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Evaluation of enzyme replacement therapy effectiveness in children with Gaucher's disease according to the international studies

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*The article presents data on the history of creation of pathogenetic enzyme replacement therapy and its introduction into clinical practice of managing patients with Gaucher's disease. 2 primary stages are distinguished: beginning of use of enzyme β -D-glycosidase analog obtained from placenta and *alglucerase*; introduction of recombinant glucocerebrosidase (*imiglucerase*). The article demonstrates that enzyme replacement therapy is the only efficient method of treating Gaucher's disease; according to the international studies; it terminates the primary clinical manifestations of the disease, thus improving quality of life of the patients without any marked side effects. *Imiglucerase* is used at present; it causes hydrolysis of glycolipid glucocerebroside down to glucose and ceramide by the common way of metabolism of membrane lipids. *Imiglucerase* is indicated for long-term enzyme replacement therapy in patients with confirmed Gaucher's disease (types 1 and 3).*

Keywords: Gaucher's disease, enzyme replacement therapy, *imiglucerase*, children.

INTRODUCTION

Gaucher's disease (GD) is the most widespread autosomal-recessive hereditary lysosomal storage disease resulting from depressed function of enzyme β -D-glucosidase caused by mutations in the glucocerebrosidase *GBA1* gene located in chromosome 1q21. Deficient activity of the enzyme results in accumulation of substrate – complex glucocerebroside glycolipid – in tissue macrophages of many organs, including liver, spleen and bone marrow [1].

Clinical onset of GD includes hepatosplenomegaly, hematological alterations (thrombocytopenia, anemia, leukopenia), skeletal disorders (chronic ostealgia, bone crises, decreased mineral density of bone tissue, long bone infarctions, osteonecrosis, osteolysis and pathological fractures) and growth disorder and is characterized by considerable degeneration of life quality of the child and his/her family [2]. Traditional GD classification acknowledges 3 clinically distinct forms: type 1 – non-neuronopathic, type 2 – acute neuronopathic, type 3 – chronic neuronopathic. Type 1 Gaucher's disease is distinguished from types 2 and 3 with absence of neurological signs and symptoms, although it may feature overlapping neurological pathology [2].

Until recently, detection of Gaucher's cells in punctates of bone marrow, liver and spleen was the only method of confirming GD. At the First European Working Group on GD (Italy) in 1994 it was established that deficient activity of enzyme β -D-glucosidase (less than 30% of the norm) is a biochemical criterion of accurate GD diagnosis. The β -D-glucosidase level may be measured in leukocytes (*in vitro*) or fibroblast culture (*in vivo*). Biochemical determination of

β -D-glucosidase activity involves use of a substrate – radioactively marked glucocerebroside or artificial substrate 4-methylumbelliferyl- β -glucopyranoside.

Type 1 Gaucher's disease was the first lysosomal disease to be successfully treated with enzyme replacement therapy (ERT): initially (from 1991), placenta-derived glucocerebrosidase (alglucerase) was used; recombinant glucocerebrosidase (imiglucerase) has been in use since 1994. Imiglucerase is as effective at visceral (organ) and hematological onset of GD as at several aspects of bone pathology in a wide range of therapeutic doses. Response to treatment is determined by disease type and involvement of cells, organs and systems. In general, the best response is observed at evaluation of hematological and organ parameters. Some aspects of bone conditions, such as osteonecrosis and osteolysis are irreversible. However, early start of treatment decreases the risk of irreversible complications [3].

Historical background

At the initial stages, GD treatment involved only symptomatic or palliative therapy consisting in splenectomy. However, that intervention was characterized by high risk of an overlapping secondary infection, increase in the rate of bone pathology, excessive substrate deposition in the liver resulting in the development of fibrosis and cirrhosis and in the lungs resulting in the development of pulmonary hypertension and aggravation of neurological manifestations at type 3.

De Duve was the first (1964) to suggest the possibility of correcting lysosomal storage diseases by administering a specific enzyme. However, this method was introduced into clinical practice only 20 years later. Experiments in the culture of cells with low activity of lysosomal enzymes revealed that the enzyme brought into the cultural environment is capable of penetrating the cell and successfully break up the accumulated intracellular substrate. It has also been demonstrated that there is no need in administering high doses of an enzyme, as maintenance of as little as 1-5% of its normal activity is sufficient to correct the metabolic defect. The pilot clinical studies performed in the beginning of the 1970s demonstrated that the viscera respond well to the therapy, although neurological deficiency cannot be compensated at lysosomal storage disease, as the enzyme does not penetrate hematoencephalic barrier [1, 4].

Placenta-derived β -D-glucosidase was first used for therapy in 1974 by R.O. Brady [5], who observed gradual condition improvement in 2 patients. Subsequent studies revealed that intravenous infusions of the native placenta-derived β -D-glucosidase reduce glucocerebroside concentration in the liver and blood; however, clinical effectiveness of this type of therapy is limited [6]. Specific impact of β -D-glucosidase on the target cells (macrophages) was made possible by modifying the enzyme by means of adding mannose-carbohydrate residues to it; the derived enzyme was named alglucerase.

