

## Outcome of enzyme replacement therapy in Turkish patients with Gaucher disease: does late intervention affect the response?

Zeynep Arıkan-Ayyıldız<sup>1</sup>, Aysel Yüce<sup>1</sup>, Serap Emre<sup>2</sup>, Gökhan Baysoy<sup>1</sup>, İnci Nur Saltık-Temizel<sup>1</sup>, Figen Gürakan<sup>1</sup>

<sup>1</sup>Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics and <sup>2</sup>Department of Medical Biology, Hacettepe University Faculty of Medicine, Ankara, Turkey

**SUMMARY:** Arıkan-Ayyıldız Z, Yüce A, Emre S, Baysoy G, Saltık-Temizel İN, Gürakan F. Outcome of enzyme replacement therapy in Turkish patients with Gaucher disease: does late intervention affect the response? Turk J Pediatr 2011; 53: 499-507.

We aimed to evaluate the outcome of enzyme replacement therapy (ERT) in Turkish Gaucher patients since it first became available in our country. Eleven patients with type I and one patient with type III Gaucher disease (GD) received therapy as 30-60 U/kg and 120 U/kg every two weeks, respectively, for at least six months, starting a mean period of 4.2 years after the diagnosis. Assessment of response included serial measurements of hematological and biochemical parameters and liver and spleen volumes. Symptoms and signs of bone disease, growth and severity scores were also evaluated. ERT in Turkish patients led to marked improvement in hematological parameters and organomegaly in the majority of them. Patients with growth failure demonstrated catch-up growth. Progression of bone disease was not observed except in two patients who experienced a delay of 15 and 8.6 years, respectively, between the diagnosis and the start of ERT.

*Key words:* late, enzyme replacement therapy, Gaucher, children, outcome.

Gaucher disease (GD), the most common of the lysosomal storage disorders, is caused by deficient activity of glucocerebrosidase, which leads to accumulation of glucosylceramide mainly in cells of the monocyte-macrophage system<sup>1</sup>. The accumulation of Gaucher cells (lipid-laden macrophages) leads to a multisystemic disease characterized by involvement of the liver, spleen, bone marrow, and bone. There are three clinical subtypes of GD: Type I GD is the most prevalent form and is differentiated from type II (acute neuronopathic) and type III (subacute neuronopathic) by the absence of neurological involvement.

Enzyme replacement therapy (ERT) has become the treatment of choice for amelioration of signs and symptoms of GD. It has been proven to be effective in type I GD but does not prevent the progression of severe neurological symptoms and death in type II GD<sup>2</sup>. In type I Gaucher patients, treatment results in reduction of

organomegaly, improvement in hematological parameters, and decrease in bone-related symptoms and complications over a period of several years<sup>3,4</sup>. ERT in type III GD also has good effects on visceral, hematological and bone disease, but effects on neurological signs and progression are unclear<sup>5</sup>. There are reports that ERT has positive effects on existing neurological symptoms, but deterioration under ERT has also been reported<sup>6,7</sup>. ERT has been available in Turkey since 2004, but it was not covered under all health insurance systems in the early years due to the high costs, and interruptions were experienced.

In this study, we report the clinical outcome under ERT in a group of young Turkish patients with GD whose ERT started relatively late.

### Material and Methods

The study group included 12 patients with GD who received ERT for 6 to 102 months. One

of the patients was able to receive ERT on his own accord before it was covered by health insurance in our country. All patients were observed at Hacettepe University, Department of Pediatric Gastroenterology, for 1 to 16 years (a mean 4.2 years before the start of therapy). Diagnosis was suspected from the clinical features and confirmed by demonstration of glucocerebrosidase deficiency. Enzymatic measurement was performed by measuring the fluorescence resulting from the incubation of leukocytes from peripheral blood with the artificial substrate 4-methylumbelliferyl- $\beta$ -glucoside<sup>8</sup>. Genetic analysis was performed in 12 patients from 2 related and 10 unrelated families. Informed consent was obtained from the patients and/or parents. DNAs were isolated from peripheral leukocytes by ammonium acetate salting-out procedure<sup>9</sup>. Vienna Lab Gaucher Strip A assay was used for mutation analysis by which two recombinant alleles (RecNci-I, RecTL) and eight mutations (N370S, L444P, R463C, 84GG, IVS2+1, V394L, D409H, R496H) could be identified. For those in whom none of these mutations was identified, DNA sequence analysis was performed. Cycle sequencing was performed with the ABI PRISM Big Dye Terminator Cycle Sequencing Kit, and sequences were analyzed on the ABI PRISM 3130 DNA Analyzer.

