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

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Chapter 12

Summary
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Section I. Enzyme replacement therapy
In chapter 2 the feasibility of less burdensome enzyme replacement therapy using low frequency of administration was prospectively studied in patients with stable and minor disease. Eleven patients were randomly assigned to either continue their original regimen in a once every week or fortnightly schedule or to lower the frequency of administration to once every four weeks, at the same monthly dose. After a study period of one year, there were no significant differences between the 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 bone marrow fat fraction (Quantative chemical shift imaging, 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. Thus, stable disease is maintained in most, but not all patients with stable and minimal disease on low frequency enzyme replacement therapy. Especially patients with a relatively low baseline lumbar fat fraction may be at risk for disease progression. Close monitoring of all disease parameters is therefore mandatory.

The much debated topic of dosing of enzyme replacement therapy is discussed in chapter 3. Worldwide, dosing varies from 15-130 U/kg/month, making a huge economic difference of €55.000 up to €300.000 per patient per year. To investigate whether this difference in dosing results in a different response, we retrospectively compared long term outcome of enzyme replacement therapy at two large European treatment centers, Amsterdam (AMC, N=49, median dose 15-30 U/kg/4 weeks) and Düsseldorf (HHU, N=57, median dose 80 U/kg/4 weeks). To correct for disease severity, all follow-up parameters were matched separately at baseline. Improvement in hemoglobin, platelet count and hepatosplenomegaly was not significantly different between both cohorts, whereas plasma chitotriosidase and bone marrow involvement by MRI (bone marrow burden (BMB) score) improved faster and more pronounced in the higher-dosed group. Major bone complications were rare in both groups. Thus, extensive organomegaly and cytopenia do not justify a high initial dose. However, severe bone marrow involvement may carry a risk for bone complications and is an important criterion to start a higher dose of enzyme.

The finding that a subset of patients has a suboptimal bone response, led us to study the effect of increasing doses of enzyme replacement therapy on pre-existing bone disease in chapter 4. We retrospectively analysed a large cohort of adult Gaucher disease patients using enzyme replacement therapy for 5-16 years. The majority of patients without pre-existing bone disease did not develop bone complications, whereas a subset of patients showed persistent bone symptoms despite increasing dosages of enzyme. Risk factors were previous bone complications, a large liver, low bodyweight and the absence of a
spleen at baseline, as well as a slow improvement in QCSI, chitotriosidase and macrophage inflammatory protein (MIP-1β) levels during enzyme replacement therapy. Pathological evidence for sanctuary sites of Gaucher cells that remain in the bone marrow probably contribute to the persisting bone disease.

**Section II. Biomarkers**

Chitotriosidase is the most commonly used marker for Gaucher cell load. Its use is hampered by the genetic defect that results in complete deficiency in 6% of the population. In chapter 5 we report the identification of an alternative marker, CCL18, which is on average 29 fold elevated in symptomatic Gaucher patients, without overlap with control values. Plasma CCL18 concentrations decrease during therapy, comparable to chitotriosidase levels. Immunohistochemistry demonstrates that Gaucher cells are the prominent source of CCL18.

In chapter 6 we investigated the levels of soluble CD163, a macrophage/monocyte specific plasma protein, in patients with Gaucher disease. As compared to controls, sCD163 plasma levels were clearly increased and decreased upon enzyme replacement therapy. sCD163 levels showed a correlation with disease severity and chitotriosidase activity.

MIP-1α and MIP-1β are chemokines that are implicated in skeletal complications in multiple myeloma. In chapter 7 we studied the possibility of these mediators as markers of skeletal disease. Levels of MIP-1α and MIP-1β were significantly elevated in plasma of Gaucher patients and decreased upon enzyme replacement therapy. The increase in plasma MIP-1β levels was associated with skeletal symptoms. More specifically, a lack of reduction of plasma MIP-1β below 85 pg/ml during 5 years of therapy was observed in patients with ongoing skeletal disease. In addition, it was found that, in contrast to chitotriosidase and CCL18, MIP-1β was not produced by Gaucher cells but by cells surrounding the mature storage cells.

Given the debate whether high dose ERT results in a faster and better bone response, we investigated whether a difference in therapeutic enzyme dosing influences the response in plasma MIP-1β concentration in chapter 8. MIP-1β responses were retrospectively determined in two comparable patient groups receiving either a relatively low dose (median 15 U/kg/4 weeks (AMC, n=15)) or a relatively high dose (median 120 U/kg/4 weeks (HHU, n=15)) of ERT. Plasma MIP-1β levels improved faster during the first year of treatment in the higher-dosed patient group. This was also observed for responses in chitotriosidase and the bone marrow burden score. Thus, not only the initial correction of Gaucher cells, but also that of associated phagocytes appear to be enzyme dose-dependent.
Section III. Associated morbidities

In chapter 9 we studied cholesterol profiles in Gaucher disease patients and carriers and the risk of cardiovascular disease. We found that Gaucher disease patients have low HDL cholesterol levels and, to a lesser extent, low LDL cholesterol levels, with decreases in the major apolipoproteins related to these cholesterol particles, ApoA-I and ApoB. Using cIMT (carotid intima media thickness) measurements and calculating the risk for cardiovascular disease by indirect standardization of historic data, we established that there is no indication that the low levels of HDL-cholesterol in GD are associated with an increased risk of cardiovascular disease. Hypothesis concerning the origin of the lipid abnormalities and the mechanisms that prevent atherosclerosis are discussed.

In chapter 10 we studied the incidence and mortality of cancer in 131 Gaucher disease type I patients from Germany and the Netherlands. A total of 14 Gaucher patients with cancer were identified of whom 5 had a hematological malignancy. These numbers correspond to an increased risk of cancer of 2.5 (95% CI 1.1-4.7) and an increased risk of a hematological malignancy of 12.7 (95% CI 2.6-37.0), when compared to the general population. In particular, the incidences of multiple myeloma and hepatocellular carcinoma in absence of pre-existing cirrhosis were highly elevated, with standardized rate ratios of 51.1 and 141.3, respectively.

In view of the results from chapter 10, we studied the prevalence, risk factors, pathogenesis and the effect of enzyme replacement therapy on benign, pre-malignant and malignant gammopathies in 63 adult Gaucher disease patients in chapter 11. The results were discussed in relation to a review of the currently available literature. Polyclonal gammopathies and monoclonal gammopathy of undetermined significance (MGUS) were found in 41% and 19% of patients. The prevalence of MGUS increased with age but was not associated with disease severity or exposure time. The serum levels of free light chains of immunoglobulins were measured and were not found predictive for the development of MGUS or multiple myeloma. Levels of pro- as well as anti-inflammatory mediators that are involved in inflammation and B cell function, most notably interleukin-10 and CCL18, were found to be disturbed. Finally, we found that enzyme replacement therapy could possibly prevent the occurrence and delay the progression of gammopathies.