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Type	Dissertation
Title	Gaucher disease type I : associated morbidities and long term efficacy of enzyme replacement therapy
Author	M. de Fost
Faculty	Faculty of Medicine
Year	2008
Pages	196

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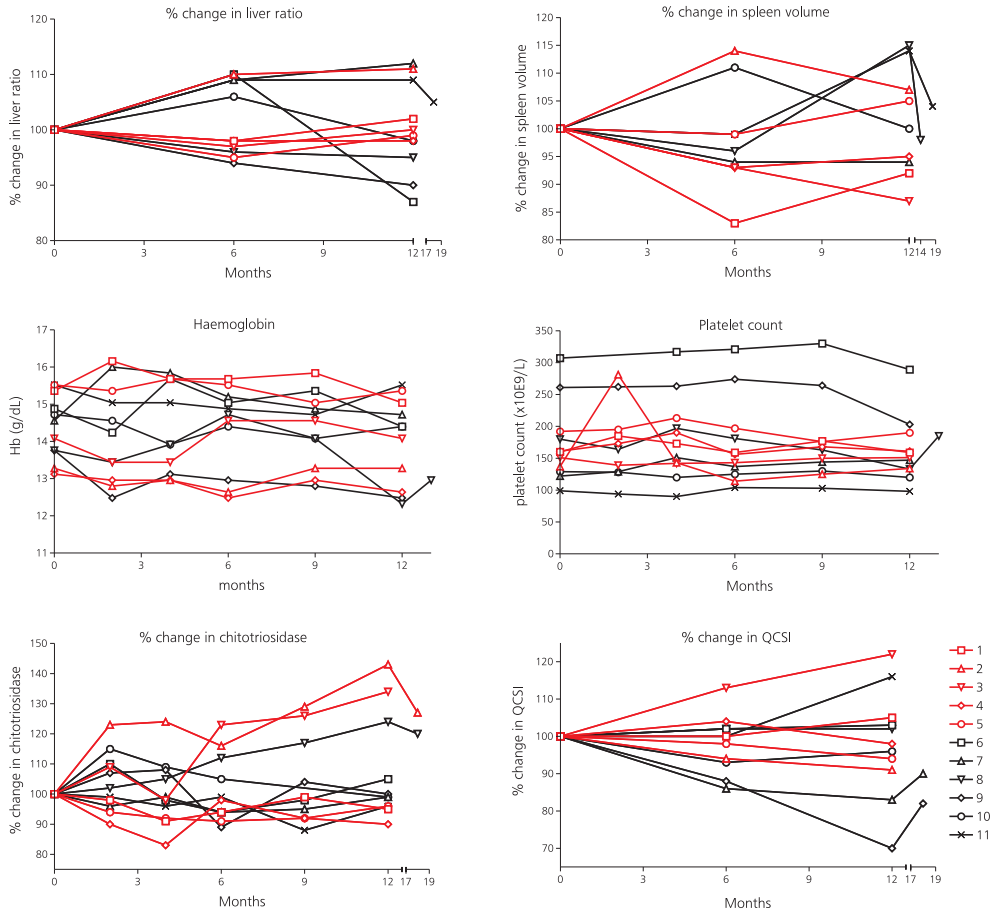
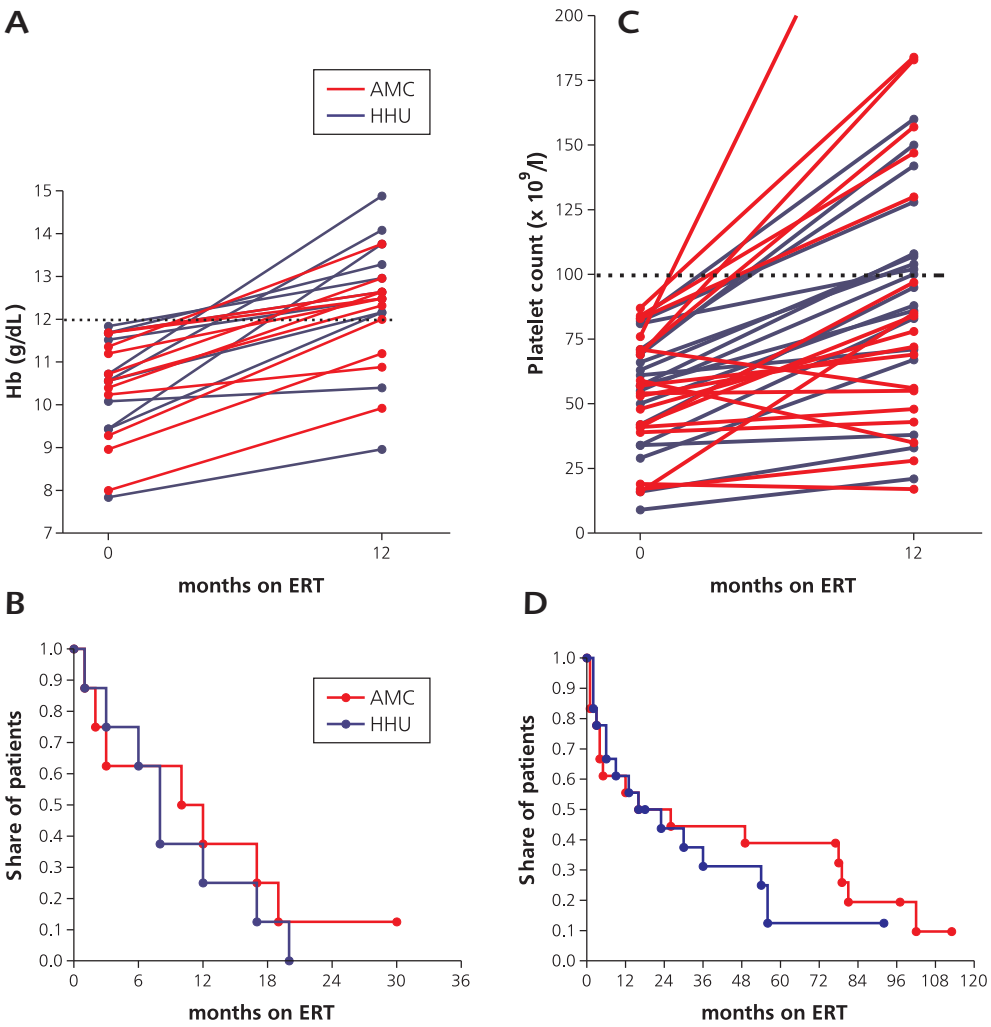
http://dare.uva.nl/record/262840

