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

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Superior effects of high dose enzyme replacement therapy in type 1 Gaucher disease on bone marrow involvement and chitotriosidase levels; a two center retrospective analysis

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Abstract

Dosing of enzyme replacement therapy (ERT) for Gaucher disease type 1 is still a subject of debate and varies from 15-130 U/kg/month, making a huge economic difference of 55,000 up to 300,000 Euro per patient per year. To investigate whether this difference in dosing ultimately translates into a different response, we retrospectively compared long term outcome of ERT at two large European treatment centers, Amsterdam (AMC, N=49, median dose 15-30 U/kg/4 weeks) and Duesseldorf (HHU, N=57, median dose 80 U/kg/4 weeks). These adult cohorts had a similar genetic background. All follow-up parameters were matched separately at baseline, to avoid bias with respect to disease severity. Improvement in hemoglobin, platelet count and hepatosplenomegaly was not significantly different between both cohorts, whereas plasma chitotriosidase and bone marrow involvement by MRI improved faster and more pronounced in the higher-dosed group. Major bone complications rarely occurred in both groups. In conclusion, different dosing regimens of ERT do not affect outcome of hematological and visceral parameters, but higher dosing leads to accelerated decrease of chitotriosidase and better objective bone response in adult type 1 Gaucher disease.
Introduction

Gaucher disease type I is the most common lysosomal storage disorder. Deficiency of the lysosomal enzyme glucocerebrosidase leads to the accumulation of glucocerebrosides 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 mannose-terminated enzyme from placental tissue (alglucerase) or recombinant enzyme (imiglucerase, both manufactured by Genzyme Corp., Mass. USA). Most patients show a remarkable clinical response to treatment, with normalization of blood counts, a reduction in liver and spleen size and improvement in bone symptoms\(^3\)-\(^11\). Even after more than 13 years of experience, the most effective dosing regimen of ERT is still a subject of debate. Advocates of low dosing regimens call attention to the extremely high costs of the enzyme, €55,000-300,000 per patient per year depending on dose and weight, in the absence of convincing evidence for superiority of high dosages\(^12\). Others argue that high dosages are required for optimal effect in severe disease, especially bone disease or in children\(^13\)-\(^15\). Guidelines for dosing protocols are based on consensus rather than on scientific evidence\(^16\)-\(^18\). Prospective studies that compare different dosing regimens are limited. Altaescu found inferior responses using 10 U/kg per two weeks compared to 60 U/kg per two weeks, but the two groups where not matched for baseline disease severity and biochemical and bone marrow assessments were not included\(^13\). Beutler showed in a meta-analysis that no relationship between dose and reduction in liver size could be established\(^19\). He argued that fractionation may be important when small doses are given\(^20\), although Zimran did not find a significant difference in response between a once fortnightly and a three times weekly schedule of 30 U/kg/4 weeks of Cerezyme\(^21\).

Currently, large differences exist in dosing regimens between treatment centers, even in the same area. An example of this situation is found in Western Europe, where patients at the Academic Medical Center (AMC) in the Netherlands are treated with an initial low dose (15-50 U/kg/4 weeks, divided in once to three times weekly doses), while patients treated at the Heinrich Heine University (HHU) in Germany, less then 225 km away, use initial dosages between 60-120 U/kg/4 weeks. The aim of the study was to compare long term outcome on hematological, visceral, biochemical and skeletal parameters in relation to these different dosing schedules.

Methods

Setting and patients

We conducted a retrospective comparative cohort study at two centers. A total of 106 adult Gaucher type I patients who started treatment between 1991 and 2002 in the referral centers for Gaucher disease in the Academic Medical Center (AMC), Amsterdam, the
Netherlands and in the Heinrich Heine University Hospital (HHU), Duesseldorf, Germany, and who received ERT with an initial dose of $\leq 50$ U/kg/4 weeks (AMC) or $\geq 60$ U/kg/4 weeks (HHU), were included in the study. A diagnosis of Gaucher disease was confirmed by measurement of deficient glucocerebrosidase activity in leukocytes\textsuperscript{22} and genotyping. Patients at the AMC are treated according to an individualized low dose protocol\textsuperscript{5}, which consists of an initial dose of 15 up to 50 U/kg/4 weeks, given initially at a three times (36/49 patients) or once a week schedule (13/49 patients), which is individually adjusted based on the response of hematological and visceral parameters, chitotriosidase and clinical bone disease. The patients who started on a three times a week schedule switched to a once a week schedule after 2-4 years of ERT for reasons of convenience. Patients treated in the HHU start with a dose of 60-120 U/kg/4 weeks, given every other week, with the higher initial doses in more severe disease, such as extensive organomegaly or bone disease. The dose is slowly decreased in some patients, who reach stable disease.

