

# Cessation of enzyme replacement therapy in Gaucher disease

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**Purpose:** Enzyme replacement therapy (ERT) is a promising therapeutic intervention for lysosomal storage diseases. Posttranslationally engineered human  $\beta$ -glucocerebrosidase (Ceredase®/Cerezyme®) is commercially available and is the standard ERT for Type I Gaucher disease. Cessation of therapy is sometimes necessary for personal or financial reasons, but the consequences of discontinuation are unknown. This study reports results of discontinuing therapy in four patients with Type I Gaucher disease with different genotypes and varying degrees of clinical involvement. **Methods:** Patient genotypes were as follows: N370S/L444P (Patients 1 and 2), K79N/K79N (Patient 3), and N370S/N370S (Patient 4). All were evaluated before, during, and after withdrawal from ERT. Patients 1, 2, and 3 were studied after reinstating ERT. The following parameters were documented at 3- to 12-month intervals in all patients: hemoglobin, platelet count, angiotensin-converting enzyme, spleen volume, liver volume, femoral magnetic resonance imaging, bone density, and urinary pyridinium crosslinks. **Results:** After cessation of therapy, Patients 1, 2, and 3 had more dramatic regression in hematological and visceral parameters than Patient 4 and required reinstatement of ERT within 2 years. All three patients recovered posttreatment status within 4 years of reinstating ERT. Patient 4 remained stable 6 years after cessation of ERT. **Conclusions:** Regression of disease status in patients with Type I Gaucher disease after cessation of ERT conformed to the genotype–phenotype relationships of disease onset. Careful monitoring and reinstatement of ERT enabled previously attained treatment status. *Genet Med* 2002;4(6):427–433.

**Key Words:** Gaucher disease, enzyme replacement therapy, cessation of therapy, genotype, phenotype

Gaucher disease is caused by deficiency of the lysosomal enzyme  $\beta$ -D-glucosyl-N-acylsphingosine glucohydrolase (E.C. 3.2.1.45) ( $\beta$ -glucocerebrosidase). Deficiency of this enzyme results in accumulation of glucocerebrosides in macrophages of the reticuloendothelial system and consequent hepatomegaly, splenomegaly, anemia, thrombocytopenia, bleeding disorders, orthopedic problems (including demineralization, cortical thinning, fractures, infarctions, osteonecrosis, and joint degeneration), pulmonary diffusion defects, and excessive fatigue.<sup>1–5</sup> In Type I Gaucher disease the central nervous system is spared.

At least 150 mutations in the  $\beta$ -glucocerebrosidase gene have been identified.<sup>6</sup> The N370S mutation is associated with nonneuronopathic (Type I) disease, either in the homozygous or heterozygous state.<sup>7</sup> Homozygosity for N370S generally presents later in life and with milder symptoms than heterozygosity for this mutation combined with other mutations such as L444P, 84GG, and IVS2(+1). Although there is clinical vari-

ability among genotypes, the presence of the N370S mutation protects the phenotype from neuronopathic Types II and III forms of Gaucher disease.<sup>8</sup>

Enzyme replacement therapy (ERT) with posttranslationally engineered human  $\beta$ -glucocerebrosidase (Ceredase®/Cerezyme®) administered intravenously is an effective treatment for Type I Gaucher disease. Prior studies have shown improved blood cell counts and reduced liver and spleen volumes in Gaucher disease patients on ERT.<sup>9,10</sup> Enzymes secreted by the glucocerebroside-laden macrophages (“Gaucher cells”), such as angiotensin-converting enzyme (ACE), decrease over the course of treatment.<sup>11</sup> Bone integrity improves with ERT, although these changes occur more slowly than visceral and hematological changes.<sup>9,12,13</sup> We previously demonstrated that pyridinium crosslink analysis was a biochemical function of increased bone collagen turnover.<sup>14</sup> This was recently confirmed in Gaucher disease.<sup>15</sup> Decreased glucocerebroside fat content of the bone marrow has been observed in treated patients and is detectable by T1-weighted magnetic resonance imaging (MRI).<sup>16–18</sup> Significant improvement in quality of life occurs in treated patients.<sup>19</sup>

Because of the overall clinical effectiveness of ERT, most patients and physicians are motivated to continue with treatment. However, the expense of ERT and the complexity of intravenous therapy at least once every 2 weeks results in some patients discontinuing therapy. The annual average cost for

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Received: July 1, 2002.

