term efficacy and safety data. Patients who had completed 12 months of treatment with open-label miglustat (100–300 mg three times daily) were enrolled to continue with therapy in an extension study. Data are presented up to month 36. Liver and spleen volumes measured by CT or MRI were scheduled every 6 months. Biochemical and haematological parameters, including chitotriosidase activity (a sensitive marker of Gaucher disease activity) were monitored every 3 months. Safety data were also collected every 3 months. Eighteen of 22 eligible patients at four centres entered the extension phase and 14 of these completed 36 months of treatment with miglustat. After 36 months, there were statistically significant improvements in all major efficacy endpoints. Liver and spleen organ volumes were reduced by 18% and 30%, respectively. In patients whose haemoglobin value had been below 11.5 g/dl at baseline, mean haemoglobin increased progressively from baseline by 0.55 g/dl at month 12 (NS), 1.28 g/dl at month 24 ($p = 0.007$), and 1.30 g/dl at month 36 ($p = 0.013$). The mean platelet count at month 36 increased from baseline by 22×10^9/L. No new cases of peripheral neuropathy occurred since previously reported. Diarrhoea and weight loss, which were frequently reported during the initial 12-month study, decreased in magnitude and prevalence during the second and third years. Patients treated with miglustat for 3 years show significant improvements in organ volumes and haematological

parameters. In conclusion, miglustat was increasingly effective over time and showed acceptable tolerability in patients who continued with treatment for 3 years.

Gaucher disease is characterized by an accumulation of glucosylceramide in the mononuclear phagocyte system resulting from an inherited deficiency of the lysosomal enzyme glucocerebrosidase. The main clinical manifestations of type I Gaucher disease include enlargement of the liver and spleen, anaemia, thrombocytopenia and bone involvement (Cox and Schofield 1997).

Although enzyme replacement therapy (ERT), the current therapeutic standard, has transformed the treatment of Gaucher disease, it has the inconvenience of repeated intravenous infusions. Treatment with ERT is expensive and access to enzyme therapy is not guaranteed for all patients in whom it is required. There is also evidence that some complications such as long-standing bone disease and neurological signs may be less responsive to ERT (Elstein et al 1996; Vellodi et al 2001). Hence there is a need for alternative treatments that are convenient and accessible.

Since the accumulation of glucosylceramide is due to an imbalance between its rates of synthesis and degradation, an alternative therapeutic strategy, termed substrate reduction therapy (SRT), has been developed. By attenuating the rate of synthesis of the substrate in patients with Gaucher disease, it should be possible to clear the accumulated glycosphingolipid even with the low residual activity of endogenous glucocerebrosidase (Platt et al 1994). Miglustat (Zavesca, *N*-butyldeoxynojirimycin, OGT 918) is an inhibitor of glucosylceramide synthase, the first committed step in the biosynthesis of glycosphingolipids (Platt et al 1997). When tested in animal models of glycosphingolipid storage disorders, the compound reduces the storage material and delays onset and progression of disease manifestations (Platt et al 2003).

We previously reported the results of a 12-month open-label study of miglustat in 28 adult patients with type I Gaucher disease who were unable or unwilling to receive treatment with ERT (Cox et al 2000). Miglustat is licensed, in Europe, the United States and Israel, for the oral treatment of mild-to-moderate type I Gaucher disease where ERT is not suitable and a position statement has recently been published in this Journal (Cox et al 2003). Here we give 36-month data from the extension phase of this study, which demonstrate its long-term therapeutic efficacy and safety and further establish SRT as a valid treatment option.

PATIENTS AND METHODS

The original 12-month study and the extension phase were approved by the respective independent ethics committee/institutional review board at each participating centre. The study was conducted in accordance with the Declaration of Helsinki and within the guidelines of ICH Good Clinical Practice.