**Data analysis and definition of therapeutic goals**

Baseline data on sex, age, splenectomy, severity score index (SSI, as described by Zimran\textsuperscript{23}), use of bisphosphonates for $\geq 2$ years, dosing and genotype were recorded. Follow-up parameters included hemoglobin, platelet count, plasma chitotriosidase levels, liver and spleen dimensions, clinical records on bone disease and scoring of bone marrow involvement by MRI of the femora. To account for differences in extent of disease between both cohorts, baseline characteristics were analyzed by Mann-Whitney U test or by Chi-square test. Since the AMC cohort included patients with more extensive disease, all parameters were analyzed separately and matched at baseline. Each parameter, except for bone disease, was analyzed in two separate ways. First, baseline values (range 12 months before up to 2 months after start of ERT for organ volumes and BMB; baseline or within 12 months before start of ERT for hemoglobin, platelet count and chitotriosidase) and values after one year (range 8-16 months after start of ERT) were determined. Differences between both cohorts after one year were assessed by Mann-Whitney-U test. Second, for each parameter, therapeutic goals were defined and analyzed by life table analysis (Kaplan Meier). The results were expressed as share of patients reaching the therapeutic goal vs. duration of ERT, reflected as median. Differences between the cohorts were determined by the log rank test.

**1. Hemoglobin and platelet count**

Matched pairs were made according to baseline values and spleen status, since hematological response is much faster in splenectomized patients with cytopenia as compared to non-splenectomized patients\textsuperscript{5,9}. Patients with a baseline hemoglobin level of $<12.0$ g/dL ($<7.5$ mmol/L) were selected and matched pairs were made according to baseline values (maximum difference of 0.5 g/dL) and spleen status. Similar matching was performed for patients with a platelet count of $<100 \times 10^9$/L at baseline (maximum difference of 10 x
10^9/L). The time to reach a hemoglobin level of >12.0 g/dL or to reach a platelet count of
>100 x 10^9/L was determined.

2. Liver and spleen size
Liver and spleen volumes at the AMC were measured by spiral computed axial tomography,
with a reported accuracy of 3-5%\textsuperscript{24-26}. At the HHU, using ultrasound, the maximum
midclavicular cranio-caudal (CC) diameter and antero-posterior (AP) diameter of the liver
were determined. For determination of spleen size, the diameter at the hilus (width), as
seen on the horizontal view, and the distance between both poles (length), as seen on the
frontal view, were determined. To allow comparison of the visceral data created by two
different methods, the above described liver and spleen dimensions were determined on
CT images in a group of 55 AMC patients (a total of 103 spiral CT’s) and compared to organ
volumes, as determined by CT. The best correlation was found for both liver and spleen
index, which is calculated by multiplying the respective diameters, yielding a correlation of
0.862 and 0.958, respectively (P<0.0001). Formulas were deducted to calculate liver and
spleen volume from the respective indices (de Fost, unpublished results). Baseline values
between the two groups did differ significantly (table 1), since the AMC cohort included
20 patients with liver volumes above 3000 mL (11 splenectomized) whereas these were
not found in the HHU cohort. Therefore patients with a liver volume of >1750 mL or spleen
volume of >250 mL were selected and matched pairs were made according to baseline
organ volumes (maximum baseline difference of 200 mL for liver volume and 300 mL
for spleen volume) and spleen status. Baseline values vs values after twelve months of
ERT were compared. The time to reach a 20% decrease from baseline in liver volume or
40% decrease in spleen volume was determined by Kaplan Meier analysis in patients with
a baseline liver volume in the range of 1750-3000 mL or spleen volume in the range of
400-2300 mL. No correction for change in body weight was performed, since in this adult
population, body weight did not change significantly.