Accepted: August 14, 2002.

DOI: 10.1097/01.GIM.0000035621.12984.FB

Ceredase®/Cerezyme® is from \$106,470 to \$425,800 for a 70-kg patient. The recommended ranges of therapeutic dosages are from 2.5 U/kg of body weight three times a week to 60 U/kg once every 2 weeks.

There are few reports on the effects of discontinuing therapy. One study from Israel reported a group of 15 patients who withdrew from therapy.<sup>20</sup> Most of these patients did not regress to pretreatment hematological, visceral, or bone values while off ERT for 8 months to 4 years. No genotypes were reported.<sup>20</sup> Here we evaluate discontinuing ERT in four patients with different genotypes and phenotypes for  $\beta$ -glucocerebrosidase deficiency. All patients had clinical improvement during initial treatment with ERT. They insisted on ceasing therapy and agreed to be monitored closely while off ERT.

## MATERIALS AND METHODS

The four patients studied had Type I Gaucher disease, which was diagnosed by  $\beta$ -glucocerebrosidase enzyme studies performed either through our laboratory or by other reference laboratories. All were treated at the Emory University Lysosomal Storage Disease Center and received  $\beta$ -glucocerebrosidase ERT as alglucerase (Ceredase®) and/or imiglucerase (Cerezyme®) (both manufactured and sold by Genzyme Therapeutics, Cambridge, MA), for at least 18 months. They then chose to discontinue therapy for 1 or more years. Each of these patients provided informed consent for their monitoring protocol, which was approved by Emory University's institutional review board. They were monitored on and off therapy with quarterly laboratory studies that included complete blood cell count with differential, platelet count, reticulocyte count, total acid phosphatase, alkaline phosphatase, aspartate aminotransferase, ACE, and urinary pyridinium crosslink studies. Also included were semiannual or annual imaging studies: MRI for assessment of liver and spleen volumes and femoral bone marrow, bone mineral density studies of the spine and hips, and plain films of the spine, hips, and knees. Liver and spleen volumes were expressed in cubic centimeters and were normalized to kilograms of body weight. Coronal T1-weighted MR sections of the femurs were obtained and analyzed for marrow signal. Two experienced musculoskeletal radiologists reviewed these films in a double-blind manner to determine change or lack of change in the T1-weighted marrow signal of the femoral shafts. Whitening of the marrow due to increased fatty marrow signal was considered improvement in decreasing glucocerebroside content, whereas darkening of the image was considered evidence for increased deposition of glucocerebrosides. The subcutaneous fat pad was used as an internal standard for "whiteness" of the femoral marrow. This approach to MRI interpretation was previously described.<sup>17</sup> Dual-energy radiographic absorptiometry (DEXA) studies of the spine and proximal femurs were used for evaluating bone mineral content. *Z* values were derived from DEXA studies.<sup>21</sup> Urinary pyridinium crosslinks were quantitated as previously described.<sup>14</sup>