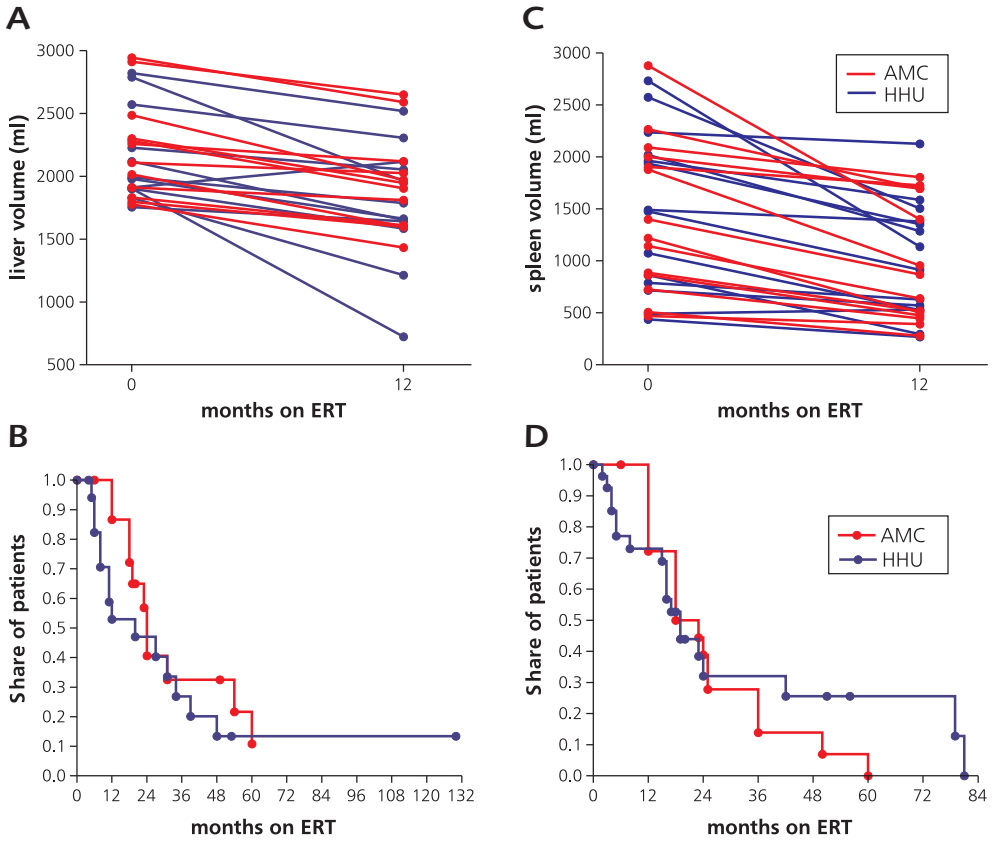
Appendix



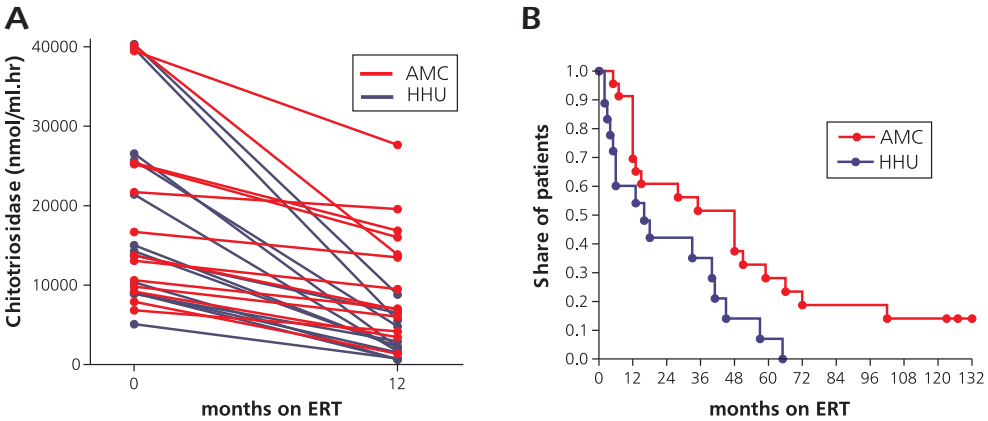
Chapter 2. Figure 1a-f: Percentage changes in liver ratio (a) and spleen volume (b), absolute changes in Haemoglobin (c) and platelet count (d), and percentage changes in chitotriosidase (e), and QCSI (quantative chemical shift imaging) (f). Patients from the high frequency group (1x/1-2weeks) are depicted in red; patients from the low frequency group (1x/4weeks) are depicted in black.