3. Chitotriosidase
Chitotriosidase activity in plasma samples from both centers were measured in one central
laboratory at the AMC. The standard enzyme activity assay with 4-MU-chitotriose (Sigma,
St. Louis, MO; normal range 7-124 nmol/mL.hr) as a substrate was performed at pH 5.2, as
described previously\textsuperscript{27}. Genotyping for the chitotriosidase null mutation\textsuperscript{28} was performed
and chitotriosidase values of patients who were heterozygous for the chitotriosidase null
mutation were multiplied by 2\textsuperscript{29}. For comparison of baseline values vs values after twelve
months of ERT, patients with a chitotriosidase activity of >5000 nmol/mL/hr were selected
and matched pairs were made according to baseline values (maximum baseline difference
of 2500 nmol/mL/hr). The time to reach a chitotriosidase activity of <5000 nmol/mL/hr
was determined in patients with baseline chitotriosidase activity in the range of 6000-
25000 nmol/mL/hr.
4. Bone disease

For assessment of bone involvement, T1 and T2 weighted MRI images of the femora were used. Scoring of the severity of involvement of the bone marrow was adapted from the earlier described Bone Marrow Burden Score (BMB)30. This scoring system correlates significantly to bone marrow fat fractions obtained with Quantative Chemical Shift Imaging (QCSI), which has been shown to be closely related to clinical bone disease31. The BMB score incorporates both the visual interpretation of signal intensity and the geographic location of the disease on conventional MR images of the spine and femur. Since images of the spine were not obtained at the HHU, the scoring was limited to the femurs. All available MRI's of the femora were scored by a radiologist, experienced in the evaluation of Gaucher patients, who was blinded for patient identity, treatment dosage and time of assessment. The BMB score for the femur ranges from 0 (no abnormalities) to 8 points (severe disease). A change in BMB score adequately reflects reappearance of fatty marrow, indicating clearance of Gaucher cells. The time to reach a decrease of 2 BMB points from baseline was determined by life table analysis in all patients with a baseline BMB in the range of 2-8, and in a separate analysis for patients with severe bone disease. Severe bone disease was defined as a baseline BMB of ≥ 6, which is comparable to a QCSI <23%, a risk factor for serious bone complications31. Results were presented as the share of patients who had reached the therapeutic goal after 24 months of ERT. The occurrence of skeletal complications, defined as new bone crisis, avascular necrosis or pathological fracture, during the 10 years prior to start of ERT or during the study period, was recorded from the patient files.

Results

Patient characteristics

Patient characteristics are presented in Table 1. Patients did not differ with respect to age, gender and number of splenectomies but some disease parameters were more severe in the AMC cohort. This was explained by the presence of several patients within the AMC cohort with very extensive disease, especially patients with severe hepatomegaly after splenectomy (20 patients, 11 splenectomized, had liver volumes >3000 mL), who were not found in the HHU cohort. This was also reflected in slightly lower hemoglobin levels and the presence of some patients with extremely high chitotriosidase levels in the AMC cohort. Oral bisphosphonates were used in none of the Duesseldorf patients and in 10% of the Dutch cohort, for a variable length of time.

In both patient groups, less than 10% of the patients were known to be of Ashkenazi-Jewish ancestry. The prevalence of the various mutations in both cohorts was comparable. Genotyping revealed that the most frequent mutation in both centers, AMC and HHU, was N370S/L444P (37% and 32%). Homozygosity for N370S was found in 10% of Dutch and
9% of German patients and absence of the N370S allele was found in none and in 3.5% respectively.

The median time of treatment at the AMC was 9 years (range 1-12) and 7 years (3-11) at HHU (P=0.03). Adjustment of the dose, as described in the methods section, occurred especially at the AMC; from 2 years onwards the median dose at the AMC had increased to 30 U/kg/4 weeks (range 15-120 U/kg/4 weeks) while the dose at the HHU remained largely stable (median 80 U/kg/4 weeks, range 60-120 U/kg/4 weeks). At all time points, the dose remained significantly different (P<0.001).

Disease parameters
There were no significant differences in age, gender, number of splenectomies and SSI in any of the matched populations (data not shown).