Imiglucerase was given every two weeks as 30-60 U/kg per dose for the type I Gaucher patients while 120 U/kg was given for type III GD. Patients were examined at baseline and every three months after the therapy started. Before initiation of enzyme therapy, spleen status, general and bone-related symptoms, physical growth (expressed as a function of the standard deviation (SD) from published height and weight standards for age-matched healthy children), and pubertal status of the patients were recorded. Physical examination and the following laboratory studies were performed in all patients: complete blood count, total acid phosphatase (ACP) and angiotensin converting enzyme (ACE). Chitotriosidase activity was analyzed in six of the patients. Radiographic evaluations included femur and lumbar vertebrae radiographs and computerized tomography (CT) determinations of liver and spleen volumes in seven of the patients before ERT and all of the patients after ERT. Therapeutic response was monitored by hematological profiles and

blood chemistries as indicated above every three and six months, respectively. Liver and spleen volume determinations were performed six months after the start of ERT and yearly thereafter.

Anemia, thrombocytopenia and leukopenia were defined as follows: In males, hemoglobin (Hb) values <14 g/dl, in females, Hb values <12 g/dl, and in children, Hb values <10.5 g/dl were accepted as anemia. Thrombocyte count <130X10<sup>3</sup>/mm<sup>3</sup> was defined as thrombocytopenia, and leukocyte count <4500/mm<sup>3</sup> was defined as leukopenia<sup>10</sup>.

The spleen and liver volumes were expressed as a multiple of the normal volume (NV) of the respective organ, considered as 0.2% and 2.5% of the patient's weight, respectively<sup>11</sup>. In detail, multiple of normal for the liver was calculated according to the formula of measured volume of liver on CT (cm<sup>3</sup>)/body weight (kg) x 25, whereas multiple of normal for spleen was calculated according to the formula of measured volume of spleen on CT (cm<sup>3</sup>)/body weight (kg) x 2.

Bone disease was evaluated by lumbar and femoral radiography and radiography of other skeletal regions where pain was reported. Osteopenia, aseptic necrosis and pathologic fractures were noted. Bone mineral density (BMD) was assessed by dual energy X-ray absorptiometry (DEXA) before the start of therapy in only two patients, but in the following years it was performed annually. At the last follow-up, BMD measurements for 11 patients were available. Severity score index (SSI) was calculated for each patient<sup>10</sup>.

Neutralizing antibodies to imiglucerase were evaluated in one of our patients in Genzyme® Boston Laboratories.

The study was approved by the Institutional Ethical Board, Hacettepe University Hospital.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows 15.0. Statistical differences between parameters at baseline and at follow-ups after ERT were assessed with paired sample T-test, and differences between the results of groups with and without splenectomy were assessed with Mann-Whitney U test. A p value <0.05 was considered significant.

