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Management of Gaucher Disease in a Post-communist Transitional Health Care System: Croatian Experience

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Aim. To evaluate the feasibility of financing the treatment of Gaucher disease with recombinant human imiglucerase in the Croatian health care system.

Methods. Treatment with enzyme replacement therapy of 5 patients with Gaucher disease was started on January 2001. In 4 patients the typical signs of Gaucher disease (organomegaly, bone changes, anemia, and thrombocytopenia) were documented at the time of diagnosis. One patient received bone marrow stem cell transplant as treatment for acute myeloid leukemia from a HLA-matching sibling with Gaucher disease. All patients underwent therapy with imiglucerase (Cerezyme®) infusion every 14 days. The outcome and actual cost of the treatment were followed during 12 months.

Results. After 3 months of therapy, hemoglobin rose above low normal range in 2 patients. After 6 months, 3 patients had platelet count above $100x10^9$/L, and bone pain crises completely disappeared in patients with severe bone involvement. After 12 months, normal blood counts were restored in all patients. At the same time point, bone destruction remained unchanged in 3 patients and showed marked improvement in one. In agreement with the Ministry of Health, the Croatian Institute for Health Insurance restructured its funds and established a special "Fund for expensive drugs." This fund covers the treatment costs for patients with Gaucher disease (approximately €150,000 per patient per year) as well as the cost of treatment for patients with Fabry disease, AIDS, adenosine deaminase deficiency, multiple sclerosis, chronic myeloid leukemia, juvenile arthritis, and ovarian cancer.

Conclusion. Collaboration of the institutions in a post-communist transition health care system can provide an effective model for financing expensive treatment for patients with rare diseases in a resource-poor health system.

Keywords: *Croatia; Gaucher disease; health care costs*

Rare diseases are defined at the level of the European Union as those with a prevalence of less than 5 in 10,000 (1). Gaucher disease is the most common lysosomal storage disorder (2). Its incidence varies between 1:40-60,000 (3). The management of the disease is complicated due to its wide clinical variability (Table 1). The cause of this storage disorder is an autosomal recessive inherited glucocerebrosidase deficiency, which results in a more or less decreased breakdown of sphingolipids, depending upon the residual activity of the enzyme (3). The enzymatic defect causes the accumulation of lipid glucocerebrosidase, which leads to hepatosplenomegaly, lassitude, adynamia, bone involvement with hematological and laboratory/chemical changes, and in rare cases to the central nervous system (CNS) involvement (4-13). The diagnosis of Gaucher disease should be considered in all cases of unexplained splenomegaly or other disease manifestations in the liver or the skeleton. In infants, Gaucher disease should be considered in case of hepatosplenomegaly and neurodegenerative course (12). The definitive diagnosis of Gaucher disease requires the demonstration of glucocerebrosidase deficiency, which is apparent in all tissues and cells, including leukocytes, cultured skin fibroblasts, amniocytes, and chorionic villi (13).

Non-neuronopathic Gaucher disease (known as Type I) takes a chronic course, which is characterized by hepatomegaly, bone involvement, and hematological changes, but not by neurological symptoms (Table 1). The time of clinical manifestation varies from early childhood to adulthood. The acute neuronopathic form (known as Type II) is characterized by severe neurological complications, which generally lead to death within the first two years of life (Table 1). The chronic neuronopathic type is accompanied by milder neurological symptoms and is less progressive. In Europe the acute and neuronopathic forms

Table 1. Phenotypes of Gaucher disease*

	Type I	Type II	Type III
Patients affected	Adults and children	Infants	Children and adolescents
Age of onset	variable – late adolescents	uniform 4 to 5 months	variable – preschool
Organs affected	spleen, liver, bones	brain, spleen, liver	brain, spleen, liver, bones
Neurological symptoms	none	severe, multiple seizures, hypertonus	myoclonus, seizures, dementia, ocular motor apraxia
Rate of progression	highly variable	rapid progressive	intermediate variable
Life span	less than normal population	death before 2 years of age	20-30 years
Ethnic predilection	100 time more common in Ashkenazi Jews	none	none

*According to the NIH Technology Assessment Panel on Gaucher Disease (4).