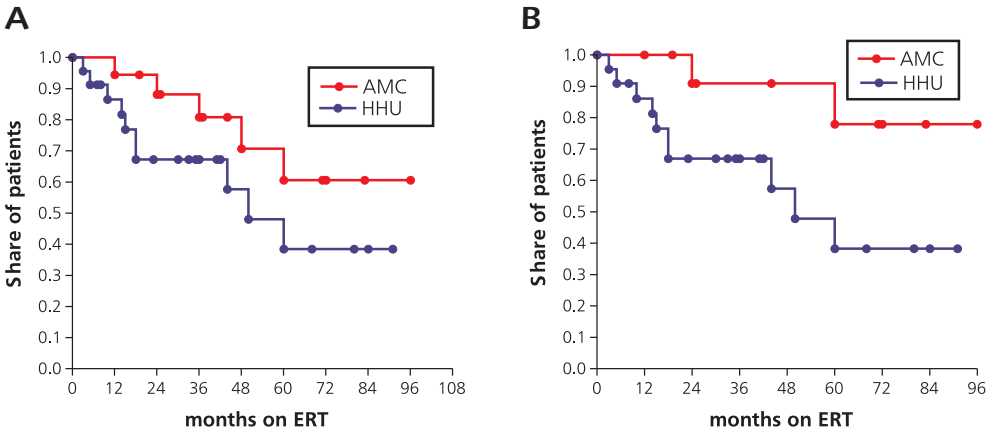
Chapter 3. Figure 1: Impact of ERT on changes in hemoglobin and platelet count. a) Hemoglobin at baseline and after 12 months, b) time to reach a hemoglobin >12 g/dL, c) platelet count at baseline and after 12 months, d) time to reach a platelet count of **>**100 x 10^9/l. Abbreviations: AMC, Academic Medical Center, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Duesseldorf; ERT, Enzyme Replacement Therapy.



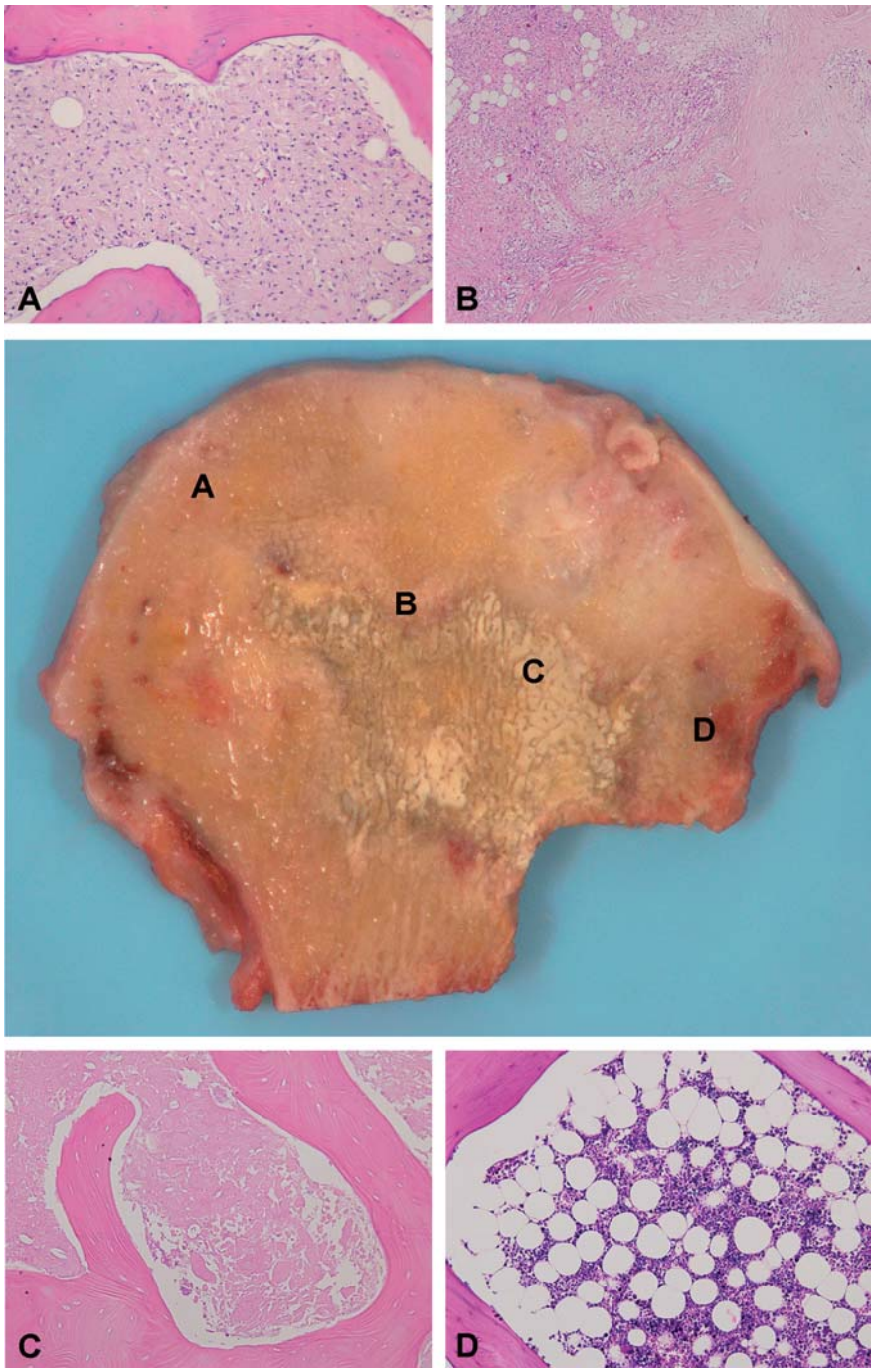
Chapter 3. Figure 2: Impact of ERT on changes in liver and spleen volume. a) Liver volume at baseline and after 12 months, b) time to reach a 20% decrease of liver volume from baseline, c) spleen volume at baseline and after 12 months, d) time to reach a 40% decrease of spleen volume from baseline. Abbreviations: AMC, Academic Medical Center, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Duesseldorf; ERT, Enzyme Replacement Therapy.



