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chapter 4

# Persistent bone disease in adult type 1 Gaucher disease despite increasing doses of enzyme replacement therapy

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# Summary

Gaucher disease type 1 (GD) is characterized by progressive hepatosplenomegaly, cytopenia and bone disease. Enzyme Replacement Therapy (ERT) can ameliorate bone disease, but not in all patients. Whether increasing doses of ERT are beneficial to treat pre-existing bone disease is unknown. We followed a large cohort of adult GD patients for 5-16 years during ERT. The majority of patients without pre-existing bone disease do not develop bone complications, whereas a subset of patients with bone disease has persistent bone symptoms despite increasing dosages of ERT. Pathological evidence for sanctuary sites in the bone marrow probably attribute to this phenomenon.



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# Introduction

In Gaucher disease type I (GD, OMIM #230800), a lysosomal storage disorder, deficient activity of the enzyme glucocerebrosidase results in accumulation of glucocerebroside in macrophages. These Gaucher cells are mainly found in liver, spleen and bone marrow, leading to hepatosplenomegaly, cytopenia and skeletal disease[1,2].

Skeletal disease is the most debilitating feature, often leading to chronic bone pain and sometimes to severe complications such as pathologic fractures, avascular necrosis and bone crises. Enzyme Replacement Therapy (ERT, Cerezyme, Genzyme, MA, USA) reverses many symptoms of the disease. Different dosing regimens, ranging between 15 and 120 U/kg/4weeks (for a review see[3]), have been proposed. Recently, it has been shown that high dose ERT results in a more robust response in Gaucher associated markers, such as chitotriosidase and the bone marrow burden score[5] (BMB, a MRI based scoring system[4]). Thus, symptomatic bone disease is usually treated with a relatively high dose (60-120 U/kg/4wks). However, even after 5 years of ERT, >30% of patients on a high dose do not show a clear improvement in bone marrow involvement[5]. Whether it is useful to continue high dose treatment, or in case of progressive bone disease, to increase the dose, is currently unknown.

In this study, the subsets of GD patients with and without persistent bone disease are compared with respect to disease markers and the effect of dose increase is evaluated. One illustrative case showing persistant skeletal complications is discussed in more detail.

## Illustrative case history

A male patient was diagnosed with GD at the age of 19 following bone marrow examination because of persistent splenomegaly during an EBV infection. His first bone crisis occurred at the age of 22 followed by recurrent crises in the femurs, bilateral avascular necrosis of the femoral heads, septic arthritis of his right knee and lower lumbar vertebral collapse. Splenectomy was performed at age 25 because of mechanical complaints and severe pancytopenia. ERT was started in 1991 (40U/kg/4weeks, at a frequency of 3x/week). There was no cytopenia. During follow up, normalization of liver volume and a modest decrease in chitotriosidase was observed. No new bone complications occurred, although bone pain persisted. The dose of ERT was increased step by step to 120 U/kg/4weeks. After 14 years of ERT, chitotriosidase had diminished with 60%, still remaining high (8018 nmol/ml.hr). QCSI (Quantative chemical shift imaging[4,6]) measurement was repeatedly very low, but the distorted bone architecture made the interpretation difficult. The BMB score remained 16 (maximum severity). In 2007 he underwent hip replacement. Pathology of the femoral head showed minimal hematopoietic tissue, large necrotic areas in the centre and extensive fields of Gaucher cells (fig 1).



