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# Patients with Gaucher type 1: Switching from imiglucerase to miglustat therapy

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## 1. Introduction

Gaucher's disease is an inherited metabolic disorder resulting from lysosomal β glucocerebrosidase enzyme deficiency and characterized by glucocerebroside accumulation in organs such as the bone marrow, liver and spleen [1]. The most common clinical findings are anemia, thrombocytopenia, hepatosplenomegaly and skeletal system findings [2,3].

The diagnosis is made on the basis of low glucocerebrosidase enzyme activity in fibroblasts cultured from skin biopsy or in peripheral blood leukocytes and can be confirmed with glucocerebrosidase (GBA) gene analysis which is located on the long arm of chromosome 1 (1q21) [4,5].

The most common initial symptom is splenomegaly or thrombocytopenia, and symptomatic patients are generally first seen by a hematologist [6]. Progressive glucocerebroside accumulation results in osteopenia and osteoporosis. Bone 'remodeling' defects, demineralization and infarct areas can be seen radiologically due to involvement of the skeletal system. Painful bone crises occur in association with acute infarcts or chronic avascular necrosis [7].

Delays in treatment increase the risk of irreversible complications [8]. Enzyme replacement therapy (ERT) with imiglucerase (Cerezyme®) is the most effective treatment option in patients diagnosed with type 1 Gaucher's disease. The enzyme imiglucerase is produced from the ovarian cells of the Chinese hamster and was approved by the Food and Drug Administration (FDA) in 1994. It is administered intravenously at a 2-week interval [9,10]. New ERT options have been added in recent years, including velaglucerase alfa (VPRIV®, FDA approval 2010) produced from human fibroblast cells and taliglucerase (Elelyso®, FDA approval 2012) produced from rabbit cell cultures [10]. Imiglucerase (Cerezyme®) is used with Health Ministry approval in patients diagnosed with type 1 Gaucher's disease in Turkey. This is an effect form of treatment in terms of hematological, visceral and bone findings [11,12].

Oral substrate reduction therapy (SRT) with miglustat (Zavesca®) is used in adult patients diagnosed with mild or moderate Gaucher's disease in many countries [13,14]. Miglustat therapy is a therapeutic option due to its healing effect on bone findings in particular [15]. Miglustat is an immunosugar (*N*-butyl deoxynojirimycin, NB-DNJ) that selectively inhibits glycosphingolipid biosynthesis and is thus capable of reducing substrate levels to those capable of being catalyzed by residual glucocerebrosidase [16].

The aim of this study is to assess the results of switching to SRT in 6 cases with a diagnosis of type 1 Gaucher's disease who were receiving ERT (imiglucerase) in our institution.

## 2. Materials-methods

The demographic characteristics, clinical findings, disease-specific laboratory findings and genotypic characteristics of patients under monitoring with a diagnosis of type 1 Gaucher's disease switching to substrate reduction therapy from enzyme replacement therapy were analyzed retrospectively. Patients' clinical, laboratory and radiological findings associated with systemic involvement throughout the time

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**Table 1**
Demographical findings and initial symptoms of the patients with Gaucher type 1.

| Patient No | Gender | Age | Age at diagnosis | Initial symptoms | β-glucocerebrosidase (nmol/ml/h) (N:0.94–5.29) | Acid phosphatase (U/L) (N: 0–6.5) | Chitotriosidase (nmol/ml/h) (N: 0–38) | GBA gene mutations |
|---|---|---|---|---|---|---|---|---|
| 1 | Female | 42 | 26 | Abdominal distension, bone pain, fatigue hepatosplenomegaly | 0.3 | 46 | 124 | N370S/N370S |
| 2 | Female | 26 | 3 | Abdominal distension, bone pain, fatigue hepatosplenomegaly | 0.5 | 13.9 | 168 | N370S/T134I |
| 3 | Female | 28 | 16 | Abdominal distension, bone pain, fatigue hepatosplenomegaly | 0.5 | 18.3 | 196 | N370S/L444P |
| 4 | Female | 34 | 26 | Abdominal distension, bone pain, fatigue splenomegaly | 0.2 | 22.1 | 0.08 | N370S/N370S |
| 5 | Female | 20 | 6 | Abdominal distension, fatigue, pallidness hepatosplenomegaly | 0.2 | 9.4 | 0.5 | N370S/L444P |
| 6 | Female | 31 | 21 | Abdominal distension, fatigue, splenomegaly | 0.15 | 8.4 | 22.4 | N370S/N370S |

