Gaucher disease type I : associated morbidities and long term efficacy of enzyme replacement therapy

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Low frequency maintenance therapy with imiglucerase in adult type I Gaucher disease: a prospective randomized controlled trial

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Abstract

**Background and Objectives.** Gaucher disease type I can be successfully treated with enzyme replacement therapy (ERT). In order to reduce the burden of the intravenously administered enzyme, low frequency of administration was prospectively studied in patients with stable and minor disease following ERT.

**Design and Methods.** Eleven patients were randomly assigned to either continue their original regimen in a once every week or fortnightly schedule (five patients) or to lower the frequency of administration to once every four weeks, at the same cumulative dose (six patients). Primary endpoint was change in liver ratio (ml/kg body weight). Secondary endpoints were spleen volume, haemoglobin level, platelet count, lumbar bone marrow fat content measured with quantitative chemical shift imaging (QCSI), white cell count, and plasma levels of ferritin, chitotriosidase, liver enzymes and angiotensin converting enzyme (ACE).

**Results.** There were no significant mean differences between both treatment arms for liver ratio or any of the other endpoints. However, there were two treatment failures in the low frequency group. These patients showed progression of disease as evidenced by a reduction of QCSI in one patient and an increase in liver ratio as well as a slow decrease in QCSI in the other. Both patients already had relatively low baseline QCSI values. One patient switched back to the original regimen at 6 months because of subjective complaints.

**Interpretation and Conclusions.** Low frequency ERT in adult Gaucher type I patients maintains stable disease in most, but not all patients with stable and minimal disease. Close monitoring of all disease parameters remains mandatory.
Introduction

Gaucher disease type I is the most common lysosomal storage disorder. Deficiency of the lysosomal enzyme glucocerebrosidase (OMIM #230800) leads to the accumulation of glucocerebroside in spleen, liver and bone marrow (1;2). In the early nineties, Gaucher disease was the first of the lysosomal storage disorders that could be treated successfully with enzyme replacement therapy (ERT), using intravenous mannose-terminated enzyme from placental tissue (algglucerase) or recombinant enzyme (imiglucerase, both manufactured by Genzyme Corp., Mass. USA). Most patients respond to treatment, with normalisation of blood counts, a reduction in liver and spleen size and improvement in bone symptoms (3-10). Dosing schedules may vary with frequencies of administration of three times a week up to once every two weeks.

At some point after starting ERT, many patients are stable with minimal residual symptoms. Reducing the frequency of treatment to once every four weeks might improve their quality of life. In one study, low frequency maintenance therapy was considered unsuccessful, but the patients exhibited significant residual disease at the time of switching to low frequency and the maintenance regimen was given at a reduced cumulative dose (11). No randomized controlled prospective trials aimed at lengthening the dose interval have been reported.

The aim of the present study was to evaluate whether stable disease could be maintained at a less burdensome schedule of ERT of once every four weeks at an equal cumulative dose, in patients with stable and minimal residual Gaucher disease after a minimum of two years of ERT.

Design and Methods

The protocol was approved by the AMC institutional review board. All patients gave written informed consent.

Eligibility criteria

- Patients, older than 18 years, with proven Gaucher type I disease, as evidenced by physical and neurological evaluation and documentation of deficient glucocerebrosidase activity in leukocytes (12) and genotyping (13).
- Enzyme therapy according to our national protocol (6) for at least two years prior to study enrolment.
- Mild, stable Gaucher disease, defined by having all of the following throughout the 24 months prior to screening:
  - haemoglobin levels within normal limits (male >12.8 g/dL, female >12.0 g/dL)
  - platelet count >100 x 10^9/L
  - no or asymptomatic organomegaly
- no significant bone complications, such as avascular necrosis, pathologic fractures, orthopedic replacement or bone-crises
- lumbar marrow fat content measured by QCSI (quantitative chemical shift imaging) > 23%
- a maximum variability of 30% in plasma chitotriosidase levels

Randomisation
Block randomisation was used to assign patients to receive infusions either once every four weeks (low frequency group) or to continue their original schedule (once every one or two weeks, control group). The total monthly dose remained unchanged. Duration of the study was twelve months or until study withdrawal.