**Table I.** Demographics and Baseline Characteristics of the Gaucher Patients Before Start of ERT

| Patient Sex Phenotype | Genotype    | Age at diagnosis | Age at start of ERT | Splenectomy | Hb (g/dl) | Plt (10 <sup>3</sup> /mm <sup>3</sup> ) | ACE (U/L) | ACP (U/L) | Characteristics before ERT     |              |               |                  |                  |     |
|-----------------------|-------------|------------------|---------------------|-------------|-----------|---|-----------|-----------|--------------------------------|--------------|---------------|------------------|------------------|-----|
|                       |             |                  |                     |             |           |   |           |           | Chitotriosidase (nmol/ml/time) | Liver volume | Spleen volume | Weight (z-score) | Height (z-score) | SSI |
| 1 /F <sup>a</sup>     | S366T/S366T | 8.4              | 13.5                | -           | 8.7       | 133                                     | 326       | 26.3      | 2419                           | 2.3          | 21            | -2.44            | -4.14            | 9   |
| 2 /F <sup>a</sup>     | N370S/?     | 10.0             | 12.6                | -           | 11.7      | 88                                      | 188       | 18.4      | -                              | 1.4          | 4.1           | -0.25            | -0.45            | 3   |
| 3 /F <sup>a</sup>     | N370S/?     | 8.6              | 16.9                | +           | 10.5      | 342                                     | 326       | 12.4      | -                              | -            | -             | -3.29            | -4.00            | 16  |
| 4 /F <sup>a</sup>     | N370S/?     | 4.1              | 4.5                 | -           | 12.6      | 156                                     | 97        | 12.5      | -                              | -            | -             | -0.16            | -0.48            | 7   |
| 5 /F <sup>a</sup>     | N370S/?     | 1.0              | 4.6                 | -           | 11.5      | 140                                     | 198       | 16        | -                              | 1.4          | 8.1           | 0.74             | 0.88             | 5   |
| 6 /M <sup>a</sup>     | N370S/D399N | 3.4              | 5.8                 | -           | 10.1      | 70                                      | -         | -         | -                              | -            | -             | 0.21             | -2.06            | 9   |
| 7 /M <sup>b</sup>     | D409H/D409H | 1.75             | 1.8                 | -           | 11.7      | 185                                     | 75        | 10.5      | 657                            | 1.0          | 3.9           | -                | -                | 22  |
| 8 /F <sup>a</sup>     | R463C/?     | 7.0              | 22                  | +           | 8.4       | 283                                     | 290       | -         | 4939                           | 3.7          | -             | -1.14            | -0.82            | 20  |
| 9 /F <sup>a</sup>     | L296V/L296V | 3.0              | 11.6                | +           | 11.4      | 411                                     | 321       | 18.2      | 16210                          | -            | -             | -1.62            | -2.24            | 14  |
| 10 /F <sup>c</sup>    | L444P/L444P | 2.0              | 3                   | +           | 12.1      | 670                                     | -         | -         | 22742                          | -            | -             | -2.02            | -4.72            | 10  |
| 11 /F <sup>a</sup>    | N370S/?     | 4.0              | 8.1                 | -           | 11.4      | 67                                      | 280       | 33.8      | 15242                          | 1.9          | 26.8          | -1.34            | -1.47            | 16  |
| 12 /F <sup>a</sup>    | L444P/?     | 1.58             | 2                   | -           | 6.6       | 27                                      | -         | -         | 14516                          | 3.2          | 61.5          | -2.33            | -2.58            | 8   |

ERT: Enzyme replacement therapy. MN: Multiples of normal. Hb: Hemoglobin. Plt: Platelet. ACE: Angiotensinogen converting enzyme. ACP: Acid phosphatase. SSI: Severity score index. <sup>a</sup>Type I Gaucher disease. <sup>b</sup>Type III Gaucher disease. <sup>c</sup>Type I or III Gaucher disease.

**Results**

This series included 10 females and 2 males. Two of the patients were siblings. Mean age at diagnosis was 4.5 ± 3.1 years (range: 1-10 years), but the mean age at the start of treatment was 8.8 ± 6.4 years (range: 1.8-22 years). The period between the diagnosis and the start of ERT was 4.2 ± 4.4 years (range: 0.16-15 years). The mean treatment period was 36.5 ± 26.8 months (range: 6-102 months). Four patients were splenectomized before initiation of the therapy.

Glucocerebrosidase enzyme activities of the patients were in the range of 0-2.7 nmol/mg pr/h (reference range: 5-13 nmol/mg pr/h). Mutation analysis revealed 5 patients with N370S/? genotypes and 1 patient each with L444P/L444P, L444P/?, S366T/S366T, N370S/D399N, D409H/D409H, R463C/?, and L296V/L296V genotypes. Clinically, 9 cases were classified as type I and two with type I or type III, since patients were too young to exclude the development of neurological symptoms. Consanguinity was present in only 16% of our study group. Patient demographics and baseline data before the start of ERT are shown in Table I.