Patients: A total of 28 patients were enrolled from four centres. Inclusion and exclusion criteria have been reported previously (Cox et al 2000). Twenty-two of these patients completed the original 12-month trial and were eligible to enter the extension phase of the study. Patients were allowed to continue if the drug was still being developed for treatment of Gaucher disease and if the investigator felt the subject would benefit from extended therapy. Patients provided written informed consent before entering the extension phase.

Treatment and assessments: Patients received miglustat 100 mg three times daily, (t.d.s.) but dose increases or decreases were permitted based on efficacy and tolerability. The dose could be decreased to 100 mg once daily or increased by 100 mg three times daily each month, with a maximum dose of 300 mg three times daily permitted. Efficacy parameters such as liver and spleen volumes were measured every 6 months using magnetic resonance imaging (MRI) or non-contrast computed tomography (CT) as previously reported (Cox et al 2000). Haematological and biochemical parameters including chitotriosidase (Hollak et al 1994) were recorded every 3 months. Adverse events, body weight and vital signs were also recorded every 3 months. Plasma concentrations of glucosylceramide, which represent the storage material that accumulates in Gaucher disease, and ceramide were measured in eight patients at baseline, month 6 and month 12. These data were not reported for the initial 12-month treatment period of the study.

Dixon quantitative chemical shift imaging (Dixon QCSI) of the lumbar spine (L3–L5) was performed for two patients at the Dutch centre according to an earlier protocol (Maas et al 2001). This technique measures the ratio between triglycerides and water content of bone marrow. In type I Gaucher disease there is displacement of the normal triglyceride-rich adipocytes in the bone marrow by Gaucher cells (Miller et al 1996) and the adipocytes are greatly reduced in number in patients with type I Gaucher disease (Johnson et al 1992; Maas et al 2002). Low bone marrow fat fractions found in patients with Gaucher disease therefore reflect the degree of infiltration with Gaucher cells.

Statistical analysis: No formal sample size calculation was performed for this extension study given that Gaucher disease is a rare genetic disorder with limited numbers of patients.

All patients with data were included in the statistical comparisons at each time point. One-sample *t*-tests were used for comparisons of within-group differences of mean changes from baseline. Analyses at the principal time points (12, 24, 36 months) were supported by a last observation carried forward (LOCF) analysis at 36 months in order to include data for patients who withdrew earlier from the study.

RESULTS

Study population: Eighteen of the 22 eligible patients entered the extension phase; of the four who did not enter, one patient was excluded because of non-response

(this patient had also responded poorly to ERT), two exclusions were patient decisions and one was due to noncompliance. One patient received 200 mg t.d.s. throughout the extension phase and two patients received 100 mg t.d.s throughout. For the remaining 11 patients, doses ranged from 100 mg once to three times daily. The most common reasons for dose modification were (a) that the subject preferred an alternative dosing schedule and (b) that the dose was increased to improve the subject's response. The majority of patients received 100 mg t.d.s.

Efficacy

Organ volume and haematological parameters: Mean changes in organ volumes from baseline and haematological parameters are shown in Table 1. Individual percentage changes in organ volume over time are plotted in Figures 1 and 2 for liver and spleen, respectively. Mean liver and spleen organ volumes continued to show a statistically significant and progressive reduction over the 36 months of treatment and were reduced by 18% and 30%, respectively. LOCF analysis of liver volume at 36 months gave a reduction of -0.34 L (-0.44, -0.25; $p < 0.001$). LOCF analysis of spleen volume at 36 months gave a reduction of -0.42 L (-0.55, -0.29; $p < 0.001$).

Haematological and biochemical parameters also improved. Mean haemoglobin concentrations and platelet counts became significantly increased from baseline in the extended treatment phase. LOCF analysis for haemoglobin concentration at 36 months gave an increase of 0.74 g/dl (0.33, 1.14; $p = 0.001$). LOCF analysis for platelet count at 36 months gave an increase of 20×10^9/L (12, 27; $p < 0.001$). Plasma chitotriosidase activity decreased throughout the 3-year period during which it was measured (Figure 3). Mean chitotriosidase activity fell significantly at all time points assessed.