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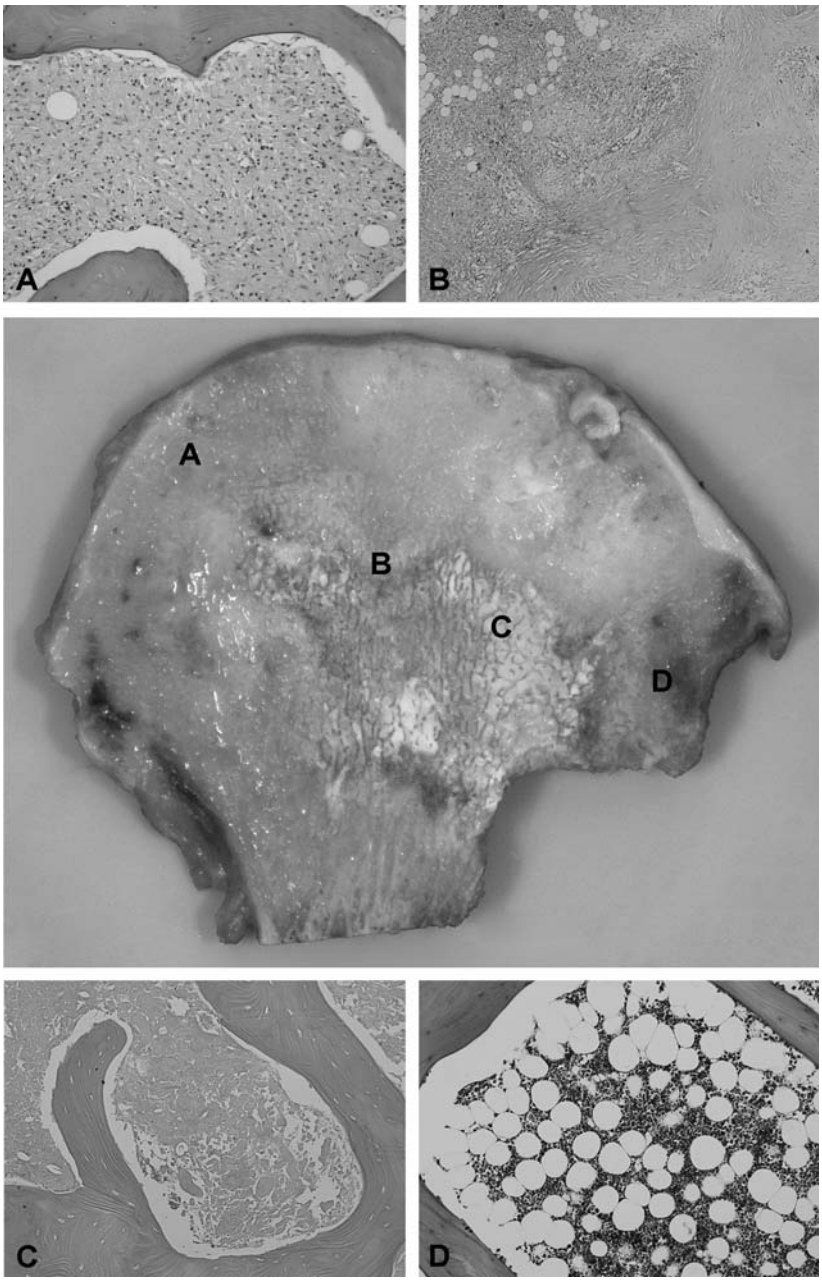


**Figure 1** Cross section of left femur head (centre). The microscopic pictures above and below highlight (a) the yellowish areas consisting of vital bone and marrow filled with confluent sheets of Gaucher cells (100x magnification), (b) the conspicuous demarcation zone with non-specific chronic inflammation with fibrosis (50x), (c) a central area of necrotic cells surrounded by avital bone devoid of osteocytes (100x), (d) small reddish islands of pre-existent bone marrow with normal haematopoietic tissue (100x).



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# Patients and methods

The files of all adult patients at the Academic Medical Centre (AMC, Amsterdam, the Netherlands), receiving ERT for >5 years (individualized-dosing protocol[7], N=40), were reviewed. Data on age, sex, splenectomy, severity score index (SSI[8]), weight, haemoglobin, platelet count, liver and spleen volume, QCSI, BMB[9], chitotriosidase, dose and bone complications were collected.
Bone response was defined by the occurrence, after start of ERT, of complications (avascular necrosis, bone crisis or pathological fractures) or persistent chronic bone pain, defined as pain requiring analgesics and which was, in the opinion of the physician, attributable to Gaucher disease. Two groups were defined:
Group 1: absence of bone complications and chronic bone pain during ERT.
Group 2: occurrence of bone complications or chronic bone pain during ERT.
Group 1 was regarded to have an adequate skeletal response to ERT, while patients from group 2 were considered treatment failures. Due to small patient numbers we did not differentiate patients with or without pre-ERT skeletal complications in group 1.