**Table 2**
Hematological findings and visceral organ volumes of the patients at presentation.

| Patient no | Hemoglobin g/dl | WBC/mm$^3$ | Platelet/mm$^3$ | Liver volume cm$^3$ | Spleen volume cm$^3$ |
|---|---|---|---|---|---|
| 1 | 10.7 | 4000 | 67,000 | 2717 | 1386 |
| 2 | 10.4 | 4800 | 233,000 | 2247 | splenectomy |
| 3 | 11.6 | 4700 | 78,000 | 2538 | splenectomy |
| 4 | 9.6 | 3600 | 86,000 | 1390 | 1200 |
| 5 | 11.7 | 5470 | 185,000 | 1310 | 450 |
| 6 | 9.8 | 5200 | 124,000 | 1288 | 433 |

they received ERT and SRT were also analyzed. Hemoglobin and platelet values in terms of hematological parameters and visceral organ volume measurements at abdominal MR or abdominal ultrasound examination were transferred. Direct radiography and whole body densitometry data were collected retrospectively to evaluate skeletal system involvement. Patients receiving ERT or SRT for less than 6 months were excluded from the study. Descriptive statistical data were used in demographic and clinical parameters (hemoglobin, platelet numbers, hepatic and splenic volumes).

## 3. Results

The median age of the six patients diagnosed with type 1 Gaucher's disease was 29.5 years (20–42). Median age at diagnosis was 18.5 years (3–26). All patients were female. Abdominal swelling and lethargy were the initial symptoms in all cases. Patients' demographic characteristics and presentation clinical findings are summarized in Table 1. Hepatosplenomegaly was present in three patients and two patients underwent splenectomy. Failure to thrive was not identified.

Low β glucocerebrosidase levels and mutation in the GBA gene were present in all patients. Diagnostic tests in terms of Gaucher's disease are summarized in Table 1. Bone marrow examination was performed in all cases and Gaucher cells were identified in all patients. Pancytopenia was present at presentation in three cases and bicytopenia in three. A 1.5 to 2.8-fold increase in patients' liver volumes and a 2 to 7-fold increase in spleen volumes were observed at presentation. Hematological findings and visceral organ volumes at presentation are shown in Table 2. Erlenmeyer deformity was present in four patients, femoral bilateral avascular sclerosis and multiple bone infarct areas were determined in one patient; bone radiography findings were normal in one patient. Osteopenia was determined in three patients with whole body densitometry at time of presentation.

The initial therapy was ERT in all patients. Median duration of ERT was 5.7 years (2 − 12). Median duration of SRT was 3.7 years (6 months-6 years). In two patients (patient No. 4 and 5) ERT was started by another institution and then continued and shifted to SRT in our institution. Detailed information concerning duration of ERT and SRT, reasons for switching from ERT to SRT and forms of treatment continuing during follow-up is shown in Table 3. In all cases switch to SRT was made when hematological and visceral findings were stable and due to patients' own request because of the ease of use. The initial ERT dosage was 55–60 U/kg intravenously at an interval of 2 weeks. The SRT dosage was 300 mg/day in all patients.

A decrease of 1.6 to 2 g/dl in hemoglobin values was determined in two patients after switching from ERT to SRT. A decrease in platelet levels also observed in two patients, the lowest value was 96,000 mm$^3$. Charts for hemoglobin and platelet values are summarized in Figs. 1 and 2.

In terms of visceral findings, a decrease in organ volumes was determined during ERT, while findings remained stable during SRT. Organ volumes measured with volumetric MR and ultrasound are shown in Table 4. Nodular lesions on the liver and spleen were determined in one patient (patient No. 1) who received three years SRT and received ERT for another three years.

No significant change was determined in the whole-body densitometry findings in any of the patients. Osteopenia persisted in three patients (L1–L4 Z scores were between −0.8 and −1.2). Multiple bone infarct areas, bilateral femoral avascular necrosis and bone fractures were observed both during ERT and SRT in patient No. 2 whom had a history of splenectomy at age 5. A clinical improvement occurred in painful bone crises during SRT, however fractures due to minor trauma were persisted. Treatment was continued with ERT at the patient's own request.

Chitotriosidase levels at presentation and during treatment were normal in two patients. We observed a decrease in chitotriosidase activity during ERT without an increase after switching to SRT (Fig. 3).

**Table 3**
Details of the treatment with ERT and SRT.

| Patient No | Treatment period | ERT time | SRT time | Reasons for switching from ERT to SRT |
|---|---|---|---|---|
| 1 | 6 years | 3 years | 3 years | After 3 years of SRT, liver and spleen nodules were recognized. Patient wanted to switch to ERT |
| 2 | 8 years | 3 years | 5 years | Severe bone pain and spontaneous fractures were seen both ERT and SRT. Patient wanted to switch to ERT |
| 3 | 9 years 4 months | 7 years 5 months | 6 months | Duration of SRT diarrhea, tremor and weight loss were detected. Patient wanted to switch to ERT |
| 4 | 8 years | 2 years | 6 years | Duration of SRT worsening of the hematological findings were revealed. Patient's therapy is continued as ERT |
| 5 | 13.5 years | 12 years | 1.5 years | Anemia was recognized, patients wanted to treat with SRT |
| 6 | 8.5 years | 4 years | 4.5 years | Current treatment is SRT. Patient is stable due to clinical and laboratory findings. |

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