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, a low frequency of administration was prospectively studied in patients with stable and minor disease following ERT.

Design and Methods

Eleven patients were randomly assigned either to continue their original regimen of a dose of ERT once every week or fortnight (five patients) or to lower the frequency of administration to once every 4 weeks, at the same cumulative dose (six patients). The primary end-point was change in liver ratio (mL/kg body weight). Secondary end-points were spleen volume, hemoglobin 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 the two treatment arms in liver ratio or any of the other end-points. However, there were two treatment failures in the low frequency of administration 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.

Key words: Gaucher disease, anemia, thrombocytopenia, randomized trial.

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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 1990s, Gaucher disease was the first of the lysosomal storage disorders treated successfully with enzyme replacement therapy (ERT), using intravenous mannose-terminated enzyme from placental tissue (alglucerase) or recombinant enzyme (imiglucerase), both manufactured by Genzyme Corporation (MA, USA). Most patients respond to treatment, with normalization 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 ranging from three times a week up to once every 2 weeks. At some point after starting ERT, many patients become stable with minimal residual symptoms. Reducing the frequency of treatment to once every 4 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 administration 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 with a less burdensome schedule of ERT of once every 4 weeks at an equal cumulative dose in patients with stable and minimal residual Gaucher disease after a minimum of 2 years of ERT.

Design and Methods

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

Eligibility criteria

In order to be eligible for the study, patients had to be older than 18 years and have proven Gaucher type I disease, as evidenced by physical and neurological evaluation and documentation of deficient glucocerebrosidase activity in leukocytes[12] and genotyping.[13] They also had to have received enzyme therapy according to our national protocol[6] for at least 2 years prior to study enrolment. Finally, they had to have mild, stable Gaucher disease, defined by having all of the following throughout the 24 months prior to screening:

(i) hemoglobin levels within normal limits (male > 12.8 g/dL, female >12.0 g/dL);

(ii) platelet count > $100x10^9$/L;

(iii) no or asymptomatic organomegaly;

(iv) no significant bone complications, such as avascular necrosis, pathologic fractures, orthopedic replacement or bone-crises;

(v) lumbar marrow fat content >23% measured by quantitative chemical shift imaging (QCSI);

(vi) a maximum variability of 30% in plasma chitotriosidase levels.

Randomization

Block randomization was used to assign patients to receive infusions either once every 4 weeks (low frequency group) or to continue their original schedule (once every 1 or 2 weeks, control group). The total monthly dose remained unchanged. Patients remained on study for 12 months or until study withdrawal.

Data collection

Baseline data on sex, age, body weight, splenectomy, severity score index (SSI),[14] dosing and genotype were recorded. Interviews, physical examination and investigations at the outpatient clinic took place at months 0, 2, 4, 6, 9 and 12. Follow-up parameters included white cell count, hemoglobin, platelet count, ferritin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), 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, USA) as a substrate at pH 5.2)[15] and hexosaminidase (using 4-methylumbelliferyl-N-acetylglucosamine (Sigma), as a substrate in citrate/phosphate buffer (0.1/0.2 M) at pH 4.0) at months 0, 2, 4, 6, 9 and 12. Chitotriosidase values of patients who were heterozygous for the chitotriosidase mutation were multiplied by two.[16,17] At months 0, 6 and 12 liver and spleen volumes were measured by spiral computed axial tomography, a method that has a reported accuracy of 3-5%.[18-20] To correct for changes in body weight, the liver ratio was calculated (liver volume/body weight [mL/kg]). The spleen ratio was not calculated, since spleen volume in adults is not influenced by changes in body weight. Bone marrow involvement was assessed by measurement of the bone marrow fat fraction using Dixon's QCSI of the lumbar spine[21,22] and clinical bone disease was assessed at each study visit.

Analysis of efficacy (two methods)

Overall outcome

Stability of the liver ratio was the primary endpoint. Secondary end-points were stability of chitotriosidase, hemoglobin, platelet count, hexosaminidase, spleen volume, QCSI, AST, ALT, γ-GT, LDH, alkaline phosphatase, ACE and ferritin. The sample size was determined based on a required power of 90% and an α of 10%. It was estimated that a difference in liver ratio of 9% in 1 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

Table 1. Characteristics of the 11 patients included in the study.