### Patient 1

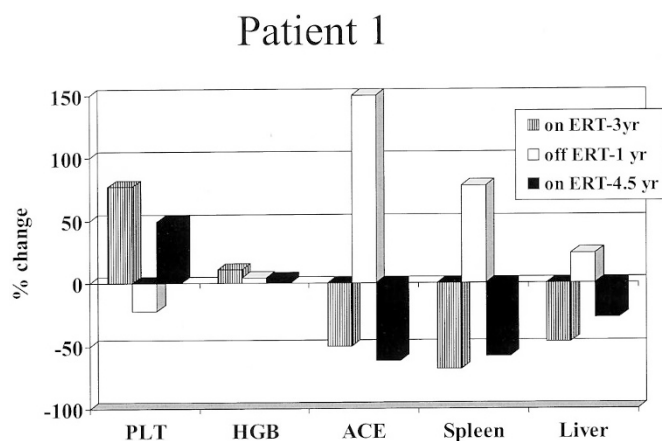
Patient 1 is a male whose Gaucher disease was diagnosed at age 5 years. In his peripheral leukocytes, 4-MU- $\beta$ -glucosidase activity was 1.3 nmol/mg protein/hour (control =  $7.9 \pm 0.1$ ) and  $\beta$ -glucocerebrosidase was 1.48 nmol/mg protein/2 hours (control =  $8.92 \pm 0.22$ ) at diagnosis. His genotype is N370S/L444P. He began treatment at age 6 years with a dose of 60 U/kg/2 weeks for his first year, 15 U/kg/2 weeks for his second year, and then 60 U/kg/2 weeks for his third year. At the mother's request, he then began a 1-year trial off therapy. At the end of that year, therapy was deemed necessary and was reinstated at 15 U/kg/2 weeks. He remains at this low dose 4½ years later at age 14½ years (Fig. 1, Table 1).

### Patient 2

Patient 2 is a male whose Gaucher disease was diagnosed at age 5 years. In his peripheral leukocytes, 4-MU- $\beta$ -glucosidase at diagnosis was 1.6 nmol/mg protein/hour (control = 12.2) and glucocerebrosidase was 0.86 nmol/mg protein/hour (control = 14.2). Like Patient 1, his genotype is N370S/L444P. He began treatment at age 13 years and received 15 U/kg/2 weeks of ERT for the first 2 years. At his request and with parental support, he was without therapy for 1.5 years until age 16½ years. Therapy was then reinstated at 15 U/kg/2 weeks, but after 6 months the patient stopped his infusions and was lost to follow-up (Fig. 2, Table 2).

### Patient 3

Patient 3 is a female whose Gaucher disease was diagnosed at age 19 years. Initial 4-MU- $\beta$ -glucosidase was 3.0 nmol/mg/hour (normal range = 5.81–6.60) and glucocerebrosidase was 0.00 (normal range = 0.37–0.48). The patient is the product of consanguineous parents (first cousins) with Cherokee Indian



**Fig. 1** Effect of ERT, discontinuation and reinstatement in Patient 1. Histograms represent percent change in platelets (PLT), hemoglobin (HGB), ACE, spleen volume, and liver volume after 3 years of ERT, followed by 1 year off therapy and 4.5 years of reinstated ERT. Dosages during the first 3 treatment years were 60 U/kg/2 weeks the first year, 15 U/kg/2 weeks the second year, and 60 U/kg/2 weeks the third year. The patient resumed therapy at 15 U/kg/2 weeks and remained at this dose for the ensuing 4.5-year period. Percent changes were calculated by subtracting values at the end of intervention from basal values divided by basal value times 100. (See Table 1.)

**Table 1**  
Absolute values of parameters of Gaucher disease off, on, off, and on enzyme replacement therapy in Patient 1

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 8.5
Age, yr	6	7	8	9	10	11	12	13	14	14.5
Dose, U/kg/2 wk	0	60	15	60	0	15	15	15	15	15
Platelets, thou/ $\mu$ L (150–450)	75	120	139	133	103	96	112	99	136	153
Hemoglobin, g/dL (13.5–18)	10.9	11.9	12.5	12.1	12.6	12.2	12.1	12.6	13	13.1
ACE, U/L (13–100)	ND	92	109	46	184	152	94	91	94	70
Spleen volume normalized to weight ( $\times$ nml)	19.5	11.1	10.5	6.18	11.02	9.81	8.3	6.6	7	6.4
Liver volume normalized to weight ( $\times$ nml)	1.8	1.61	1.33	1.06	1.32	1.22	1.26	1.08	0.97	0.95
MRI score <sup>a</sup>	NA	0	+	0	0	+	0	0	0	0
Total PYR <sup>b</sup>	ND	340.2	276.7	314.6	208.3	179.0	292.4	232.7	287.2	ND
DEXA <sup>c</sup>										
g/cm <sup>2</sup>	0.564	0.538	0.577	0.606	0.625	0.539	0.543	0.598	0.637	ND
Z score <sup>d</sup>	-0.36	-0.88	-0.64	-0.53	-0.56	-2.09	-2.50	-2.39	-2.49	ND

NA, not available; ND, not determined.