Anemia was present in 5 patients (41.6%) before the therapy, and the mean Hb level was 10.5 ± 1.79 g/dl. During the first 6 months, Hb levels in 92% of the patients reached normal levels, and mean Hb level was 12.3 g/dl at the sixth month. The improvement was statistically significant (p=0.002).

Thrombocytopenia was present in 4 patients (33.3%) before the therapy. Of these patients, 1 reached normal thrombocyte levels after 6 months and 2 after 12 months. The last one was still thrombocytopenic after 2 years of irregular therapy and needed splenectomy. At the last follow-up under ERT, only 1 patient (8.3%) was still thrombocytopenic. The improvement in thrombocyte counts with therapy was not statistically significant (p=0.168). Improvements in Hb and thrombocyte levels were similar in patients with and without splenectomy. Hb and platelet response to ERT is shown in Figures 1 and 2.

Liver volumes were available in 7 and spleen volumes were available in 6 patients before ERT. Assessment at the last follow-up showed that liver volumes in 9 of 11 patients (81.8%)

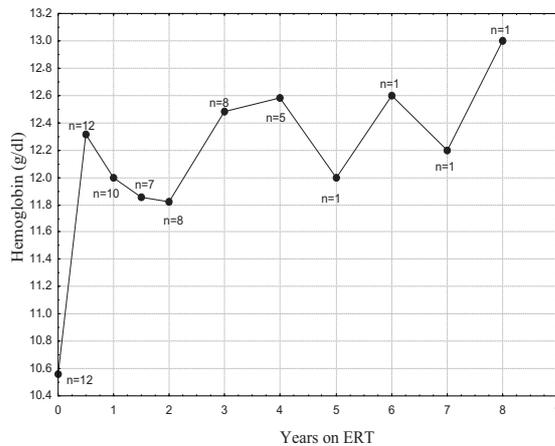


Fig. 1. Hemoglobin response to enzyme replacement therapy.

and spleen volumes in 4 of 6 patients (66.6%) decreased with ERT. One of the patient's organ volumes increased and hematologic parameters deteriorated under irregular ERT and she needed splenectomy after 2 years of treatment (Patient 12). She also developed a huge abdominal mass after splenectomy, which consisted of lymph nodes infiltrated by Gaucher cells (12). Neutralizing antibodies to the enzyme were suspected in this patient and found to be negative. The liver and spleen volume changes with ERT are summarized in Tables II and III. The mean decrease in liver volumes between patients with or without spleens could not be analyzed because of the small numbers of groups.

Angiotensin converting enzyme (ACE) levels were high in all patients before ERT (mean:  $233.4 \pm 98.2$ , range: 75-326 U/L, normal: 8-52 U/L). With ERT, ACE levels of all patients fell and 33.3% reached normal levels (mean:  $94.8 \pm 69.2$ , range: 24-224 U/L) at the last follow-up. ACP levels were also high in all patients before ERT (mean:  $18.5 \pm 7.9$  U/L, range: 10.5-33.8 U/L, normal: <6.5 U/L). A mean decrease of  $48.6 \pm 25.6\%$  was noted in patients, and 33.3% reached normal levels with ERT (mean:  $8 \pm 3.2$ , range: 3.2-13.8 U/L). Chitotriosidase activity (normal: 2-90 nmol/ml/h) was measured before and after therapy in 6 patients, and except for 1, all patients had a mean fall of 80.2%. Mean chitotriosidase activity level before ERT was  $12678 \pm 7600$  nmol/ml/h (range: 2419-22742 nmol/ml/h), and it decreased to a mean level

of  $3939 \pm 6338$  nmol/ml/h (range: 308-16762 nmol/ml/h).

Reported symptoms of bone disease before ERT were pain, bone crisis and fractures in some of our patients. Patients who had bone pain before the onset of therapy were free of pain during ERT after a mean period of  $2.6 \pm 2.1$  years. No bone crisis was encountered during ERT. Osteopenia and osteoporosis were encountered in 1, aseptic femur necrosis in 3 and pathologic fracture in 2 of the patients before ERT. Two patients developed new pathologic fractures under ERT (Patients 8 and 9), while bone disease stabilized in others. Signs of osteopenia and osteoporosis were noted to disappear on plain radiography after ERT. BMD was determined in only 2 of the patients before ERT, but assessments continued during ERT. Although improvement of BMD was noted in 7 patients at the last follow-up, 4 patients showed decrease in BMD under ERT. We could not make a comparison between the groups with and without splenectomy because of insufficient BMD data.