1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*
1	H	M	53	0	N370S/L444P	15,4	160	19	440	56	4175	1244	15	4	9	1575	4	24415
2	H	F	66	1	N370S/L444P	13,3	137	21	230	53	2173	1183	15	2	11	2070	4	9262
3	H	F	55	4	N370S/R120W	14,1	151	20	446	32	5184	854	18	4	12	4152	6	30583
4	H	F	58	1	N370S/L444P	13,1	161	26	231	52	9068	1222	15	4	10	1800	7	23084
5	H	M	48	2	N370S/L444P	15,5	192	18	303	50	133	1038	15	4	9	1695	4	7387
6	L	M	39	4	N370S/N370S	14,9	307	21	Sx	65	5744	1223	30	4	3	1170	6	40184
7	L	M	43	3	N370S/IVS2+1	14,6	122	25	1093	29	6229	926	50	2	12	6835	7	26082
8	L	M	56	3	N370S/L444P	13,8	180	32	613	43	5082	1233	30	4	9	3120	5	25706
9	L	F	34	5	N370S/L444P	13,8	261	31	Sx	33	3056	1382	30	4	3	1110	8	19363
10	L	F	75	4	N370S/RECNCIL	14,8	129	23	862	55	3410	1288	15	2	10	3540	8	16703
11	L	M	38	3	N370S/L444P	15,5	99	24	1111	38	8338	1236	40	4	8	3540	5	45211

1: Patient n.; 2: high/low frequency; 3: gender; 4: age; 5: SSI; 6: genotype; 7: Hb (g/dL); 8: platelet count (x10^9/L); 9: Liver ratio (mL/kg); 10: Spleen volume (mL); 11: QCSI (%); 12: Chitotriosidase (nmol/mL.hr); 13: Hexosaminidase (nmol/mL.hr); 14: Dose (U/kg/4weeks); 15: Original frequency (x/4 weeks); 16: No. of years on ERT; 17: cumulative dose since starting ERT (U/kg); 18: SSI before starting ERT; 19: Chitotriosidase (nmol/ml.hr) before starting ERT. Chitotriosidase levels of patients who were heterozygous for the chitotriosidase mutation (patients #6 and 8) were multiplied by two. H: high frequency (ERT once every 1-2 weeks); L: low frequency (ERT once every 4 weeks); M: male; F: female; SSI: Severity Score Index (21); Sx: splenectomy; QCSI: Quantative chemical shift imaging.

with stable disease and those in whom treatment failed were evaluated by the Mann-Whitney U test or the χ^2 test. Relative changes of follow-up parameters compared to to baseline values were analyzed by the Mann-Whitney U test. Correlations between the relative changes of the follow-up parameters were determined using Spearman's ρ test.

Individual patient outcomes

Outcomes 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 2 years. In these patients the standard deviation for percentage variability of chitotriosidase activity, liver ratio, spleen volume and QCSI were 12.5%, 3.9%, 4.4% and 4.1%, respectively. Disease progression was defined as any one of:

(i) an increase in liver ratio of > 10% from baseline or an enlarged liver (>25 mL/kg);

(ii) an increase in chitotriosidase level by ≥30% from baseline in two consecutive laboratory evaluations (extra monitoring was performed within 1 month in the case of a >15% increase);

(iii) a decrease in QCSI to ≤23%;

(iv) the occurrence of avascular necrosis, pathologic fractures or bone-crises;

OR two of the following:

(i) an increase from baseline in spleen volume of > 10%;

(ii) a reduction in hemoglobin level to <12.8 g/dL (males) or 12.0 g/dL (females) at two consecutive laboratory evaluations (performed within 1 month of each other);

(iii) a reduction in platelet count to <100x10^9/L at two consecutive laboratory evaluations (performed within 1 month of each other.)

(iv) a relative decrease in QCSI of ≥20% from baseline at two consecutive evaluations.

Treatment was considered to have failed if patients showed manifestations of disease progression according to these criteria. Patients in the low frequency group in whom treatment failed 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. The baseline characteristics of the 11 patients who were enrolled in the study are shown in Table 1. These 11 patients were randomly assigned to continue their original high frequency dosing schedule (once every week, patients n. 1, 3, 4 and 5, or once every 2 weeks, patient n. 2) or to receive the same monthly dose at a frequency of once every 4 weeks (patients n. 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 splenectomy, a slightly lower SSI (p=0.05) and lower liver ratio's (p=0.05) as compared to the low frequency group. Also, the monthly dose of ERT was approximately 50% lower in the control group (p=0.03). The total cumulative dose and the number of years of having received ERT were comparable p=0.247 and p=0.792, respectively). Two patients (#6 and 8) were heterozygous for the chitotriosidase mutation: their chitotriosidase levels were multiplied by two. None was chitotriosidase deficient.