<sup>a</sup>For MRI scores, 0 indicates no change in appearance of marrow, + indicates improvement in appearance of marrow with whitening of T1-weighted image, - indicates darkening. In children, there is expected normal conversion from hematopoietic to fatty marrow during bone growth. These normal changes may be difficult to discern from the increases in normal marrow fat seen with response to ERT.

<sup>b</sup>PYR indicates total pyridinium crosslinks quantified in nmol/mol creatinine in urine. Normal values for males in age group 2–10 are  $262 \pm 70$ , for ages 9–11 are  $250 \pm 22$ , and for ages 11–15 are  $234 \pm 58$ .

<sup>c</sup>Spine bone mineral density.

<sup>d</sup>Z score is derived from DEXA and is the standard deviation from age- and sex-matched controls. There are limited bone density reference data for children, making it somewhat problematic to compare patients' results with "normal."

ancestry. We previously reported her genotype, which is K79N/K79N.<sup>22</sup> The patient had a splenectomy at age 22 years. She began ERT at age 49 years at 60 U/kg/2weeks for her first year and at 15 U/kg/2 weeks for her second year. After these 2 years of treatment, she elected to cease therapy for 2 years. ERT was then reinstated at 30 U/kg/2 weeks at age 53 years and her response was monitored over the following 2 years of treatment (Fig. 3, Table 3).

#### Patient 4

Patient 4 is a male whose Gaucher disease was diagnosed at age 35 years. His  $\beta$ -glucocerebrosidase activity was 1.9 nmol/mg protein/hour (control =  $8.9 \pm 0.22$ ) at diagnosis. His genotype is N370S/N370S. He began treatment at age 50.5 years at 60 U/kg/2weeks for 6 months and then received 1 year of therapy at 15 U/kg/2weeks. His personal concerns about the cost of the medication and future insurability led him to pursue a trial off therapy, which has now extended to 7 years (Fig. 4, Table 4).

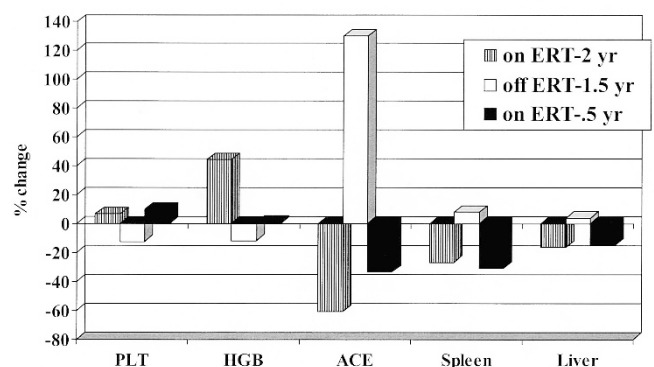
## RESULTS

#### Patient 1

Patient 1 required ERT at age 6 years based on thrombocytopenia, anemia, splenomegaly (20 times normal), hepatomegaly (1.8 times normal), and decreased bone mineral density (Fig. 1, Table 1). While on ERT for the first 3 years, his liver

and spleen volumes decreased, platelets and hemoglobin increased, and ACE decreased to normal. During 1 year off therapy, his platelet levels fell, spleen size increased almost two-fold, liver size increased, and ACE increased four-fold. Hemoglobin remained stable. When low-dose ERT was rein-

## Patient 2



**Fig. 2** Percent change in platelets (PLT), hemoglobin (HGB), ACE, spleen volume, and liver volume on ERT at 15 U/kg/2 weeks (2 years), off treatment (1.5 years), and back on treatment at 15 U/kg/2 weeks (0.5 years) in Patient 2. Percent changes were calculated by subtracting values at the end of intervention from basal values divided by basal value times 100. (See Table 2.)