1. Hemoglobin and platelet count
Only 31% of the HHU cohort and 53% of the AMC cohort had anemia (Hb <12.0 g/dL) at baseline. Matching for baseline-hemoglobin of <12.0 g/dL and splenectomy status resulted in 2 groups of 11 patients. There was no significant difference in the increase of hemoglobin after 12 months of ERT (Fig. 1a, P=0.37). In 16 patients, follow-up data were available for life table analysis. The time to normalization was not significantly different between both

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The data reflect absolute (and percentual) numbers or median (and range). Abbreviations: AMC, Academic Medical Center, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Duesseldorf; SSI, Severity Score Index21; BMB, Bone Marrow Burden31; ERT, Enzyme Replacement Therapy; NS, not significant.
cohorts (median time to normalization: 10 months for AMC, 8 for HHU, Fig. 1b, P=0.60). For all but one patient, hemoglobin normalized during ERT within 2 years.

In both cohorts, 58% of patients had thrombocytopenia. Matching for baseline-platelet count <100 x 10^9/L and splenectomy status resulted in 2 groups of 19 patients. There were no significant differences in the increase in platelet count after 12 months of ERT (Fig. 1c, P=0.58). In two times 18 patients follow-up data were available for life table analysis. The time to reach a value of >100 x 10^9/L was not significantly different between both cohorts (median time to >100 x 10^9/L: 16 months for AMC, 16 for HHU, Fig. 1d, P=0.50).

Figure 1: Impact of ERT on changes in hemoglobin and platelet count. a) Hemoglobin at baseline and after 12 months, b) time to reach a hemoglobin >12 g/dL, c) platelet count at baseline and after 12 months, d) time to reach a platelet count of >100 x 10^9/L. Abbreviations: AMC, Academic Medical Center, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Duesseldorf; ERT, Enzyme Replacement Therapy.
2. Liver and spleen volume

A total of 24 patients with hepatomegaly, defined as a liver volume of >1750 mL, were selected and matched according to baseline values and splenectomy status. Decrease in liver volume was not different in the two cohorts after 12 months of ERT (Fig. 2a, P=0.59).

Sixteen patients from the AMC and 18 from the HHU with a baseline liver volume of 1750-3000 mL were included in the life table analysis. There were no significant differences in the time to reach a 20% decrease from baseline values (median time to decrease 20% from baseline: AMC 24 months and HHU 20 months, Fig. 2b, P=0.32).

A total of 28 patients with a spleen volume of >250 mL were selected and matched according to baseline values. There were no significant differences in the decrease of spleen volume after 12 months of ERT (Fig. 2c, P=0.84).

Figure 2: Impact of ERT on changes in liver and spleen volume. a) Liver volume at baseline and after 12 months, b) time to reach a 20% decrease of liver volume from baseline, c) spleen volume at baseline and after 12 months, d) time to reach a 40% decrease of spleen volume from baseline. Abbreviations: AMC, Academic Medical Center, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Duesseldorf; ERT, Enzyme Replacement Therapy.
Nineteen patients from the AMC and 27 from the HHU with a baseline spleen volume of 400-2300 mL, were included in the life table analysis. There was no significant difference in time to reach a decrease of 40% from baseline (median time to decrease 40% from baseline: AMC 18 months and HHU 19 months, Fig. 2d, P=0.69).

3. Chitotriosidase
Four patients were excluded because of homozygosity for the chitotriosidase null mutation. Twenty-seven patients were carriers of the chitotriosidase null mutation and had their levels multiplied by two.29 Matching of patients with a chitotriosidase activity of >5000 nmol/mL/hr resulted in two groups of 13 patients. The decrease in chitotriosidase activity after 12 months of ERT was significantly stronger in the HHU cohort than in the AMC cohort (Fig. 3a, P=0.001). Twenty-three patients from the AMC and 18 patients from the HHU with a baseline chitotriosidase level of 6000-25000 nmol/mL/hr were included in the life table analysis. There was a significant difference between both cohorts in time to reach a value of <5000 nmol/mL/hr (median time to <5000 nmol/mL/hr: AMC 48 months and HHU 16 months, Fig. 3b, P=0.015). All patients from the HHU reached a chitotriosidase level <5000 nmol/mL/hr, while 15% of the AMC cohort did not.

4. Bone disease
Comparison of the time to reach a decrease of 2 points in BMB score from baseline, for patients with a baseline BMB of 2-8, showed a trend towards a quicker response in the HHU cohort, with 12% of patients from AMC (N=19) reaching the therapeutic goal after 24 months of ERT vs 33% of patients from HHU (N=23, Fig. 4a, P=0.11).