Other parameters: The results of the Dixon QCSI assessments on two patients showed a progressive improvement in bone marrow fat fraction over the 3-year study period and there was a trend towards the normal range (Figure 4).

Glucosylceramide analysis, conducted in eight of the patients, showed mean decreases from baseline (14.2 nmol/ml) of 2.2 and 2.8 nmol/ml at months 6 and 12, respectively, which were not statistically significant ($p = 0.074$ and $p = 0.172$, respectively), with ceramide levels remaining constant at these time points.

Safety: The majority of adverse events reported during the trial were mild in intensity. The proportion of patients experiencing diarrhoea (the most common adverse event) declined with time, from 86% during the first 6 months of treatment to 36% by month 36. Diarrhoea improved spontaneously or responded to treatment with loperamide or codeine phosphate. Approximately 60% of patients reported transient loss of weight during the study, with a mean weight loss of 6–7% at 12 months, which recovered by 24 months of treatment (Figure 5).

Peripheral neuropathy had been reported earlier in two patients (Cox et al 2000). It is noted that these two patients experienced the largest reductions in body weight (patient 101, 27.8% maximum reduction; patient 105, 14.6% maximum reduction). As a result of these findings, neurological assessments including electromyography

Table 1 Baseline values with mean changes in organ volumes and haematological parameters after 6–36 months of treatment with miglustat in patients entering the extension phase

	Baseline ($n=28$)	*12 months* ($n=22$)	*24 months* ($n=14$)	*36 months* ($n=14$)
Liver volume	($n=27$)	($n=21$)	($n=12$)	($n=12$)
Absolute (L)	2.38 (1.4, 3.70)	−0.28** (−0.38, −0.18)	−0.36** (−0.48, −0.24)	−0.44** (−0.53, −0.34)
Percentage	N/A	−12.11%** (−16.37, −7.85)	−14.46%** (−19.27, −9.65)	−17.51%** (−19.96, −15.06)
Spleen volume	($n=20$)	($n=18$)	($n=10$)	($n=10$)
Absolute (L)	1.66 (0.68, 3.36)	−0.32** (−0.42, −0.22)	−0.42** (−0.53, −0.30)	−0.53** (−0.69, −0.36)
Percentage	N/A	−18.98%** (−23.71, −14.25)	−26.40%** (−30.36, −22.44)	−29.64%** (−34.08, −25.21)
Haemoglobin <11.5 g/dl	($n=9$)	($n=9$)	($n=8$)	($n=8$)
Absolute (g/dl)	10.22 (9.30, 11.35)	0.55 (−0.20, 1.31)	1.28* (0.47, 2.10)	1.30* (0.37, 2.22)
Percentage	N/A	5.71% (−1.91, 13.32)	12.99%* (4.45, 21.52)	12.92%* (3.26, 22.59)
Platelet count	($n=28$)	($n=22$)	($n=13$)	($n=13$)
Absolute ($\times 10^9$/L)	88.10 (33, 334)	8.3* (1.88, 14.69)	13.58** (7.72, 19.43)	22.15** (12.33, 31.97)
Percentage	N/A	16.02% (−0.76, 32.81)	26.09%** (14.65, 37.54)	34.31%** (20.78, 47.85)

Baseline values in parentheses are the ranges
Post-baseline values in parentheses are 95% confidence intervals for the change from baseline
Values marked * and ** are statistically significantly different from baseline (*$p<0.05$, **$p<0.001$)