**Table 2**

Absolute values of parameters of Gaucher disease off, on, off, and on enzyme replacement therapy in Patient 2

	Baseline	Year 1	Year 2	Year 3.5	Year 4
Age, yr	14.5	15.5	16.5	18	18.5
Dose, U/kg/2 wk	0	15	15	0	15
Platelets, thou/ $\mu$ L (150–450)	120	135	128	108	123
Hemoglobin, g/dL (14–18)	10.5	12.9	15.1	13.3	13.4
ACE, U/L (12–67)	147	101	57	99	87
Spleen volume normalized to weight ( $\times$ nml)	11.86	8.99	8.67	9.51	6.39
Liver volume normalized to weight ( $\times$ nml)	1.59	1.43	1.33	1.29	1.08
MRI score <sup>a</sup>	NA	+	+	0	0
Total PYR <sup>b</sup>	335.9	254.4	93.4	61.4	49.7
DEXA <sup>c</sup>					
g/cm <sup>2</sup>	0.807	0.899	0.984	1.045	1.055
Z score <sup>d</sup>	-1.11	-0.77	-0.35	0.02	0.16

NA, not available.

<sup>a</sup>For MRI scores, 0 indicates no change in appearance of marrow, + indicates improvement in appearance of marrow with whitening of T1-weighted image, - indicates darkening.

<sup>b</sup>PYR indicates total pyridinium crosslinks quantified in nmol/mol creatinine in urine. Normal values for males in the age group 11–15 are  $234 \pm 58$  and in age group 15–18 are  $82 \pm 20$ .

<sup>c</sup>Spine bone mineral density.

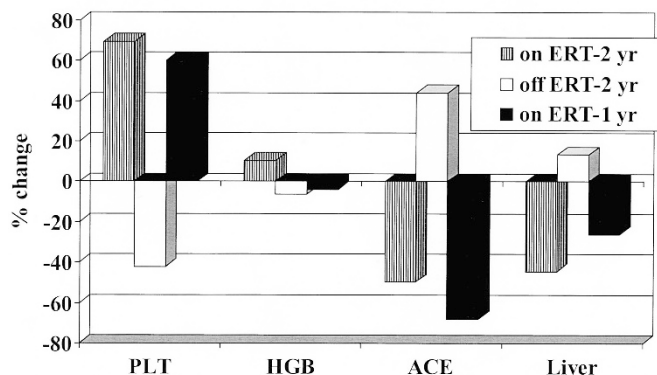
<sup>d</sup>Z score is derived from DEXA and is the standard deviation from age- and sex-matched controls.

stituted, his organ volumes returned to their precessation sizes within 3 years, platelet count within 4 years, and ACE decreased to normal within 2 years (Fig. 1). MRI T1-weighted images of the patient's femurs showed improvement after 2 years of therapy (Table 1). No change in the marrow signal was noted off therapy. With reinstated therapy there was further improvement in the marrow signal after 1 year, suggesting a decrease in glucocerebroside content. Urinary pyridinium crosslinks and bone density values remained stable throughout. Of some continuing concern was a fall in bone density Z scores that may reflect his delayed puberty or suboptimal mineral content.

### Patient 2

Patient 2 began therapy at age 13 years for anemia, mild thrombocytopenia, splenomegaly, mild hepatomegaly, and reduced bone mineral density. While on low-dose ERT (15 U/kg/2 weeks), his liver and spleen volumes decreased, hemoglobin rose to the normal range, platelets stabilized, and ACE fell to the normal range (Fig. 2, Table 2). During his time off therapy, there was little change in spleen and liver volumes. Platelets and hemoglobin levels decreased and ACE rose. When ERT was reinstated at 15 U/kg/2 weeks, his liver and

## Patient 3



**Fig. 3** Response to ERT, cessation of therapy, and reinstatement in Patient 3. Histogram shows percent change in platelets (PLT), hemoglobin (HGB), ACE, and liver volume after 2 years of ERT, after 2 years off treatment, and after 1 year of reinstated therapy. ERT dosages were 60 U/kg/2 weeks the first treatment year, 15 U/kg/2 weeks the second year, and 30 U/kg/2 weeks when therapy was restarted. The patient had a splenectomy at age 22 years and ERT began at age 49 years.