Severity scores decreased after ERT (mean SSI before ERT:  $10.6 \pm 5.2$ , range: 3-20; mean SSI after ERT:  $5.8 \pm 4.9$ , range: 1-16) in type I Gaucher patients. Quality of life was reported to be improved in all of the patients. Mean height z-score of children before ERT was  $-2 \pm 1.76$ , and it improved in all and reached a mean of  $0.93 \pm 0.96$ . Mean weight z-score before ERT was  $-1.24 \pm 1.25$ , and it also improved in all and reached a mean of  $-0.17 \pm 1.05$ . Patients at the age of puberty were able to complete the pubertal period under ERT although two

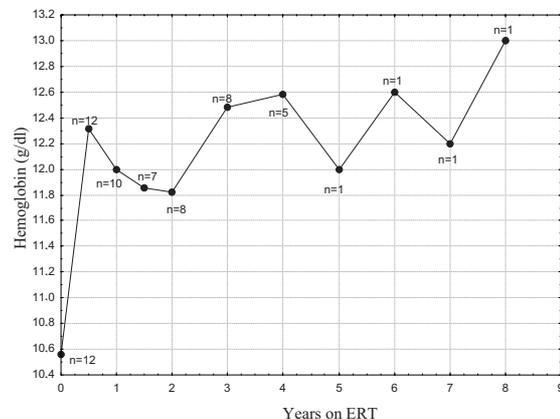


Fig. 2. Platelet response to enzyme replacement therapy.

**Table II.** Changes in Liver Volumes of the Patients Under ERT

|    | Liver volume (Multiples of Normal) |                 |               |                |                |                |                |
|----|------------------------------------|-----------------|---------------|----------------|----------------|----------------|----------------|
|    | Before ERT                         | 6 months of ERT | 1 year of ERT | 2 years of ERT | 3 years of ERT | 4 years of ERT | 8 years of ERT |
| 1  | 2.3                                | 1.8             | 1.7           | 1.1            | 1.1            | 1.1            |                |
| 2  | 1.4                                | 1.3             |               |                |                |                |                |
| 3  | -                                  | 3.6             | 2.8           | 2.2            | 1.4            |                |                |
| 4  | -                                  | 1.3             | -             | 1.3            | 0.9            | 0.9            |                |
| 5  | 1.4                                | 1.5             |               |                |                |                |                |
| 6  | -                                  | -               | -             | -              | -              | -              | 1.1            |
| 7  | 1.0                                | 1.2             | 1.1           |                |                |                |                |
| 8  | 3.7                                | 2.7             | 2.3           |                |                |                |                |
| 9  | -                                  | -               | 1.6           | 1.3            | 0.9            | 1              |                |
| 10 | -                                  | 2.1             | 2.1           | 1.8            | 1.7            |                |                |
| 11 | 1.9                                | -               | 1.4           | 1.3            |                |                |                |
| 12 | 3.2                                | 2.1             | -             | 2.4            | 1.4            | 1.2            |                |

of the female patients experienced delay before the start of ERT.

Expected improvements in organ volumes were not seen in the patient with type III GD, but neurological improvement in oculomotor apraxia was noted by the same physician performing the neuro-ophthalmological examination. Mental and motor development was assessed as normal by Denver developmental screening test. No clinical convulsions were encountered, and electroencephalography, evoked brain stem potentials and auditory assessments were also normal in this patient.

### Discussion

Enzyme replacement therapy (ERT) has been available in many countries since 1991. It is proven to be clinically effective for GD and currently is a standard care for type I and type III disease. ERT has been available since 2004 in our country. After 2004, patients with GD on follow-up and those who exited follow-ups were called and assessed for ERT. In the present study, we report the therapeutic outcome after ERT in mainly these subsets of patients and also those diagnosed afterwards.