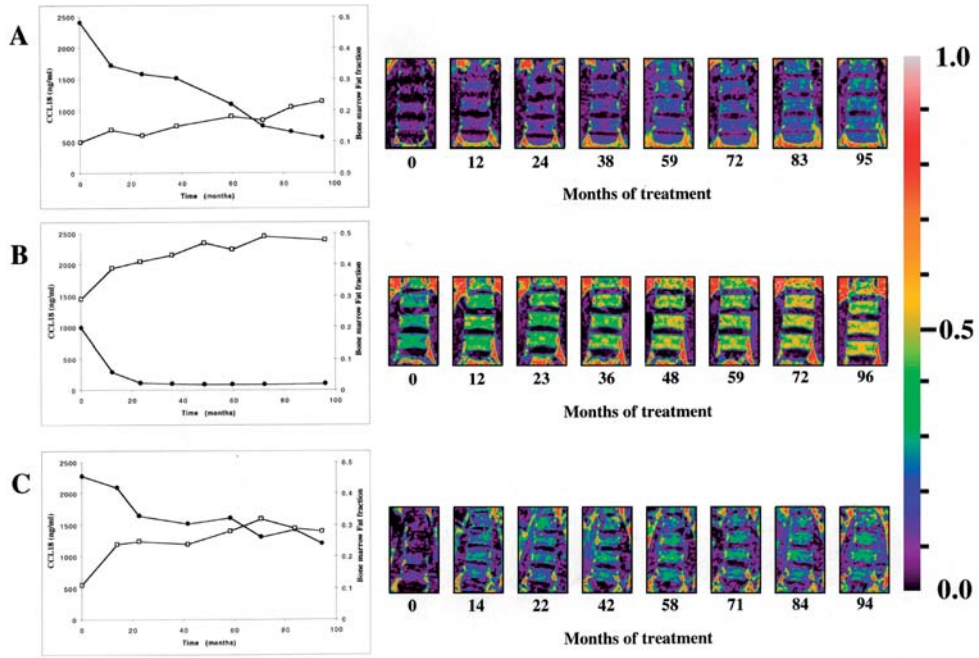
Chapter 3. Figure 3: Impact of ERT on changes on plasma chitotriosidase activity. a) Plasma chitotriosidase at baseline and after 12 months; b) Time to reach a chitotriosidase of <5000 nmol/mL/hr. Chitotriosidase levels of carriers of the chitotriosidase null mutation were multiplied by two[29]. Abbreviations: AMC, Academic Medical Center, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Duesseldorf; ERT, Enzyme Replacement Therapy.