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Figure 3: Impact of ERT on changes on plasma chitotriosidase activity. a) Plasma chitotriosidase at baseline and after 12 months; b) Time to reach a chitotriosidase of <5000 nmol/mL/hr. Chitotriosidase levels of carriers of the chitotriosidase null mutation were multiplied by two.29 Abbreviations: AMC, Academic Medical Center, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Duesseldorf; ERT, Enzyme Replacement Therapy.
Sub-analysis of patients with more severe bone disease (BMB ≥6) resulted in a significant difference (Fig. 4b, P=0.04). After 24 months of ERT 10% of patients from the AMC cohort (N=13) reached a decrease of 2 points BMB from baseline, vs 33% of the HHU cohort (N=22). Analysis of the clinical records showed that, during the ten years before start of ERT, the number of patients with a serious bone complication was comparable (43% in AMC; 44% in HHU). During ERT skeletal complications occurred in two patients from the AMC (a mild bone crisis after trauma and an avascular necrosis of the left head of the femur without any clinical symptoms, detected by routine MRI) and one patient from HHU (pathological fracture of the left toe V)(P=0.47). Atypical bone pain persisted in some patients from both groups, but was not analyzed systematically.

**Discussion**

Because ERT for type 1 Gaucher disease is extremely expensive, the long-standing controversy about relative efficacy of high dose versus low dose treatment regimens has great socioeconomic as well as medical significance. Comparative studies have been limited. Beutler performed a meta-analysis on several disease parameters from published cohorts, and showed no difference in response19. However, parameters on bone disease and biochemical markers were not available for analysis. One prospective trial compared doses of 10 U/kg/2 weeks to the ‘standard’ dose of 60 U/kg/2 weeks13. Although it was shown that the low dose was less effective with respect to improvement in hemoglobin values and liver and spleen volumes, the patient populations were not matched for disease...
severity, and skeletal parameters as well as biochemical parameters were lacking. In this retrospective study, we compared the response of all major disease parameters, including bone disease parameters and chitotriosidase values, in a large number of adult Gaucher type 1 patients from the AMC (Netherlands) and HHU (Germany) that were treated for up to 12 years with a relatively low (AMC) and relatively high dosage (HHU) of ERT. Both populations were similar with respect to age, gender, genotypes and splenectomy status. However, because several very severely affected patients in the AMC cohort had no counterparts in the HHU cohort, patients were matched for baseline values of the separate parameters. This resulted in a reduction of the size of the parameter-specific cohorts, but allowed a more accurate analysis.

We found that improvement of hemoglobin, platelet count, and liver- and spleen volume is not dose-dependent. However, chitotriosidase does respond better to a relatively high initial dose. Improvement in BMB, a MRI based scoring system of bone marrow involvement, shows a strong trend towards a better response to higher doses, particularly in patients with more extensive bone marrow disease in whom the difference is statistically significant. For all parameters, except for bone disease, two separate statistical methods were used to assess dose responsiveness. Life table analysis is good for depicting long term changes, but is influenced by the length of the interval between consecutive samples. This is relevant because the HHU cohort was followed at less frequent intervals than the AMC cohort, possibly leading to an underestimation of the responses in the patients treated with higher dose ERT. However, this is unlikely, because of the alternate analysis, in which baseline values were compared to values after one year of therapy, which is independent of the interval between samples. Both methods showed similar outcomes: dose independence for anemia, thrombocytopenia and organomegaly and dose dependence for chitotriosidase and bone marrow burden.

Whether the higher initial frequency at the AMC could have beneficially influenced the outcome is unknown. Zimran showed no difference in a three times a week schedule compared to a fortnightly administration of imiglucerase, but Altarescu applied a low dose of 20 U/kg/4 weeks in a fortnightly schedule with inferior responses, compared in retrospect to data obtained from the literature with even lower doses given at high frequency. The current study cannot give an answer to this issue, but it is very likely that, should there be an effect at all, the differences between the cohorts with respect to response in chitotriosidase and BMB would have been even more pronounced if the low dose was given at low frequency.