The mean age at diagnosis was 4.5 years (1-10) in our study, and it was generally in agreement with the Gaucher registry<sup>13</sup>. Unfortunately, the mean time from diagnosis to the start of ERT was 4.2 years. This long period before ERT resulted in bone involvement in some of our patients, and some also needed splenectomy because of severe

splenomegaly and thrombocytopenia. In the era of enzyme therapy, it is now emphasized that splenectomy should be avoided in GD because of the undesired effects on the course of the disease<sup>14</sup>.

Regarding the genotype of unrelated patients, we identified seven different mutations in our study group with 30% unknown mutations. The N370S mutation was in heterozygous state in five of the patients (23%). The L444P mutation occurred in homozygous state in one of the patients and in compound heterozygous state in another (14%). The presence of L444P allele was related with younger presentation (2 and 1.58 years of age) as indicated in the literature<sup>13,15</sup>. In our previous study of 57 patients with GD, L444P was the most frequent mutation, with 42%, followed by N370S, with 30%<sup>16</sup>. In another study of 28 Gaucher patients from Turkey, N370S was the most frequent mutation, with 50%, while L444P ranked second, with 14%<sup>17</sup>. Our study group seems to reflect the mutations seen mostly in Turkey (N370S 23%, L444P 14%).

Hematological alterations in our patients at baseline were similar to the international Gaucher registry for anemia (41.4% versus 36%) and lower for thrombocytopenia (33.3% versus 60%), keeping in mind that 30% of the patients were splenectomized<sup>18</sup>. Marked improvement of anemia with ERT was reached after six months. This is in agreement with the literature, in which most of the patients reached normal Hb levels after 6-12 months of

**Table III.** Changes in Spleen Volumes of the Patients Under ERT

| Patients | Spleen volume (Multiples of Normal) |                 |               |                |                |                |                |
|----------|-------------------------------------|-----------------|---------------|----------------|----------------|----------------|----------------|
|          | Before ERT                          | 6 months of ERT | 1 year of ERT | 2 years of ERT | 3 years of ERT | 4 years of ERT | 8 years of ERT |
| 1        | 21.2                                | 16.2            | 10.9          | 8.1            | 7.2            | 6.7            |                |
| 2        | 4.1                                 | 6.9             |               |                |                |                |                |
| 3        | S                                   | S               | S             | S              | S              | S              |                |
| 4        | -                                   | 7.2             | -             | 4.1            | 1.7            | 3.3            |                |
| 5        | 8.1                                 | 6.6             |               |                |                |                |                |
| 6        | -                                   | -               | -             | -              | -              | -              | 9.3            |
| 7        | 3.9                                 | 5               | 4.9           |                |                |                |                |
| 8        | S*                                  | S               | S             | S              | S              | S              |                |
| 9        | S                                   | S               | S             | S              | S              | S              |                |
| 10       | S                                   | S               | S             | S              | S              | S              |                |
| 11       | 26.8                                | -               | 9.02          | 7.3            |                |                |                |
| 12       | 61.5                                | 43.5            | -             | 51.4           | S              | S              |                |

\*S: Splenectomy.

therapy<sup>4,19,20</sup>. Thrombocytopenia of our patients improved more slowly than anemia. Generally, thrombocyte levels are reported to improve more slowly and reach normal levels after 12-18 months<sup>4,19-21</sup>. Most of our patients reached therapeutic goals of ERT hematologically according to Pastores et al.<sup>22</sup>

The clinical outcome of organomegaly was mainly consistent with the therapeutic goals<sup>22</sup>. One patient was unresponsive to ERT after two years of therapy and required splenectomy. Irregularity of therapy for economic reasons and neutralizing antibodies could explain the unresponsiveness of such a patient to ERT<sup>23-29</sup>. Neutralizing antibodies were found negative in our case, and the lack of response to therapy was mainly due to the irregularity of ERT. This patient also developed an abdominal mass infiltrated by Gaucher cells after splenectomy while under ERT, suggesting a very severe clinical phenotype<sup>12</sup>. There are also similar reported cases of severely affected young Gaucher patients who developed mesenteric or mediastinal lymphadenopathies<sup>30-32</sup>. Most of the cases presented before as well as ours have a history of partial or total splenectomy. Thus, it can be hypothesized that in a splenectomized case, the storage cells may tend to infiltrate poorly enzyme-accessible regions such as lymph nodes.