**Table 3**

Absolute values of parameters of Gaucher disease off, on, off, and on enzyme replacement therapy in Patient 3, postsplenectomy

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Age, yr	49	50	51	52	53	54
Dose, U/kg/2 wk	0	60	15	0	0	30
Platelets, thou/ $\mu$ L (150–450)	230	338	390	210	225	302
Hemoglobin, g/dL (12–16)	13.3	14.5	14.7	13.5	13.8	13.9
ACE, U/L (8–52)	357	120	179	230	258	138
Liver volume normalized to weight ( $\times$ nml)	2.15	1.4	1.19	1.26	1.35	1.17
MRI score <sup>a</sup>	NA	+	+	0	0	0
Total PYR <sup>b</sup>	53.3	81.3	50.1	78.9	55.9	49.1
DEXA <sup>c</sup>						
g/cm <sup>2</sup>	0.890	0.868	0.873	0.870	0.848	0.837
Z score <sup>d</sup>	-0.77	-0.96	-0.80	-0.71	-0.89	-0.92

NA, not available.

<sup>a</sup>For MRI scores, 0 indicates no change in appearance of marrow, + indicates improvement in appearance of marrow with whitening of T1-weighted image, - indicates darkening.

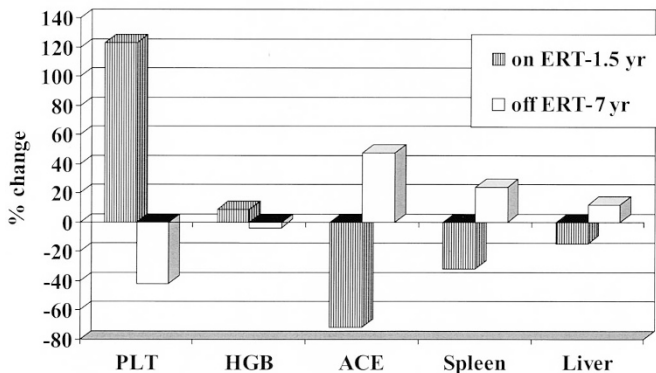
<sup>b</sup>PYR indicates total pyridinium crosslinks quantified in nmol/mol creatinine in urine. Normal values for postmenopausal females are  $41.9 \pm 13$ .

<sup>c</sup>Spine bone mineral density.

<sup>d</sup>Z score is derived from DEXA and is the standard deviation from age- and sex-matched controls.

spleen volumes decreased, platelets increased, and hemoglobin and ACE remained stable over the 6-month period. MRI T1-weighted images indicated an increase in marrow signal after 1 and 2 years of therapy (Table 2). No change in the marrow signal was noted for the year and half off therapy. His DEXA

## Patient 4



**Fig. 4** Relative response by Patient 4 to  $\beta$ -glucosidase ERT and to its cessation. Percent change in platelets (PLT), hemoglobin (HGB), ACE, spleen volume, and liver volume on ERT (1.5 years) and off therapy (7 years). The patient received 60 U/kg/2 weeks of enzyme the first 6 months and then 15 U/kg/2 weeks for the next year while on ERT. His  $\beta$ -glucocerebrosidase genotype is N370S/N370S.

spine bone density values increased throughout the course of initial therapy, cessation, and reinstatement of ERT. Urinary pyridinium crosslinks were elevated prior to ERT, indicating increased bone turnover with puberty. Pyridinium crosslinks excretion returned to normal and remained in the normal range with cessation and reinstatement of ERT.