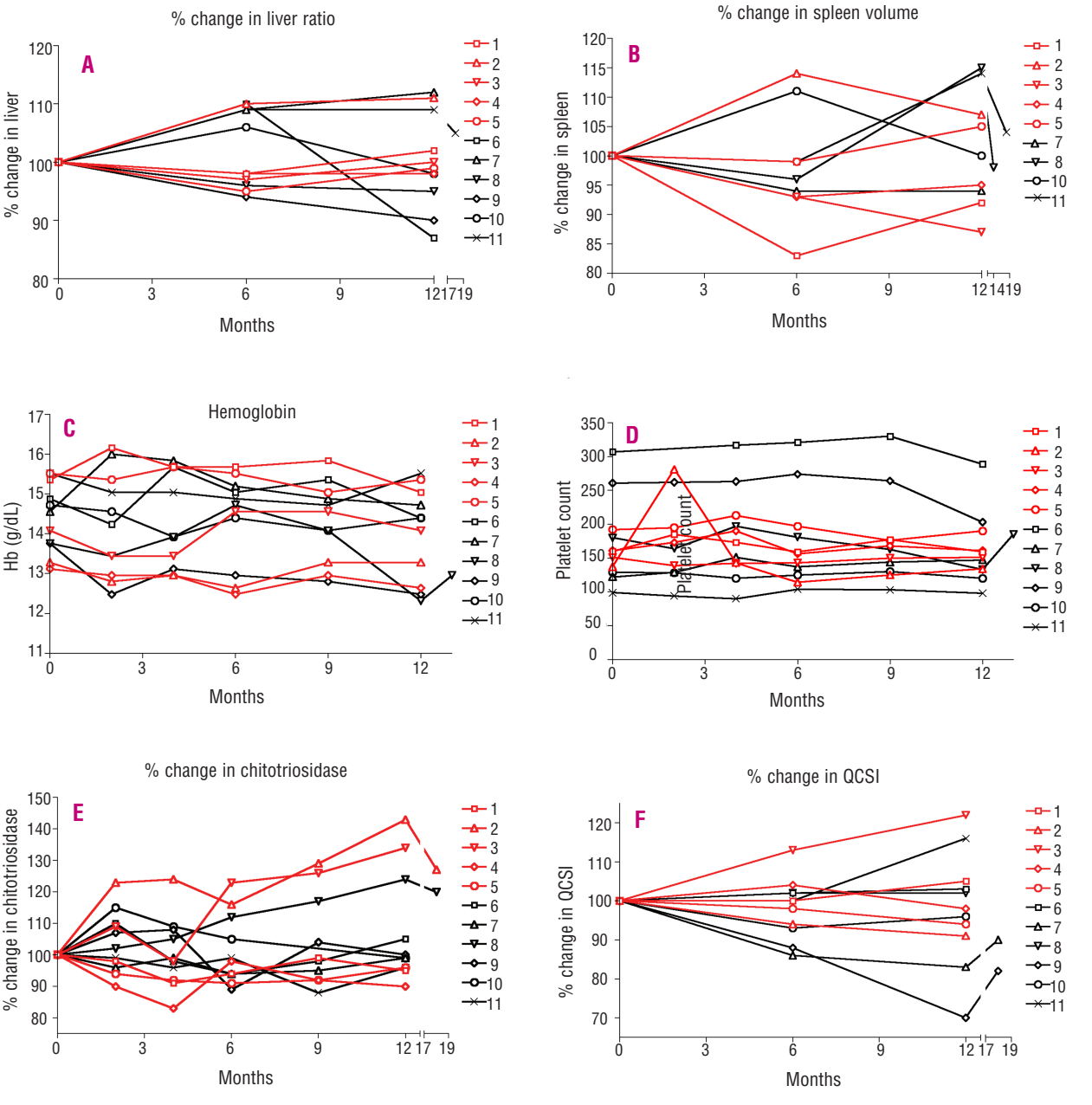

Figure 1A-F. Percentage changes in liver ratio (A) and spleen volume (B), absolute changes in hemoglobin (C) and platelet count (D), and percentage changes in chitotriosidase (E), and QCSI (F). Patients from the high frequency group (ERT once every 1-2weeks) are represented in red; patients from the low frequency group (ERT once every 4 weeks) are represented in black.

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, Figure 1A). Likewise, the mean changes in the secondary parameters (spleen volume, hemoglobin level, platelet count, chitotriosidase, QCSI, white cell count, ferritin, liver enzymes and ACE) did not show significant differences between the low frequency group and the control group. No bone complications occurred during the study period in either group.

No strong correlations (i.e. ρ>0.6) were found between the relative changes of the different parameters, except for change in liver and spleen volume (ρ=0.632, p=0.004).