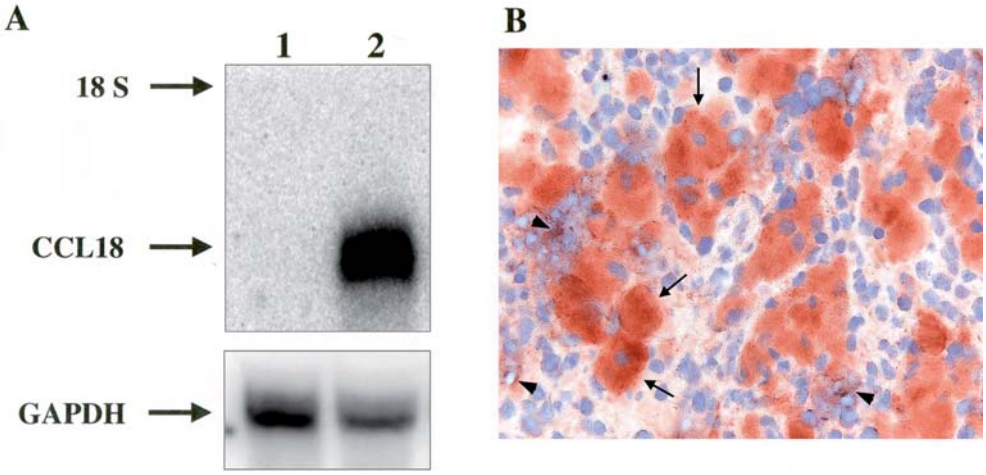
Chapter 3. Figure 4: Impact of ERT on changes in bone marrow burden score. a) Time to reach a decrease of 2 points in BMB score, as measured by MRI, from baseline of patients with a baseline BMB of 2-8, b) time to reach a decrease of 2 points in BMB score from baseline of patients with a baseline BMB of 6-8. Abbreviations: AMC, Academic Medical Center, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Duesseldorf; BMB, bone marrow burden, as determined by MRI[27]; ERT, Enzyme Replacement Therapy.



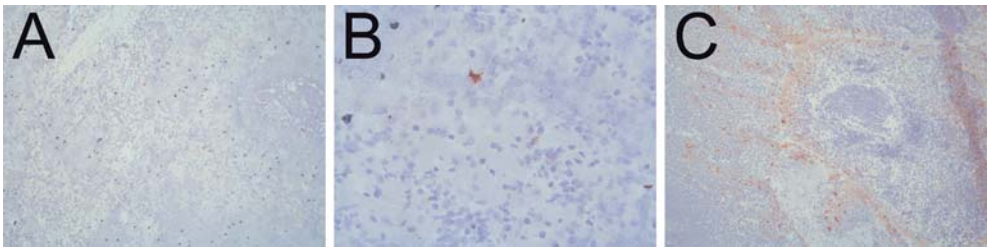
Chapter 4. Figure 1 Cross section of left femur head (centre). The microscopic pictures above and below highlight (a) the yellowish areas consisting of vital bone and marrow filled with confluent sheets of Gaucher cells (100x magnification), (b) the conspicuous demarcation zone with non-specific chronic 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).



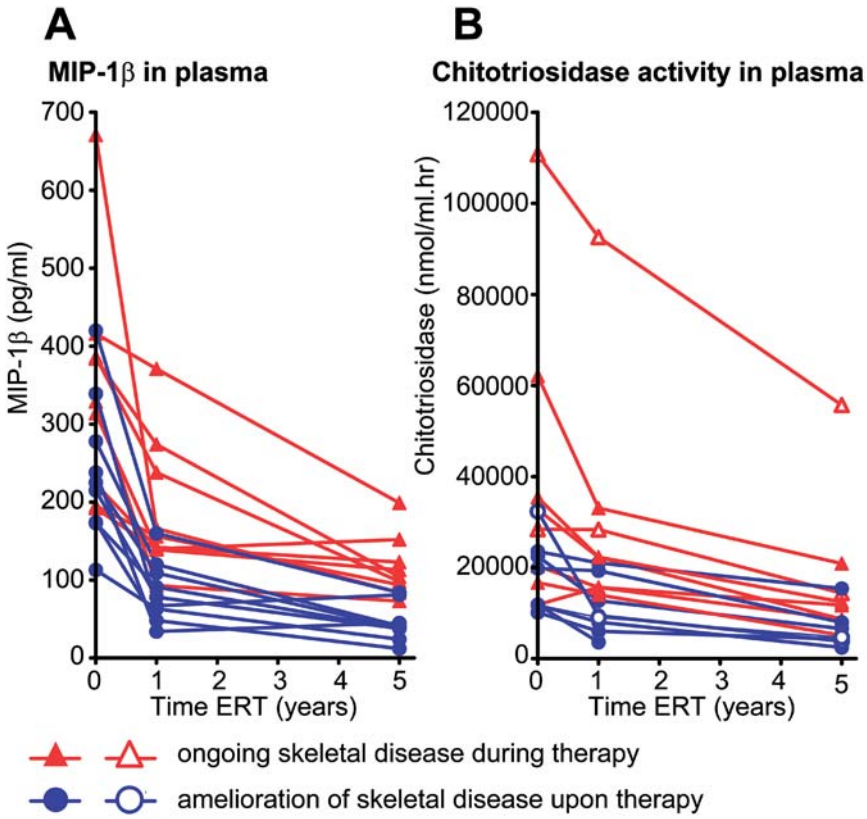
Chapter 5. Figure 5. Relationship between decrease in CCL18 plasma levels and lumbar spine bone marrow fat fraction. Panel A, B and C: Inverse relationship between the decrease in plasma CCL18 levels and increase in lumbar spine marrow fat fraction upon enzyme replacement therapy. Patient A: Spearman ρ -0.952; p = 0.0011, patient B: Spearman ρ -0.802; p = 0.0218, patient C: Spearman ρ -0.815; p = 0.0108. (● = CCL18, ○ = bone marrow fat fraction). Right hand side, changes in the bone marrow fat fraction of the lumbar spine during enzyme replacement therapy as visualized by quantitative chemical shift imaging.