## Patient 3

Patient 3 received her diagnosis at age 19 years and underwent splenectomy at age 22 years. She began therapy at age 49 years based on hepatomegaly (liver size 2.15 times normal), decreased bone mineral density, fatigue, and bone pain (Fig. 3, Table 3). Her liver volume decreased to normal size during treatment. Hemoglobin and platelets, which were in the normal range at baseline, increased. ACE fell by 50% but remained elevated. Off therapy, her liver size increased, hemoglobin and platelet counts decreased but continued normal, and ACE increased. When ERT was reinstated at 30 U/kg/2 weeks, her liver size decreased to precessation volume, platelets increased, hemoglobin was unchanged, and ACE decreased. MRI T1-weighted images suggested decreased glucocerebroside deposition while on therapy (Table 3). During the 2 years off therapy, no change in the MRI signal was noted. Bone density did not change by either DEXA values or Z scores on or off ERT. Urinary pyridinium crosslinks increased with initial ERT and in the first year off therapy, indicating increased bone collagen turnover during both initial phases of ERT and after discontinuing ERT.

## Patient 4

Patient 4 (genotype N370S/N370S) began ERT at age 50.5 due to splenomegaly, thrombocytopenia, and worsening fatigue (Fig. 4, Table 4). While on ERT, his spleen volume decreased, platelet count increased to the normal range, and ACE decreased to normal. His liver volume and hemoglobin re-

**Table 4**  
Absolute values of parameters of Gaucher disease off, on, and off enzyme replacement therapy in Patient 4

	Baseline	Year 0.5	Year 1.5	Year 2.5	Year 3.5	Year 4.5	Year 5.5	Year 6.5	Year 7.5	Year 8.5
Age, yr	50.5	51	52	53	54	55	56	57	58	59
Dose, U/kg/2 wk	0	60	15	0	0	0	0	0	0	0
Platelets, thou/ $\mu$ L (150–450)	92	196	205	171	135	129	113	141	114	128
Hemoglobin, g/dL (12.5–17)	14.7	15.4	16	15.3	15.7	15.5	15.1	15.3	15.4	14.8
ACE, U/L (8–52)	141	42	40	60	97	59	23	<5	<5	42
Spleen volume normalized to weight ( $\times$ nml)	5.3	4.03	3.58	3.67	4.43	4.75	4	4.8	4.5	4.8
Liver volume normalized to weight ( $\times$ nml)	0.93	0.9	0.79	0.87	0.99	0.83	0.83	1.05	0.9	0.9
MRI score <sup>d</sup>	NA	+	+	–	(+)	0	0	0	0	0
Total PYR <sup>b</sup>	21.5	28.4	23.9	34.5	22.2	ND	19.8	12	18.3	26.2
DEXA <sup>c</sup>										
g/cm <sup>2</sup>	0.796	0.775	0.769	0.768 <sup>d</sup>	0.803	0.821	0.827	0.820	0.839	0.981
Z score <sup>e</sup>	–0.21	–2.49	–2.52	–2.5	–2.15	–1.97	–1.88	–1.92	–1.72	–1.2

NA, not available; ND, not determined.

<sup>a</sup>For MRI scores, 0 indicates no change in appearance of marrow, + indicates improvement in appearance of marrow with whitening of T1-weighted image, – indicates darkening, (+) indicates whitening in the acetabular region, but not the femur.

<sup>b</sup>PYR indicates total pyridinium crosslinks quantified in nmol/mol creatinine in urine. Normal values for men are 31.6  $\pm$  9.2.

<sup>c</sup>Spine bone mineral density

<sup>d</sup>Fosamax<sup>®</sup> began at age 53 (10 mg/day)

<sup>e</sup>Z score is derived from DEXA and is the standard deviation from age- and sex-matched controls.

mained in the normal range. Despite improved quality of life after 1.5 years of ERT, the patient elected to stop treatment because of financial concerns and was monitored over the next 7 years. His spleen volume increased but remained below pretreatment volume. Platelet count fluctuated below the normal range but did not reach pretreatment levels. Hemoglobin and liver volume stayed in their normal ranges (Fig. 4). The patient began ACE inhibitors for treatment of hypertension 2 years after cessation of therapy, and ACE values then fluctuated. The patient did not report a significant change in quality of life during this 7-year interval off ERT. MRI T1-weighted images showed an increase in marrow signal during initial treatment. During the first year off ERT, the MRI signal suggested increased glucocerebroside deposition. However, no further changes in the marrow signal were seen over the next 6 years. The patient had low spine bone mineral density by DEXA at baseline, with decreasing values despite a year and a half of ERT. He started Fosamax® (bisphosphonate) therapy within a year of discontinuing ERT, and there was a progressive increase in his bone mineral density for the first time. Urinary pyridinium crosslinks decreased after initiation of Fosamax®, indicating reduced bone collagen turnover (Table 4).