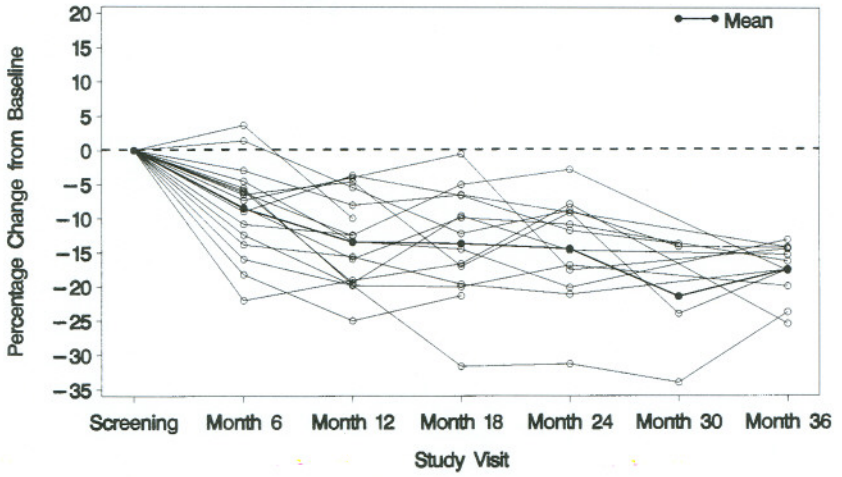

Figure 1 Percentage change from baseline in liver volume during 3 years of treatment with miglustat: individual data and mean

(EMG) and nerve conduction velocity (NCV) studies were conducted in all patients. No other unexpected cases of peripheral neuropathy were reported. About 20% of patients reported tremor during treatment that resolved spontaneously or following dose reduction or discontinuation of treatment. On investigation, the tremor appeared to be an exaggerated physiological tremor similar to that seen with sympathomimetic agents. One 66-year-old patient experienced cognitive impairment of unknown cause following discontinuation of miglustat after nearly 3 years of

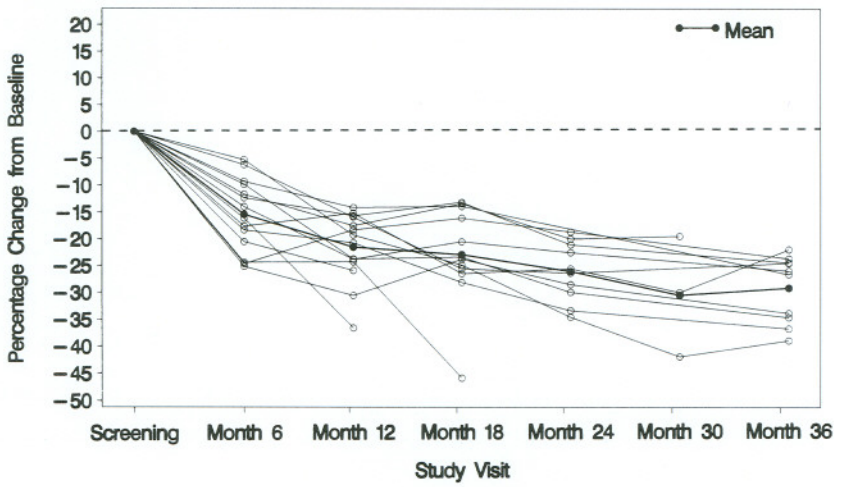

Figure 2 Percentage change from baseline in spleen volume during 3 years of treatment with miglustat: individual data and mean