Data collection
Baseline data on sex, age, bodyweight, splenectomy, severity score index (SSI (14)), dosing and genotype were recorded. Interviews, physical examination and investigations at the outpatient clinic took place at month 0, 2, 4, 6, 9 and 12. Follow-up parameters included white cell count, haemoglobin, platelet count, ferritin, alkaline phosphatase, alanine transaminase (ALAT), aspartate transaminase (ASAT), gammaglutamyl transferase (γ-GT), lactate dehydrogenase (LDH), angiotensin converting enzyme (ACE), chitotriosidase (performed by standard enzyme activity assay with 4-MU-chitotriose (Sigma, St. Louis, MO) as a substrate at pH 5.2 (15)) and hexosaminidase (using 4-methylumbelliferyl-N-acetylglucosamine, Sigma, St Louis, MO, as a substrate in citrate/phosphate buffer (0.1/0.2 M) at pH 4.0) at month 0, 2, 4, 6, 9 and 12. Chitotriosidase values of patients who were heterozygous for the chitotriosidase mutation were multiplied by 2 (16;17). At month 0, 6 and 12 liver and spleen volume were measured by spiral computed axial tomography, with a reported accuracy of 3-5% (18-20). To correct for changes in bodyweight, liver ratio was calculated (liver volume/bodyweight (mL/kg)). Spleen ratio was not calculated, since in adults spleen volume is not influenced by changes in bodyweight. Bone marrow involvement was assessed by measurement of the bone marrow fat fraction using Dixon quantitative chemical shift imaging (QCSI) of the lumbar spine (21;22) and clinical bone disease was assessed at each study visit.

Analysis of efficacy (2 methods):

Overall outcome
Stabilization of liver ratio was the primary endpoint. Secondary endpoints were stabilization of chitotriosidase, haemoglobin, platelet count, hexosaminidase, spleen volume, QCSI, ASAT, ALAT, γ-GT, LDH, alkaline phosphatase, ACE and ferritin.
Sample size was determined using a power of 90% and an alpha of 10%. It was estimated that a difference in liver ratio of 9% in one year between the two treatment arms could be excluded using six patients in each group.

Differences in baseline characteristics between the low frequency group and the control group and between patients in the low frequency group with stable disease versus treatment failures were evaluated by Mann-Whitney U test or Chi-square test. Relative changes as compared to baseline of follow up parameters were analyzed by Mann-Whitney U test. Correlations between the relative changes of the follow up parameters were determined using Spearman rho test.

**Individual patient outcomes**

These were assessed using criteria for disease progression, based on prior data of variability in 18 patients with clinically stable disease, defined as an unchanged maintenance dose of Cerezyme for at least two years. In these patients the standard deviation for percentage variability of chitotriosidase activity, liver ratio, spleen volume and QCSI was 12.5%, 3.9%, 4.4% and 4.1% respectively. Disease progression was defined as follows:

**One of:**
- an increase in liver ratio of > 10% from baseline of an enlarged liver (>25 mL/kg)
- an increase in chitotriosidase level by ≥ 30% from baseline for two consecutive laboratory evaluations (extra monitoring was performed within one month in case of a >15% increase.)
- a decrease in QCSI to ≤ 23%.
- the occurrence of avascular necrosis, pathologic fractures or bone-crises.

**OR two of:**
- an increase from baseline in spleen volume of > 10%
- a reduction in haemoglobin level to < 12.8 g/dL (male) or 12.0 g/dL (female) for two consecutive laboratory evaluations (performed within 1 month after each other)
- a reduction in platelet count to < 100 x 10^9/L for two consecutive laboratory evaluations (performed within 1 month after each other.)
- a relative decrease in QCSI for two consecutive evaluations of ≥ 20% from baseline.

Patients that showed progression of disease manifestations according to these criteria were considered treatment failures. Treatment failures from the low frequency group were reverted to their original dosing frequency and followed closely for improvement.
Results

Of the 53 patients in our institution who were treated with ERT, 12 fulfilled the entry criteria. One patient was not willing to participate in the study. Baseline characteristics of a total of eleven patients that were enrolled in the study are shown in Table I. They were randomly assigned to continue their original high frequency dosing schedule (once every week, no 1, 3, 4 and 5, or once every two weeks, no 2) or to receive the same monthly dose at a frequency of once every four weeks (no 6-11). Both groups were genetically identical; one patient in the low frequency group was homozygous for the N370S mutation and all others were compound heterozygotes for N370S and L444P or another mutation. The control group had slightly milder disease as indicated by the presence of smaller spleens (p=0.02), absence of patients with splenectomies, a slightly lower SSI (p=0.05) and lower liver ratio’s (p=0.05) as compared to the low frequency group. Also, monthly dose was approximately 50% lower in the control group (p=0.03). Total cumulative dose and the number of years

Table I: Patient characteristics of the eleven patients included in the study.