Chitotriosidase activity was measured as described previously[10]. Genotyping for the chitotriosidase null mutation[11] was performed. Chitotriosidase values of patients who were heterozygous for the chitotriosidase mutation were multiplied by 2[10]. Two patients from group 1 and one patient from group 2 were deficient for chitotriosidase.
Levels of MIP-1β were measured in plasma by ELISA as described by the manufacturer (DuoSet Developmental kit, R&D Systems Inc. Minneapolis, MI).
Liver and spleen volumes were measured by spiral computed axial tomography[12-14]. To correct for changes in bodyweight, liver ratio was calculated (liver volume/bodyweight (mL/kg)).
Bone marrow involvement was assessed using Dixon QCSI of the lumbar spine[4,6]. Since this method was introduced in 1993, when most patients with severe disease were already being treated, baseline QCSI's were available in 15 patients from group 1 and one patient from group 2. Follow-up QCSI data were available in 13 patients from group 1 and 6 from group 2.

## Statistics

Differences in baseline characteristics were analyzed by Mann-Whitney U test or by Chi-square test. The time to reach a 80% decrease in chitotriosidase levels and the time to reach a QCSI of more than 23%, for patients with a baseline QCSI of <23%, were analyzed by life table analysis (Kaplan Meier). Analysis of longitudinal QCSI data of our patients has shown that QCSI does not decrease during therapy (data not shown). Therefore, follow up QCSI's of patients without baseline data could be used for Kaplan Meier analysis. A threshold of 23% was chosen because bone complications occur primarily below this cuttoff[4]. The



proefschrift.indb 53 13-12-2007 13:47:39

results were expressed as the median time to reach the therapeutic goal. Differences were determined by the log rank test.

# Results

At baseline, patients from group 2 had more severe disease, as evidenced by a higher SSI and liver ratio and more splenectomies than those from group 1 (table 1). Patients from group 2 also had a lower body weight. In group 2, 10/12 patients (83%) had bone complications prior to ERT, compared to 7/28 (25%) from group 1 (P<0.0001).

In Group 1, dose was increased in 10/28 of patients (36%), primarily because of suboptimal platelet or visceral response. In 3 of these, chitotriosidase and/or fat fractions showed an accelerated improvement after a dose increase (data not shown), while no uniform change was seen in the other seven.

In group 2, 10/12 patients (83%) had a dose increase; two patients refused dose adjustments. Chitotriosidase showed a considerably better response after a dose increase

**Table 1.** Baseline characteristics of patients with (group 2) and without (group 1) severe bone disease after start of ERT. NS: not significant

| | **Group 1** | **Group 2** | **P** |
|---|---|---|---|
| N | 28 | 12 | |
| age | 48 (21-68) | 51 (37-77) | NS |
| Sex (male/female) | 14/14 | 9/3 | NS |
| Weight (kg) | 74 (50-104) | 66 (47-72) | 0.026 |
| Splenectomy | 6 (21%) | 8 (67%) | 0.011 |
| Severity Score Index | 6 (3-18) | 14 (7-19) | <0.0001 |
| Haemoglobin (mmol/L) | 7.6 (6.4-9.0) | 7.3 (6.5-9.1) | NS |
| Platelet count (x10x9/L) | 77 (41-240) | 126 (16-473) | NS |
| Chitotriosidase (nmol/mL/hr) | 35134 (12430-143758) | 44973 (29703-151400) | NS |
| MIP-1β (pg/mL) | 199 (72-472) | 250 (113-671) | NS |
| Liverratio (mL/kg) | 37 (22-93) | 63 (30-130) | 0.014 |
| Spleenvolume (mL) | 1131 (470-4526) | 1400 (501-4821) | NS |
| Patients with pre-ERT bone complications | 7 (25%) | 10 (83%) | <0.0001 |
| Start dose (U/kg/4weeks) | 15 (15-60) | 15 (15-50) | NS |
| Highest dose (U/kg/4weeks) | 30 (15-120) | 60 (25-120) | 0.007 |

in only two patients; in none of the patients an accelerated improvement in QCSI was seen. In 4 patients dosing was increased to 120 U/kg/4weeks. In none of these patients this resulted in further improvement in chitotriosidase or QCSI; at 10 years of ERT, absolute QCSI was 14%, 6%, 21% and 15%, compared to a median (range) of 48,5% (25-65%) in group 1 patients. The relative decrease in chitotriosidase at that moment was 48%, 57%, 80% and 52%, compared to a median (range) of 85% (64-88%) in group 1.