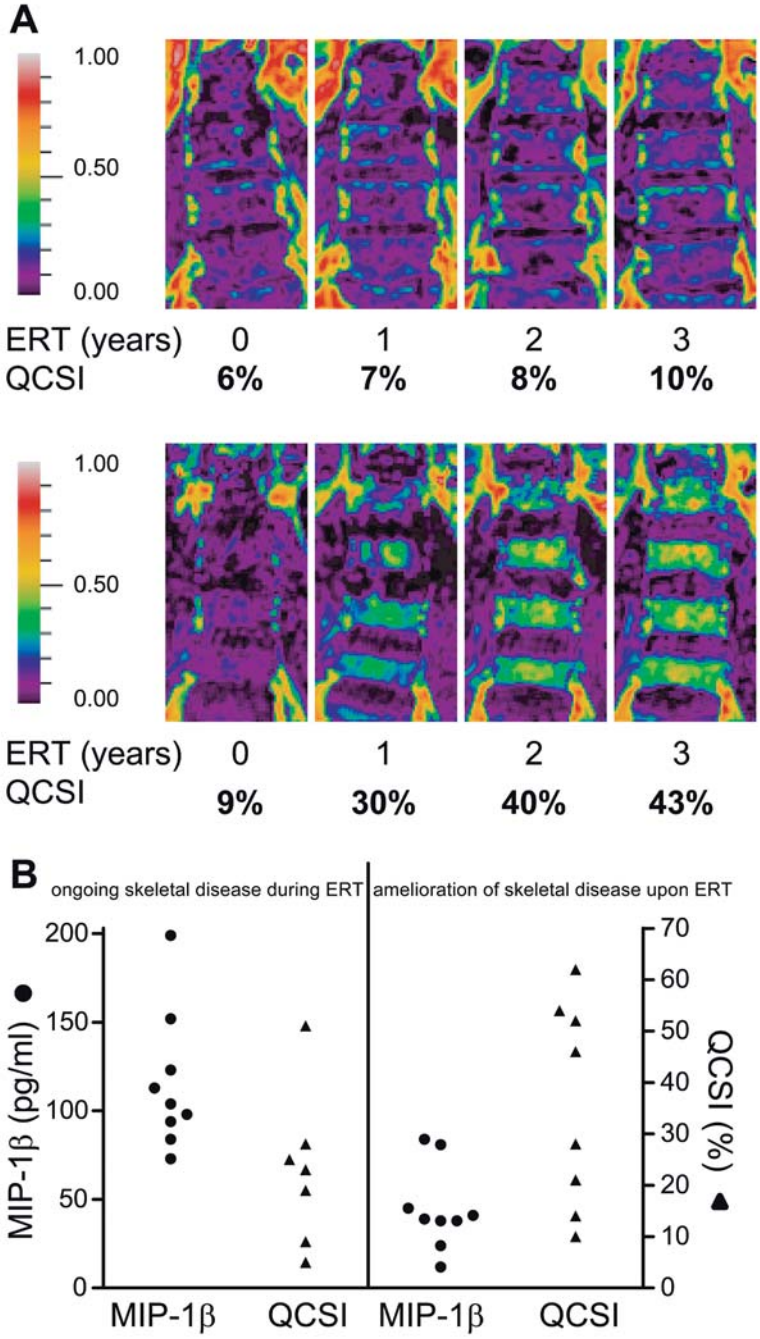
Chapter 5. Figure 6. Expression of CCL18 in Gaucher spleen. Panel A: Detection of CCL18 mRNA in Gaucher spleen by northern blot analysis. Control and Gaucher spleen total RNA was analyzed by northern blotting as described in Material and Methods. Lane 1: Control spleen; Lane 2: Gaucher spleen. The probes used: full length CCL18 cDNA and glyceraldhyde-3-phosphate dehydrogenase (GAPDH) as a RNA control. The 18S ribosomal band is indicated. Panel B: Detection of CCL18 protein by immunohistochemistry in Gaucher spleen. Clustered large swollen cells are Gaucher cells and label massively for CCL18 protein (arrows). Some surrounding spleen cells also show some labeling (arrowheads)(magnification, x400).