(known as Type II and III) are much rarer (5-10%) than the non-neuronopathic variant (known as Type I) (5,6).

An effective therapy of Gaucher disease has now been available for more than 10 years. It consists of life-long, intravenous replacement of the deficient enzyme, glucocerebrosidase. If the therapy is started early enough and at an appropriately high dose, it usually leads to complete reversal of the intestinal, laboratory/chemical changes, and almost all symptoms and complications, resulting in a considerable improvement of the patient's general health condition (14). The current price of the treatment ranges from US$70,000 to US$550,000 per year for a typical adult with Gaucher disease, depending on the enzyme preparation technique and dosage (11). In European Union countries, the treatment cost is covered by insurance companies, whereas in some other countries treatment is restricted to children and patients with advanced disease (12). According to the estimated incidence of the disease of 1:40-60,000 population (3,10), there should be 20-25 patients with Gaucher disease in Croatia. Their treatment would be a significant burden to both the patients and the health care system, which is under constant financial strain (15,16). The aim of our report was to describe an effective mechanism within the health care system to provide funds for the therapy of patients with Gaucher disease.

Patients and Methods

Since June 2001, 5 patients (2 women and 3 men) underwent enzyme-replacement therapy with Cerezyme® at the Department of Internal Medicine, Zagreb University Hospital Center. Four of them were diagnosed with anemia, thrombocytopenia, splenomegaly, and bone changes. One patient received hematopoietic stem cells from a sibling donor suffering from Gaucher disease. Their median age was 31 years (range 24-51). Median beta-glucosidase activity in leukocytes was 2.2 nmol/h/mg protein ranging from 1.0-4.6 (normal range, 9-45 nmol/h/mg protein). All patients received Cerezyme® every 14 days in 2 hour infusion. Four of them received 30 units/kg, and the patient with severe bone destruction received 60 units/kg per day.

Results

Bone changes were diagnosed in 4 patients. Severe bone involvement was observed in 2 patients. One of them had bone pain crises very frequently because of extensive hip joints destruction, and was maintained on several anti-rheumatic drugs.

Three months after the onset of the enzyme therapy, hemoglobin concentration improved in 2 patients, rising above low normal range. After one year, all patients had platelet count above $100x10^9$/L (Table 2). In the patient with severe bone changes, low number of white blood cells was documented at the time of enzyme replacement therapy introduction. After 6 months, the number of white blood cells returned to the normal range. Organomegaly was documented in all patients at the time of diagnosis. After twelve months it remained unchanged, but patients reported that they felt lowering of abdominal pressure and pain. Bone destruction remained unchanged after one year in 3 patients and improved in 1 patient. Within the first 6 months of the treatment, bone pain crises completely disappeared in patients with severe bone involvement and the remission was sustained after a year of therapy.

Table 2. Monitoring Croatian patients with Gaucher disease

Variable	At time of diagnosis	After 6 months of therapy	After 12 months of therapy
Hemoglobin (≤100 g/L)	4/4	1/4	0/4
Platelet count ($\leq 100 \times 10^9$/L)	4/4	3/4	0/4
WBC count ($\leq 2 \times 10^9$/L)*	1/4	0/4	0/4
Splenomegaly	4/4	4/4	4/4
Hepatomegaly	4/4	4/4	4/4
Bone changes	4/4	4/4	3/4
Bone pain crisis	1/4	0/4	0/4

*WBC – white blood cell.