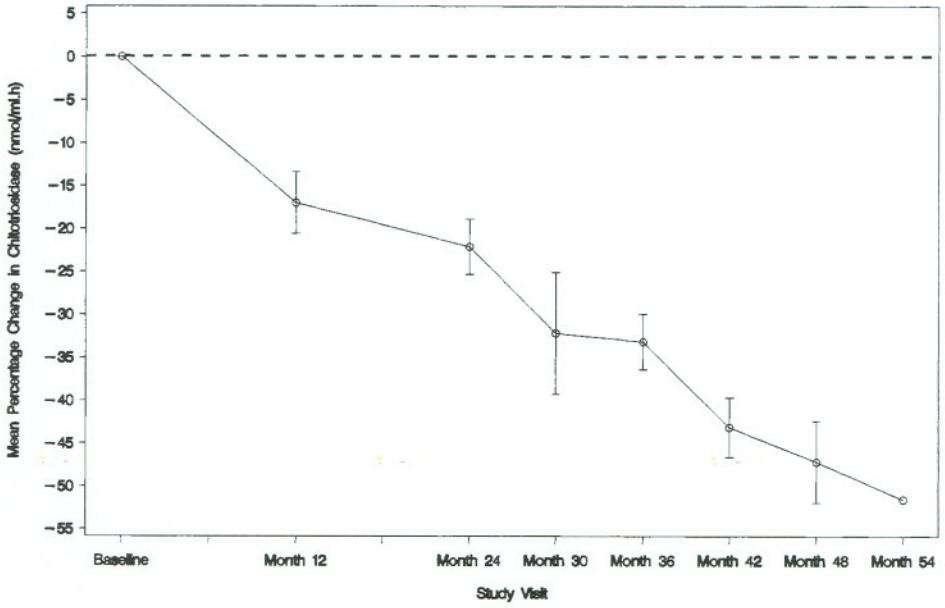

Figure 3 Mean percentage change in chitotriosidase activity from baseline to month 54 (with SEM). (Only patient 202 had a visit at month 54; therefore, the value plotted at month 54 is not an average but is the actual value)

treatment. This event was consistent with early-stage Alzheimer disease and was considered unlikely to be related to drug treatment.

Withdrawal: Of the 18 patients who entered the extension phase, two withdrew because of peripheral neuropathy (as reported in the original publication; Cox et al 2000), and two withdrew as a precautionary measure as a result of these events. Therefore, data on 14 patients were available at 36 months of treatment with miglustat.

DISCUSSION

Here we report a long-term therapeutic study in type I Gaucher disease. The improvement in key clinical features of Gaucher disease observed after 12 months of treatment with miglustat (Cox et al 2000) was maintained during the extension phase and the drug continued to be well tolerated. In this study we observed continued and increasing efficacy, with sustained safety of miglustat after 36 months of treatment. Liver and spleen volumes continued to decline during the second and third years of the study despite dose adjustment throughout the study. No new cases of peripheral neuropathy were reported during this extension study, highlighting the need for systematic medical history recording and expert neurological assessment at baseline for patients with Gaucher disease.

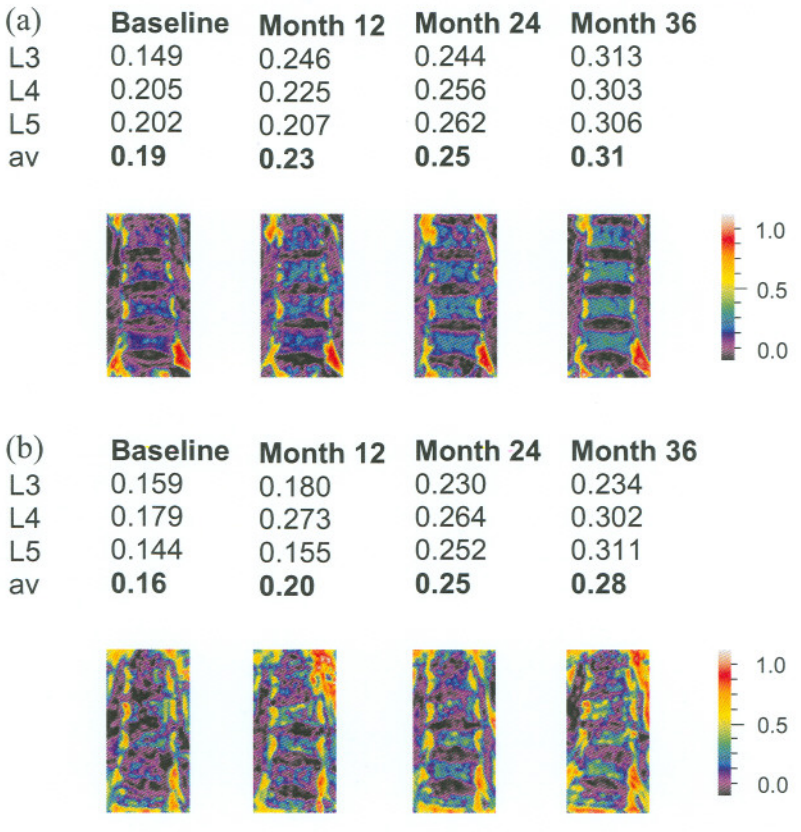

Figure 4 Changes in bone marrow fat fraction during 3 years of treatment with miglustat as determined by quantitative chemical shift imaging. Results are mean values for spinal vertebrae L3–L5. (a) Patient 201; (b) patient 202