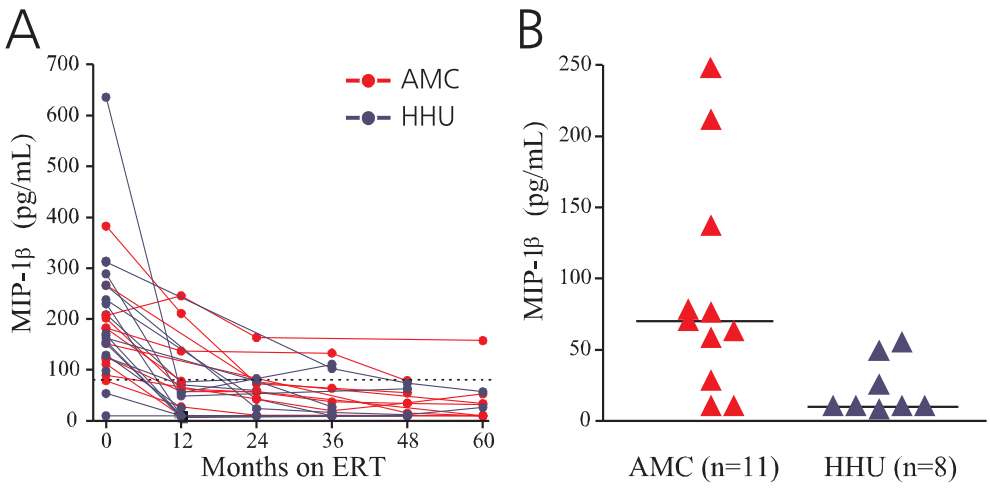
Chapter 7. Fig. 3. Detection of MIP-1β protein by immunohistochemistry in Gaucher spleen. Immunohistochemistry, using an antibody against MIP-1β, was performed on frozen sections of Gaucher spleen (A, B) and human tonsil as an internal positive control tissue (C). (A) Overview of Gaucher spleen section. Original magnification × 100. (B) Magnification of the same (Gaucher spleen) section. Original magnification × 400. Stained Gaucher spleen sections show that Gaucher cells (clustered large swollen cells) do not have detectable levels of MIP-1β protein. Some surrounding cells do show labeling. (C) Overview section of human tonsil (control tissue) confirms MIP-1β protein expression as predicted. Original magnification × 100.



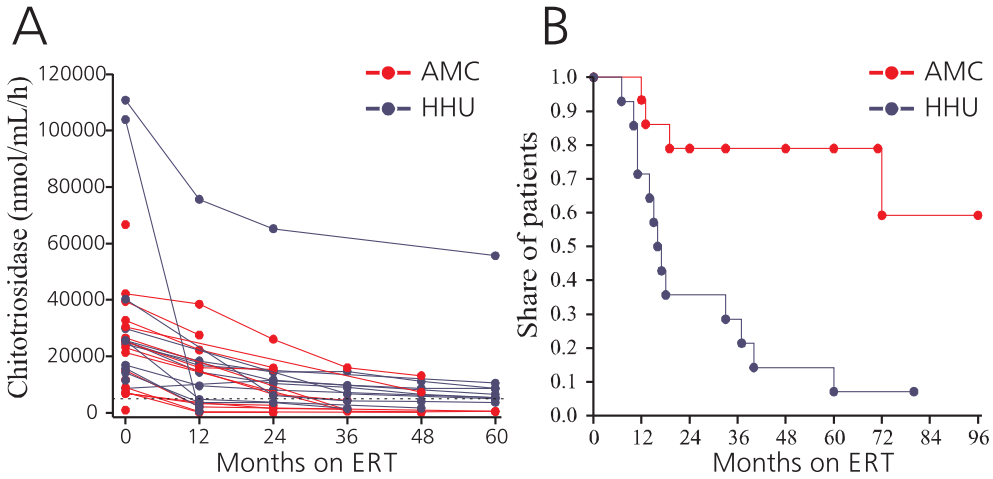
Chapter 7. Fig. 5. Effect of treatment (0, 1 and 5 years ERT) on MIP-1β levels and chitotriosidase in plasma of Gaucher patients with or without amelioration of skeletal disease upon therapy. (A) Plasma MIP-1β levels. (B) Plasma chitotriosidase levels. Gaucher patients with ongoing skeletal disease during therapy (n=9) and Gaucher patients with amelioration of skeletal disease upon therapy (n=9) are represented by a red triangle and a blue circle, respectively. Closed symbols represent chitotriosidase wild-type individuals; open symbols, chitotriosidase carrier individuals for which chitotriosidase activity is corrected by doubling the measured activity.