Individual outcomes

Treatment was not considered to have failed in any of

the patients in the control group. Two patients (#7 and 9) from the low frequency group met the protocol criteria for treatment failure. Prior to randomization to low frequency treatment, these patients differed from the others in this group only with respect to a baseline fat fraction of <35%. Patient #10 withdrew from the study at 6 months because of persisting subjective complaints. The three patients who continued the once every 4 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 #1, 4 and 5 remained stable. Patient #2 showed an increase in spleen volume of >10% at 6 months and also an increase in chitotriosidase of >30% at a single measurement, which was not confirmed by a second analysis. Although this patient had a relative increase of 11% in the liver ratio the ratio remained within the normal range (<25 mL/kg). Thus, the criteria for treatment failure were not met. No explanation (e.g. infection, non-compliance) was found for the temporary deterioration. Patient #3 showed an increase in chitotriosidase including one value that increased >30% of baseline, but 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

The disease parameters of patient n. 6 remained stable. After completion of the study the low frequency regimen was continued. Patient n. 7 showed a decrease in QCSI from 29% at baseline to 24% at 12 months (relative decrease of 17%), without clinical bone problems. The liver ratio increased by 12% and he complained of fatigue and abdominal discomfort. The criteria for treatment failure were met and at 12 months the patient returned to his original dosing regimen of once every 2 weeks. Six months after the switch the QCSI had increased to 26% but tiredness persisted.

Patient n. 8 had an increase in spleen volume of >10% with a single hemoglobin value below the normal range. His chitotriosidase levels tended to increase, but by less than 30% (maximum 22% at 12 months). The QCSI remained stable. This patient possibly suffered from an intercurrent infection although serological tests and polymerase chain reaction analysis gave no indication of a recent Epstein-Barr virus or cytomegalovirus infection. He continued the low frequency regimen. Chitotriosidase, spleen volume and hemoglobin concentration recovered quickly. Patient n. 9 had a decrease in QCSI from 33% to 23% in 12 months, 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% (at 18 months).

Patient #10 showed an increase in splenomegaly of 11% from baseline at 6 months. Before starting the study this patient had suffered from chronic bone and muscle pain which continued throughout the study. Magnetic resonance imaging of the upper leg indicated a possible myositis. Biopsy was refused and the diagnosis could not be confirmed. The patient chose to return to the higher frequency dosing regimen after 6 months because of uncertainty of the cause of the leg pain as well as the increase in spleen size. According to protocol this was not mandatory. The woman's spleen volume returned to the baseline value, but the pain in her legs persisted.

After 12 months of low frequency therapy, patient n. 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 the intravenous access, which may have caused the deterioration. Criteria for treatment failure were not fulfilled and the study regimen was continued. Six months later his 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 greater convenience for 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 stabilization on ERT is currently being 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 to be very successful. Grinzaid *et al*. withdrew four

patients from ERT for 1-7 years. All showed deterioration in hematologic 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 15 patients who withdrew 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 randomized trial of a maintenance regimen in which total dosage was unchanged but frequency of drug administration was reduced to once every 4 weeks. Although there were no significant mean differences in any of the end-points between the control and test arms, treatment failed in two patients 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 randomized to low frequency maintenance ERT had more severe disease at baseline, evidenced by a trend towards a higher SSI and liver ratio, significantly larger spleens and the need for 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 whose disease progressed, patient #7 had a slow decrease in QCSI as well as an increase in liver ratio, and patient #9 had a decrease in QCSI, with other parameters remaining stable. In both patients, the deterioration in these parameters represented an increase in Gaucher cell mass.[30-32] After reinstitution of the original treatment regimen, both patients showed improvements. Although the two patients in whom low-frequency treatment failed did not have the worst composite disease severity either before the initiation of ERT or at the start of the study, nor had they received the lowest cumulative dose of treatment, it is important to note that these 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 with 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 control also needs further study.

In conclusion, maintenance therapy, using a schedule of ERT once every 4 weeks 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 of disease progression with less frequently administered ERT. It is important to monitor all disease parameters closely for early detection of disease progression and to adjust the dosing frequency accordingly.

Authors' Contributions

MdF drafted the manuscript, contributed to the conception and design of the study and acquisition, analysis and interpretation of data; CH contributed to conception and design of the study and acquisition, analysis and interpretation of data; JA contributed to the conception and design of the study and analysis and interpretation of data; JG, MM and EA contributed to the acquisition and analysis and interpretation of data; MW contributed to the acquisition of data. All authors revised the manuscript critically for important intellectual content and approved the final version. The order of authorship was based on the amount of input. In addition, Carla Hollak supervised the study.

Conflicts of Interest

The authors reported no potential conflicts of interest. This study was made possible as part of governmental funding of the Acedemic Medical Center for the centralizaed treatment and monitoring of patients with Gaucher disease in the Netherlands.

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