Unlike ERT, which has a direct effect on the breakdown of glycosphingolipids, the concept of SRT in Gaucher disease involves reduction of the delivery of potential storage material to the macrophage system. With SRT it is expected that further accumulation of glycosphingolipids would be prevented by the inhibition of their synthesis in membranes of newly formed blood cells, ultimately restoring the balance of formation and degradation and thus allowing elimination of stored material by the residual glucocerebrosidase activity. For this reason, the onset of benefit would be slower than that with ERT. Indeed, our study showed progressive improvement during the course of therapy such that all key features of the disease had improved significantly over the study period. Measurements of chitotriosidase activity, a well-characterized biomarker of Gaucher disease, also decreased progressively over this period.

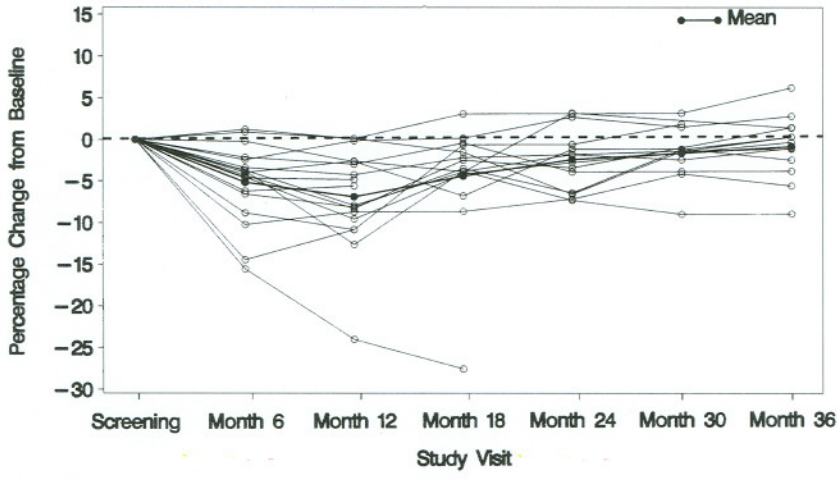

Figure 5 Percentage change in body weight during 3 years of treatment with miglustat: individual data and mean

It is noteworthy that by 24 months there was a marked improvement in platelet count and haemoglobin concentration, which had shown minimal response by 12 months of therapy (Cox et al 2000). An additional means to examine the effect of miglustat on pathological storage in the bone marrow can be provided by Dixon QCSI; a higher fat fraction indicates reduced pathological storage and correlates with a reduced risk of bone complications (Hollak et al 2001; Maas et al 2002). We were able to assess Dixon QCSI in the vertebrae of two patients over the full 36-month period: in both, miglustat was associated with a reduction in the pathological signal due to displacement of normal adipocytes by Gaucher cells, indicating that there was intrinsic correction of bone marrow disease. Furthermore, serial determinations of plasma glucosylceramide in a subset of study patients have shown a trend to a decrease in the concentrations of the glycosphingolipid substrate, with no change in ceramide levels. Overall, the clinical data, in addition to animal data, show that reductions in substrate are associated with regression of disease activity, thus further validating the concept of SRT.

The present study demonstrates a sustained and increasing beneficial effect of miglustat on clinical and laboratory measures of disease activity of type I Gaucher disease over 3 years and its acceptable safety profile. These long-term data on the safety and efficacy of miglustat in patients who were essentially naive to enzyme replacement suggest future applications of oral SRT in those unwilling or unable to receive ERT.

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