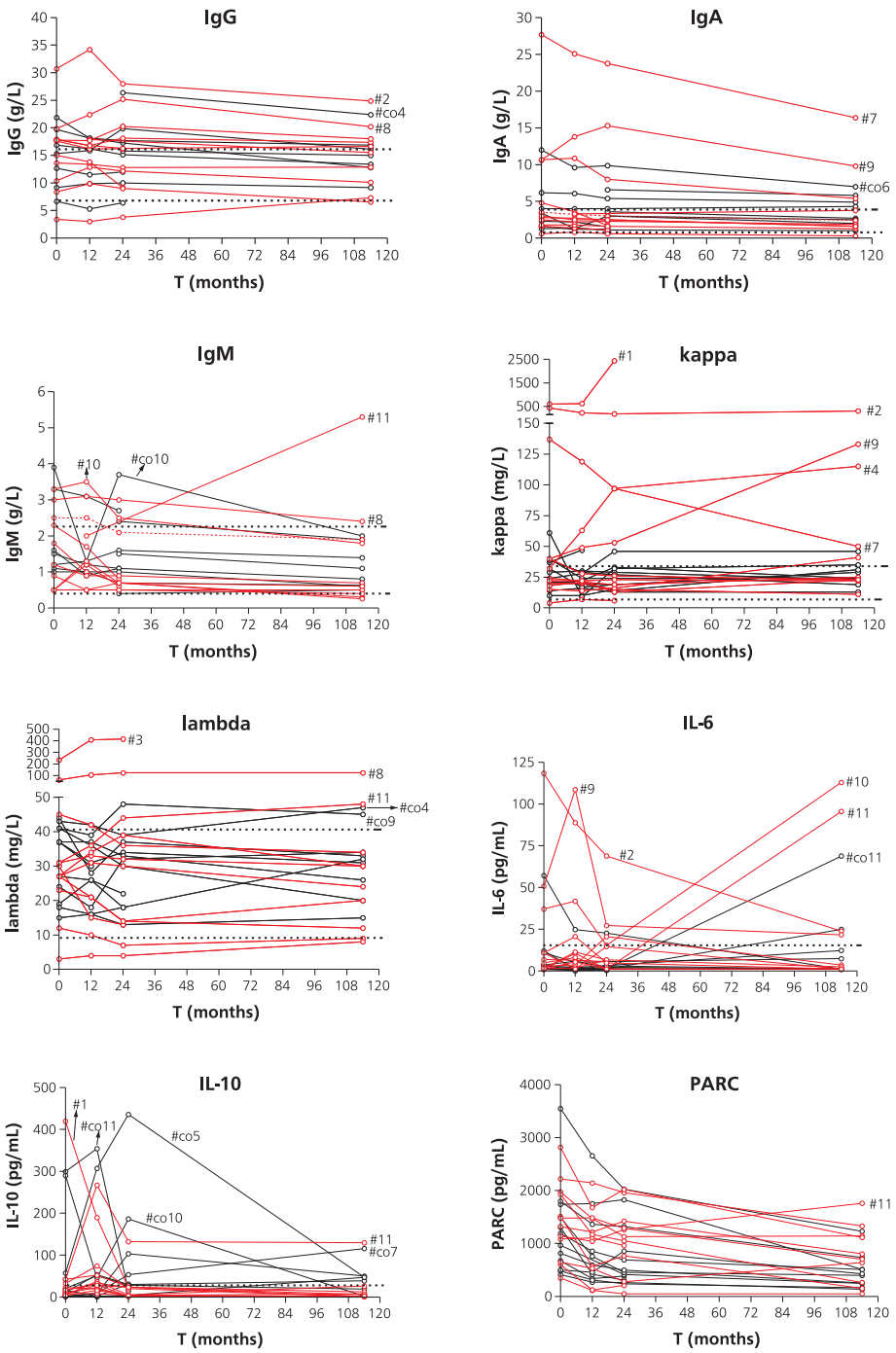
Chapter 7. Fig. 6. Effect of treatment on the fat fraction of the lumbar spine and plasma MIP-1β levels. (A) Examples of response in bone marrow fat fraction of the lumbar spine upon therapy as visualized by QCSI. Upper panel: characteristic response in patients showing ongoing skeletal disease. Lower panel: characteristic response in patients without bone complications during therapy. (B) Plasma MIP-1β levels and lumbar bone marrow fat fraction after 5 years of therapy. Plasma MIP-1β levels (circles) and lumbar bone marrow fat fractions (triangles) in patients with ongoing skeletal disease (left panel) and those without (right panel).



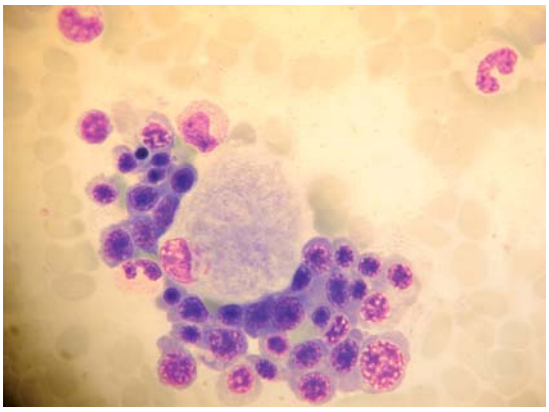
Chapter 8. Figure 2. Impact of ERT on changes in plasma MIP-1β levels. (A) Plasma MIP-1β at baseline, and after 1, 2, 3, 4 and 5 years of ERT. (B) Plasma MIP-1β after 1 year of ERT. Abbreviations: AMC, Academic Medical Center, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Duesseldorf; ERT, Enzyme Replacement



Chapter 8. Figure 3. Impact of ERT on changes in plasma chitotriosidase activity (A) Plasma chitotriosidase at baseline and after 1, 2, 3, 4 and 5 years of treatment. (B) Time to reach a chitotriosidase of <5000 nmol/mL/hr. Chitotriosidase levels of carriers of the chitotriosidase null mutation were multiplied by two [9]. Abbreviations: AMC, Academic Medical Center, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Duesseldorf; ERT, Enzyme Replacement Therapy.



Chapter 11. Figure 3. Longitudinal changes in plasma levels of immunoglobulin heavy – and free light chains, IL-6, IL-10 and PARC. Dotted lines reflect the normal range. Numbers reflect Gaucher disease patients with a monoclonal gammopathy as described in table 1 (#1-13) and matched Gaucher disease controls (#co1-co13) without a monoclonal gammopathy. Abbreviations: IL, interleukin; PARC, pulmonary and activation-regulated chemokine.



Chapter 11. Figure 4. Bone marrow aspirate showing plasma cells surrounding a Gaucher cell in a patient with Gaucher disease type I and multiple myeloma.