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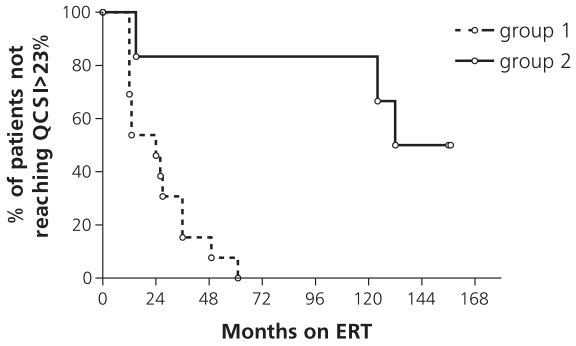
Comparison of the time to reach a QCSI of > 23% showed a significantly slower response in group 2 (N=6, median time 132 months) compared to group 1 (N=13, median time 24 months, P=0.001). At 5 years of ERT, all patients from group 1 had reached the therapeutic goal, compared to 1 patient (17%) from group 2 (fig 2a).
The time to reach a decrease in chitotriosidase levels of >80% was significantly shorter in group 1 (N=26, median time 70 months), as compared to group 2 (N=11, median time172 months, P=0.0076) (fig 2b).



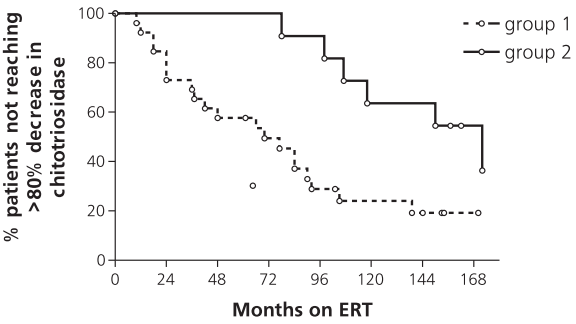




**Figure 2: Changes in QCSI and plasma chitotriosidase activity** Time to reach a QCSI > 23% (fig 3a) and time to reach a decrease in chitotriosidase level of > 80% (fig 3b). Chitotriosidase levels of carriers of the chitotriosidase null mutation were multiplied by two.

# Discussion

In this study we show that a subset of Gaucher type I patients experience ongoing bone disease despite increasing doses of ERT. The selected case illustrates that areas of Gaucher cells can remain in the bone marrow, contributing to persisting bone disease and probably to the high levels of biomarkers. The low fat fraction and high BMB score can be attributed to Gaucher cells and possibly also to fibrosis, both displacing adipocytes.
Possibly, the remaining Gaucher cells escape the effects of ERT due to altered vascularization and fibrosis, although no pathological evidence for this was found. Alternatively, different sub-populations of Gaucher cells may exist, that differ in their ability to take up the exogenous enzyme. For example, in splenic tissue of a patient with longstanding Gaucher disease, Gaucher cells showed little immunoreactivity for the mannose receptor[15].



proefschrift.indb 55 13-12-2007 13:47:40

We identified 12/40 patients who still experienced bone disease despite >5 years ERT with increasing doses of enzyme. In 5 patients this consisted primarily of chronic pain that could not be explained by pre-existing deformities or other causes. We have recently described that these patients have generally higher MIP-1β levels and lower bone marrow fat fractions as compared to the responders[4,16]. In patients with advanced bone disease a combined assessment of baseline characteristics and response parameters may provide a risk indication for failure of skeletal response. Risk factors are longstanding and severe pretreatment disease manifestations, exemplified by previous bone complications, hepatomegaly, low bodyweight and splenectomy at baseline, as well as slow improvement in QCSI, chitotriosidase and MIP-1β[16] during ERT. In these patients, further dose increases are probably not effective. Thus, alternative strategies should be considered such as preventive and supportive measures, the addition of bisphosphonates and combination with substrate reduction therapy. Meanwhile, the goals for ERT in this subgroup may change to maintaining adequate control of visceral disease. Tapering of the dose can then be considered.

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