## DISCUSSION

This study further supports the relationship between genotype and the age of onset and clinical severity of Type I Gaucher disease. It extends this observation to support the notion that the return of signs and symptoms after discontinuation of ERT is related to genotype. Disease onset was in childhood for both patients with the N370S/L444P genotype and was more aggressive with regard to hepatosplenomegaly, thrombocytopenia, anemia, and fatigue. The patient with the unique K79N/K79N genotype of Cherokee origin presented with these symptoms in early adulthood and has had a milder course despite splenectomy. By contrast and in keeping with observations by others, the patient homozygous for N370S presented with mild symptoms in midlife including bone symptoms. This relationship of genotype to phenotype was directly proportional to the rate of decline after cessation of ERT. Patients 1 and 2 lost gains achieved on ERT within the first year off therapy. Patient 3 (K79N/K79N) had an intermediate decline over 2 years. Patient 4 (N370S/N370S) remained stable with mild thrombocytopenia but otherwise acceptable clinical findings 7 years after cessation of treatment. Of interest was improvement in his bone density with Fosamax® when ERT had not altered its steady decline. ERT resumption improved visceral and hematological parameters in Patients 1, 2, and 3 over time and returned them to prior goals achieved with initial ERT. We did not observe permanent sequelae related to withdrawal of therapy in any of the patients.

Our data support the use of T1-weighted MRI signal of the femoral bone marrow to monitor glucocerebroside storage and clearance in Gaucher patients on and off ERT. We observed improvement in marrow signal within months of initiating treatment. Patient 4 had decreased whitening (increased

glucocerebroside content) off ERT. These changes in the marrow signal occurred sooner than changes in bone density by DEXA.

Although not as evident from studies of these patients off therapy, in previous patients in whom ERT was initiated we developed the following notion for the effect of ERT on glucocerebroside deposition in bone marrow. As ERT lowers glucocerebroside content of macrophages, remodeling of bone spicules occurs rather rapidly in days to weeks and can be documented by increased urinary excretion of pyridinium crosslinks that then returns to baseline. In weeks to months, glucocerebroside content is reduced to the degree that the T1-weighted MR images reflect “whitening” of the femoral marrow due to presumed increased fatty marrow content. However, bone density and mineral content as measured by DEXA may take months to years to change and reflect multiple genetic and environmental issues. Of note is the dramatic effect on DEXA bone density values afforded by Fosamax® in Patient 4 in the absence of response to and after cessation of ERT (Table 4). The use of Fosamax® as an adjunctive therapy in combination with ERT for osteopenia in Gaucher disease has been investigated.<sup>2,3</sup>

It should be noted that only 11% (4/35) of our patients with Type I Gaucher disease who are receiving ERT elected to cease therapy. Thus, despite the cost and inconvenience of this intravenous medication, almost 90% of our patients remain satisfied and gratified that a therapeutic intervention for this progressive and potentially fatal disease is available.

We conclude that ERT results in clinical improvement in patients with Type I Gaucher disease, regardless of genotype. Patients with more severe involvement, specifically non-N370S homozygotes, lose gains achieved on ERT more rapidly than N370S homozygotes. While none of our patients who stopped treatment had life-threatening or irreversible complications, our study highlights the importance of close monitoring for patients while off treatment. Finally, our data show that, when necessary, ERT may be reinstated with satisfactory outcomes.

## Acknowledgments

This work was supported in part by NIH grant M01-RR00039 to the General Clinical Research Center of Emory University and by research and educational grants from Genzyme, Inc., for the Emory Center for Lysosomal Storage Disease Research.

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