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<th>platelet count (x10^9/L)</th>
<th>Liver ratio (mL/kg)</th>
<th>Spleen volume (mL)</th>
<th>QCSI (%)</th>
<th>Chitotriosidase (nmol/ml.hr)</th>
<th>Hexosaminidase (nmol/ml.hr)</th>
<th>Dose (U/kg/4weeks)</th>
<th>Original frequency (x/4weeks)</th>
<th>No of years on ERT</th>
<th>Cumulative dose since start ERT (U/kg)</th>
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Chitotriosidase levels of patients who were heterozygous for the chitotriosidase mutation (patient no 6 and 8), were multiplied by two. Abbreviations: H, high frequency (1x/1-2weeks); L, low frequency (1x/4weeks); M, male; F, female; SSI, Severity Score Index (21); Sx, splenectomy; QCSI, Quantative chemical shift imaging.
receiving ERT were comparable (p=0.247 and p=0.792, respectively). Two patients (no 6 and 8) were heterozygous for the chitotriosidase mutation, their chitotriosidase levels were multiplied by two. None was chitotriosidase deficient.

**Overall outcome**

There were no differences in the mean percentage change from baseline at 12 months in liver ratio between the low frequency group and the control group (mean percentage ± SD: 102.0 ± 5.0 in the control group vs 98.1 ± 10.1 in the low frequency group, p=0.329, see figure 1a). Also the mean change of the secondary parameters (spleen volume, haemoglobin level, platelet count, chitotriosidase, QCSI, white cell count, ferritin, liver enzymes and angiotensin converting enzyme (ACE)) did not show a significant difference between low frequency patients and controls. No bone complications occurred during the study period in both groups.

![Graphs showing percentage changes in liver ratio, spleen volume, haemoglobin, platelet count, chitotriosidase, and QCSI.](image_url)

*Figure 1a-f: Percentage changes in liver ratio (a) and spleen volume (b), absolute changes in Haemoglobin (c) and platelet count (d), and percentage changes in chitotriosidase (e), and QCSI (quantitative chemical shift imaging) (f). Patients from the high frequency group (1x/1-2weeks) are depicted in red; patients from the low frequency group (1x/4weeks) are depicted in black.*
No strong correlations (i.e. \( \rho > 0.6 \)) were found between the relative changes of the different parameters, except for change in liver and spleen volume (\( \rho = 0.632, p = 0.004 \)).

**Individual outcomes**

None of the patients from the control group were considered treatment failures. Two patients (no 7 and 9) from the low frequency group met the protocol criteria for treatment failure. Prior to randomisation to low frequency treatment, these patients differed from the others in this group only with respect to a baseline fat fraction of < 35%. Patient no 10 withdrew from the study at 6 months because of persisting subjective complaints. The three patients that continued the once every four weeks schedule considered the new regimen an important improvement that made them feel less restricted in their free time, although one patient was dissatisfied with the longer dose related duration of the infusion.

**Control group**

Patients no 1, 4 and 5 remained stable.

Patient no 2 showed an increase in spleen volume of >10% at 6 months. Also an increase in chitotriosidase of >30% at a single measurement, which was not confirmed by a second analysis, was established. Although there was a relative increase of 11%, liver ratio remained within the normal range (<25 mL/kg). Thus, the criteria for treatment failure were not met. No explanation was found for the temporary deterioration (i.e. infection, non-compliance).

Patient no 3 showed an increase in chitotriosidase including one value of >30%, which was again not confirmed in a second analysis. Other parameters remained stable. Also in this patient, there was no indication of non-compliance.

**Low frequency group**

Disease parameters of patient no 6 remained stable. After completion of the study the low frequency regimen was continued.

Patient no 7 showed a decrease in QCSI of 29% at baseline to 24% at twelve months (relative decrease of 17%), without clinical bone problems. Liver ratio increased by 12% and the patient complained of fatigue and feelings of abdominal discomfort. The criteria for treatment failure were met and at 12 months the patient returned to his original dosing regimen of once every two weeks. Six months after the switch QCSI had increased to 26%; tiredness persisted.

Patient no 8 showed an increase in spleen volume of >10% with a single haemoglobin value below the normal range. There was a trend towards increase in chitotriosidase levels, but less than 30% (maximum 22% at 12 months). QCSI remained stable. Possibly this patient suffered from an intercurrent infection. Serology and PCR gave no indication for a recent EBV or CMV infection. He continued the low frequency regimen. Chitotriosidase, spleen volume and Hb recovered quickly.
Patient no 9 had a decrease in QCSI from 33% to 23% in 12 months time, without bone complications or complaints. Other parameters did not change significantly. Following protocol she returned to her previous high frequency regimen, after which QCSI increased to 27% (18 months).

Patient no 10 showed an increase in splenomegaly of 11% from baseline after 6 months. Before start of the study she suffered from chronic bone- and muscle pain which continued throughout the study. MRI of the upper leg indicated a possible myositis. Biopsy was refused and the diagnosis could not be confirmed. The patient chose to reinstate the high frequency regimen after month 6 because of uncertainty of the cause of the pain in the legs as well as the increase in spleen size. According to protocol this was not mandatory. Spleen volume returned to baseline value, the pain in the legs persisted.