The fifth patient was a woman with acute myeloid leukemia who underwent hematopoietic stem cell transplantation after obtaining stable complete remission. She had a HLA-identical brother who suffered from unrecognized Gaucher disease. The diagnosis of Gaucher disease was established during the routine donor examination. Enzyme replacement therapy for the donor was started. We decided to proceed with hematopoietic stem cell transplantation and start immediately with enzyme replacement therapy of the recipient in a dose of 30 units/kg. Up to the time of writing this report, we could not find any signs of Gaucher disease in the hematopoietic stem cell recipient. We did not observe any adverse events during Cerezyme® infusions in any of the five patients.

The average cost of the treatment of one patient with Gaucher disease in Croatia was about €150,000 per year. The treatment costs for the estimated 20-25 patients with Gaucher disease would take only 0.6% of the whole Croatian drug budget (17). In agreement with the Ministry of Health, the Croatian Institute for Health Insurance restructured its budget and established a special fund for the treatment of rare diseases with expensive drugs. This fund covers the treatment costs for patients with inherited metabolic disorders,

AIDS, adenosine deaminase deficiency, multiple sclerosis, chronic myeloid leukemia, juvenile arthritis, and ovarian cancer. The main goal of the fund is to offer equal treatment to all Croatian citizens suffering from such diseases.

Discussion

Our experience with enzyme-replacement therapy for Gaucher disease showed similar results to the large published series (17-23). After six months of the therapy, the normalization of hemoglobin level and platelet count was observed in all patients. There was no worsening of bone changes and all patients experienced subjective reduction of organomegaly, although no normalization of spleen or liver volume was objectively established. This is also in concordance with the large published series (17-23).

The management of Gaucher disease is complicated due to its wide clinical variability. The disease is extremely serious, disabling, and in some cases lethal, ie, without efficient treatment. Enzyme-replacement therapy with imiglucerase prevents progressive manifestations of the disease (14) and offers very good relief of symptoms, but it is lifelong and very expensive, which leaves the patients and physicians in developing and restructuring countries at great disadvantage in the management of the disease (24).

Because of high treatment cost, equal accessibility of enzyme-replacement therapy for all patients with Gaucher disease is endangered. We showed that, even in a financially burdened health care system, it is possible to finance such expensive treatments through establishing a separate fund. In this way, individuals with rare diseases are not left without medical benefits of state-of-the-art treatment just because the illness they suffer from is rare. According to the agreement between the Ministry of Health and the Croatian Institute for Health Insurance, each tertiary-level hospital in Croatia will be able to negotiate the cost of treatment for newly diagnosed patients with Gaucher disease. Hospital physicians have been informed of the existence of the fund. If they have patients with diseases requiring treatments that are on the list covered by the Fund, they need to submit a request to the hospital's Board for Pharmacotherapy at the beginning of the year. The Board forwards the requests to the Institute for Health Insurance, and can also suggest new drugs and new diagnoses. Any new requests outside this scheme have to be negotiated separately with the Institute or postponed until the beginning of the next year.

Up to date, the Fund has covered a variety of costly therapies: etanercept in the treatment of juvenile arthritis; enzyme replacement therapy in Fabry's disease, adenosine deaminase deficiency, and mucopolysaccharidosis type I; hormone replacement therapy in growth retardation; five-drug combination regimen in patients with AIDS who failed to respond to the conventional triple-drug treatment; imatinib mesylate in treatment of chronic myeloid leukemia; hemophilia; beta-interferon in multiple sclerosis; treatment with monoclonal antibodies – trastuzumab for breast cancer and rituximab for B-cell non-Hodgkin's lymphoma; and some chemotherapy drugs – irinotecan for colon cancer, gemcitabine for pancreatic cancer, and paclitaxel for ovarian cancer. We expect this list to expand at the beginning of the next year, after clinical reports and proposals to the Croatian Institute for Health Insurance.

In conclusion, we showed that collaboration among the institutions in the health care system can provide a model for financing an expensive treatment for all patients with Gaucher disease in a resource-poor health care system. Croatian Institute for Health Insurance and the Ministry of Health will in this way collect information on the true incidence of this disease in Croatia, allocate resources for its treatment, and plan more cost-effective treatment modalities for future patients.

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