Biochemical markers of GD such as ACP, ACE and chitotriosidase activity decreased with ERT in our study. Chitotriosidase is accepted as the best marker for reflecting the disease activity<sup>33</sup>.

Our ERT-unresponsive patient's chitotriosidase level was also consistent with this knowledge and did not decrease with ERT, while the levels in all others did.

Concerning the bone disease, clinical response can be regarded as favorable. Disappearance of bone pain occurred after two years of therapy, and no bone crisis was encountered thereafter. It is generally in line with the other reported data<sup>4,34</sup>. Magnetic resonance imaging is the recommended imaging modality of bone disease in children<sup>35,36</sup>. However, it could not be performed in our patients because of economic and logistic issues. The therapeutic response was poorer when evaluated by objective criteria. In two patients, new pathologic fractures occurred. There was a long delay between the disease onset and start of ERT in these patients (15 and 8.6 years, respectively), and they were also splenectomized before the onset of therapy. Additionally, BMD further decreased in four of the patients under ERT. Two of these patients were splenectomized before ERT, and the other was the patient who deteriorated under ERT and required splenectomy later. Splenectomy is known to be a factor contributing to the severity of bone disease<sup>37,38</sup>. We think that splenectomy and the long interval between the diagnosis and the start of ERT could explain the progressive outcome of bone disease in some of our patients. We could not perform DEXA in most of our patients before ERT and it could be done only during follow-ups. Thus, this criterion could not be used as a measure

of improvement of bone disease in our study. It is generally accepted that the improvement in bone disease requires a longer period than hematologic or organ-related complications of GD<sup>21</sup>. However, we think that the irreversible focal bone disease in some of our patients caused by late intervention is the major factor resulting in poor response.

Mean weight and height z-scores improved in all patients with ERT. It is known that growth failure is usual in pediatric GD, and linear growth accelerates after the start of ERT<sup>39,40</sup>. The prevalence of puberty delay is also higher in severe GD<sup>40</sup>. Two of the female patients experienced delay before ERT but all completed their puberty under ERT.

Severity score index (SSI) was modified in the 1990's and nowadays it is thought to be inappropriate for assessing the response to ERT, and a new scoring system was developed<sup>41</sup>. We could not use the new scoring as it was not convenient for our data. In two of the studies using Zimran's score, mean SSI decreased from 11 to 9 after 18 months of ERT and from 14.2 to 8.1 after 12 months of ERT<sup>42,43</sup>, respectively. In our study, SSI also decreased, from 10.6 to 5.8, similar to those reports.

Enzyme replacement therapy (ERT) in type III GD is also known to be effective in reversal of hematological complications and reduction of organomegaly, and it may also slow down the neurological impairment<sup>5,6</sup>. The expected reduction in organ volumes could not be seen in our patient with mild hepatosplenomegaly after a year of ERT, although the enzyme dosage was 120 IU/kg, but no neurological deterioration was established.

Neurologic involvement in type I GD is not an expected finding, but there are some reports that some patients homozygous for N370S mutation have signs of neurologic involvement<sup>44,45</sup>. Our patients homozygous for N370S mutation did not develop any symptoms or signs of neurologic involvement in the follow-up period.

Unresponsiveness of some patients to ERT in terms of hepatosplenomegaly and thrombocytopenia can be attributed to irregularity and the late start of therapy. Bone disease also progressed in some of our patients because of the late start of ERT and splenectomy performed before ERT.

This study reports the first evaluation of response to ERT in Turkish patients with GD. In conclusion, ERT with imiglucerase in young Turkish patients with severe GD was safe and it was effective in the reversal of hematological complications and organomegaly in most of the patients, despite being started late. ERT was also effective in achieving complete resolution of bone-related symptoms and ameliorated reversal of bone disease in some of our patients. We think that earlier treatment of symptomatic patients in our country from this point forward will result in much greater improvements in maintaining the health of children with GD.

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