Chitotriosidase is a lysosomal enzyme which originates from Gaucher cells and is closely associated with total body burden of Gaucher cells. It is increased 100- to more than 4000-fold in symptomatic patients while it is not or only slightly increased in asymptomatic patients. Several studies have also shown a relationship between parameters of disease burden such as SSI and organ volumes and chitotriosidase levels. Its utility as a biomarker is limited by the observation that 6% of the population lack activity and 30% carry a
mutation that results in lower activities. In heterozygote patients, chitotriosidase levels may be multiplied by two to allow adequate comparison with Gaucher patients with normal chitotriosidase genotypes. The clinical usefulness of chitotriosidase has been the subject of a limited number of studies. First of all it was documented that in patients after cessation of treatment, chitotriosidase impressively precedes deterioration of clinical symptoms. It was also established that patients who did not reach a decrease in chitotriosidase of 15% from baseline within the first 12 months also had a lack of clinical response. These data provide an indication that the persistence of high chitotriosidase levels reflect the presence of a high burden of Gaucher cells. Whether this can be translated into an increased risk for Gaucher related morbidity, remains to be determined.

Of all disease parameters, bone disease is the most difficult to evaluate. MR imaging is the preferred modality, due to its sensitivity for the detection of both focal and diffuse disease. Ideally, quantification is done by fat fraction measurements of the lumbar spine obtained through the use of Dixon QCSI, which shows a close correlation with the occurrence of clinical complications. However, since QCSI is not widely available, and vertebral MRI was not performed in the HHU cohort, in this study, we resorted to use the bone marrow burden score of the femora (BMB), a semi-quantitative scoring system that is significantly correlated to QCSI.

The decision to use the modified BMB score may have affected our results, because in contrast to the BMB score of the axial skeleton, small changes in bone disease are difficult to recognize in the femora due to irreversible changes such as marrow infarction or avascular necrosis that are more common in the lower extremities than in the spine. A potential bias lies in the larger number of MRI examinations in the HHU (high dose) patients relative to the AMC (low dose) patients, which may exaggerate the difference in response between relatively low and high dosing. However, the median time interval between examinations, was not very different (12.2 months for the AMC and 14.9 months for the HHU group) and analysis of the data at a fixed time interval, between baseline and 12 months, showed the same results: a trend toward better response to high dosing for the whole group, which was significant in patients with a BMB ≥ 6 (P=0.03). The restriction of MRI examinations to the femora may also explain why, aside from any purported dose effect, favorable hematologic and organ responses do not necessarily correlate with a good bone marrow response.

In fact, although most patients achieved hematologic and organ therapeutic goals, even among the HHU (high dose) patients a significant proportion failed to achieve the BMB therapeutic goal. Whether failing to reach the therapeutic goal for BMB is associated with a higher risk of severe bone complications cannot be answered with this study, since the number of events during ERT was low in both groups (two for AMC, one for HHU). Whether the groups differed with respect to chronic bone complaints is uncertain, since these data were not collected systematically. Nevertheless, the clearly established identification of low fat in the bone marrow as a risk factor for skeletal complications points towards a clinically relevant difference in favor of high dosing in patients with severe bone disease, at least
in the initial treatment period. This conclusion is supported by the observation that both patients from the AMC who developed post-treatment skeletal complications had no history of prior skeletal events, but did have persistently high BMB scores while on low dose ERT. Based on the results of this study the following recommendations can be made. First, as improvement of hemoglobin, platelet count and liver and spleen volume is not dose-dependent, extensive organomegaly and cytopenia do not justify a high initial dose. Severe bone marrow involvement on the other hand may carry a risk for bone complications and is an important criterion to start a higher dose of enzyme. Nevertheless, because the number of major bone complications was low in both groups, this hypothesis merits further investigation. The determination of the most cost-effective dosing regimen should be made individually and on the basis of a complete disease profile, including proper assessment of bone marrow involvement in addition to hematological, visceral and biochemical parameters. This should be done not only for initiation and monitoring of ERT, but also in future studies on ERT as well as alternative treatments for Gaucher disease such as chaperone based therapies or substrate reduction. Chitotriosidase proves to be a sensitive indicator of dose effects and may be used in that respect to monitor response. Subsequent follow-up of all disease parameters is mandatory to allow adequate dosing and appropriate dose adjustment.

Reference List

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