After 12 months of low frequency therapy, patient no 11 had a 14% increase in spleen volume compared to baseline and an increase in liver ratio of 9%. Interestingly, neither chitotriosidase nor QCSI values changed significantly within this period of time. During the study, the patient had skipped at least one infusion because of problems with intravenous access, which may have caused the deterioration. Criteria for treatment failure were not fulfilled and the study-regimen was continued. Six months later liver ratio and spleen volume had almost returned to baseline values, again without changes in chitotriosidase and QCSI values.

Discussion

Despite the tremendous success of ERT for Gaucher disease type I, lifelong intravenous administration is burdensome for most patients. Several strategies for achieving higher convenience for the patients have been considered. Home treatment with ERT has proven to be safe and feasible, specifically by creating more flexibility (23). Substrate reduction ( miglustat, Zavesca®, Actelion, Basel, Switzerland) offers an oral alternative, although its use is limited to patients who have mild to moderate disease and who are unsuitable to receive ERT (24;25). Its value as maintenance therapy after stabilisation on ERT is currently studied. Decreasing the frequency of administration of ERT was proposed more then a decade ago for patients with minimal disease symptoms after initial therapy (26). In a recent consensus statement from the International Collaborative Gaucher Group, it is recommended that dose adjustments for maintenance therapy should be made on an individual basis, but no monthly administration schedules are included (27). In an uncontrolled study, signs and symptoms of disease worsened on a monthly schedule, but patients had unstable and significant residual disease at the time treatment was changed and a reduced cumulative dose was given (11). Drug holidays to alleviate the burden of intravenous therapy do not seem very successful. Grinzaid et al withdrew four patients from ERT for 1-7 years. All showed deterioration in haematological and visceral parameters, and in three patients ERT
had to be reinstituted (28). Elstein suggested that adult patients with stable disease could be withdrawn from ERT for circumscribed periods. However, of the fifteen patients that had withdrawn from ERT for an average of 26 months (range 8-47), six had to restart therapy because of deterioration of clinical features (29).

Our study, in patients with stable and minimal residual disease following ERT, is the first prospective randomised trial of a maintenance regimen where total dosage is unchanged but frequency of administration is reduced to once every four weeks. Although there were no significant mean differences between the control and test arms for any of the endpoints, there were 2 treatment failures in the low frequency group, whereas all patients in the control group remained stable. One patient from the low frequency group did not want to continue the study regimen because of subjective complaints, although she did not meet the criteria of treatment failure. The patients randomised to low frequency maintenance ERT had more severe disease at baseline, evidenced by a trend towards a higher SSI and liver ratio, and significant larger spleens and a higher treatment dose compared to the control group. This may have influenced the number of failures in this group.

When taking a closer look at the patients in the low frequency group that showed disease progression, patient no 7 had a slow decrease in QCSI as well as an increase in liver ratio, and patient no 9 had a decrease in QCSI, with other parameters remaining stable. For both patients, the deterioration in these parameters represents an increase in Gaucher cell mass (30-32). After reinstitution of the original treatment regimen, both patients showed a subsequent improvement. Although the two patients in whom treatment failure occurred did not have the worst composite disease severity either before the initiation of ERT or at start of the study, or the lowest cumulative dose, it is important to note that both patients had the lowest baseline QCSI of all patients in the low frequency group.

Of interest is the fact that deterioration was not always reflected in all parameters at the same time or to the same extent. Only liver and spleen volume changes showed a strong correlation to each other. These observations emphasize the importance of adequate follow-up of all parameters, including assessment of bone marrow infiltration, because deterioration in this compartment is not always reflected by concomitant changes in other parameters. The sensitivity of disease markers as predictors of deterioration and the correlation between the different parameters needs more study.

It should be noted that in many patients worldwide, the average monthly ERT maintenance dose is usually higher than that used in our study. Whether this higher dose results in better maintenance of disease manifestations needs further study.

In conclusion, maintenance therapy, using a once every four weeks schedule of ERT in adult Gaucher type I patients, is feasible for some patients with stable and minimal residual disease. It is likely that patients with a relatively low baseline lumbar fat fraction may be at risk for disease progression with less frequently administered ERT. It is important to closely monitor all disease parameters for early detection of disease progression and adequate frequency adjustment.
Reference List

(1) Brady RO, Kanfer JN, Shapiro D. METABOLISM OF GLUCOCEREBROSIDES. II. EVIDENCE OF AN ENZYMIC DEFICIENCY IN GAUCHER’S DISEASE. Biochem Biophys Res Commun 1965; 18:221-225.