Alglucerase (Ceredase) – human placenta-derived macrophage-targeting glucocerebrosidase – was for the first time used by N.W. Barton et al. [6] to treat 12 patients with GD in 1991. The scientists discovered that size of the liver would diminish by 15-20% within the first 6 months of treatment and by more than 25% after 12 months of treatment if the Ceredase dose is 60 U/kg administered parenterally once per 2 weeks. It was later discovered that replacement therapy effect may be achieved with lower enzyme doses – 15-40 U/kg administered once per 2 weeks [7].

Thus, pathogenetic therapy of type 1 GD (GD1) based on lifelong replacement administration of an enzyme analogous to human enzyme β -D-glucosidase, which helps to attenuate pathological alterations of affected organs and recover function thereof, has been used around the world since 1991.

Success of this treatment method stimulated scientists to develop ERT for other forms of lysosomal storage diseases. This process was promoted by advancement of genetic engineering methods: creation of the systems capable of producing large amounts of human enzyme and the line of mice for preclinical ERT tests. Chinese hamster ovary cells were chosen as the first

systems for production of human enzymes. These cells are easily cultivated and realize a protein modification system, which is very to a human one. It is also important that lysosomal enzyme DNA overexpression results in secretion of human protein into the cultural environment; this helps to obtain large amounts of the enzyme [8].

Appraisal of hematological and organ response and bone exacerbations is the standard minimal criterion of therapy effectiveness appraisal at GD1 in everyday practice.

Imiglucerase – human recombinant glucocerebrosidase (Cerezyme, Genzyme, USA) – was approved for use in 1994 on the basis of two clinical studies. One of the first studies aimed at comparing effectiveness of imiglucerase and alglucerase was performed by G.A. Grabowski et al. in 1995. It involved 15 patients with type 1 GD; the study demonstrated equal effectiveness of the drugs [9]. Imiglucerase causes hydrolysis of glycolipid glucocerebroside down to glucose and ceramide by the common way of metabolism of membrane lipids. The first study assessed safety and effectiveness of alglucerase and imiglucerase in the dose of 60 U/kg per 2 weeks; the second study compared effect of frequency of administration of 15 U/kg (once per 2 weeks and TIW); no significant differences between the groups were observed [1].

Imiglucerase is the standard of treatment and has been clinically used for 19 years in more than 5,500 patients. Indications: long-term enzyme replacement therapy in the patients with confirmed type 1 (without neuronopathic manifestations) or type 3 Gaucher's disease (with chronic neuronopathic manifestations), who feature clinically significant non-neurological manifestations of the disease. Non-neurological manifestations include 1 or more of the following symptoms: anemia (after other causes, such as iron deficiency, have been ruled out), thrombocytopenia, bone diseases (after other causes, such as vitamin D deficiency, have been ruled out), hepatomegaly or splenomegaly. Methods of efficient therapy of type 2 GD have not been described, as the drug does not penetrate hematoencephalic barrier. Cerezyme is manufactured in dosage forms of 200 or 400 U. The drug's dose ought to be selected on an individual basis due to GD heterogeneity: it may be increased or decreased depending on the progress in attaining therapeutic goals evaluated on the basis of clinical manifestations. The initial dose is 30-60 U/kg for type 1 and 120 U/kg for type 3 GD. The drug is slowly intravenously administered by drop infusion once per 14 days [10].

There are international recommendations on Gaucher's disease treatment: use of the doses below 2.5 U/kg TIW or singular administration of 15 U/kg of body weight every 2 weeks resulted in improvement of hematological parameters and decrease in organomegaly; however, it did not affect parameters of the bone system. Use of initial doses of 60 U/kg of body weight once per 2 weeks resulted in improvement of hematological and visceral parameters and subsequently led to interrupted progress or decrease in the pronounced bone disorders. Reactions to the drug's administration are associated with generation of antibodies against the administered protein, although they are not constant and may be arrested with the standard means [11, 12].

Data of clinical studies

The first large-scale results on ERT efficacy evaluation in 1,028 patients in the setting of a 2-5-year-long enzyme therapy were obtained in 2002 (data of the international GD register). In patients with anemia, hemoglobin level rose up to normal or close to normal values within 6-12 months. In patients with thrombocytopenia and preserved spleen, the response was attained in the first two years and gradual improvement in the subsequent year; in splenectomized patients, the platelet count normalized in the first 6-12 months. Liver volume decreased by 30-40% (1-1.5 times), spleen volume – by 50-60% (2-8 times). Manifestations of the disease terminated after 2 years of therapy in 52 and 94% patients with ostealgia and bone crises, respectively [13].

The most recent data on the results of a 10-year-long ERT in patients with type 1 GD were published in 2012. 2 groups of non-splenectomized and splenectomized patients were analyzed. The initial therapy dose was 15-90 U/kg; after 10 years – 15-45 U/kg per 2 weeks (in most

patients). Considerable continuous improvement in the condition of patients with GD ($p < 0.05$) was observed; it was evaluated on the basis of such parameters as hemoglobin level, platelet count, liver and spleen (in non-splenectomized patients) volume, ostealgia and bone crises [3].

Therapeutic objectives of ERT in pediatrics have specific peculiarities, as a child features a growing, developing body. The most complete alglucerase/imiglucerase ERT effectiveness analysis in pediatric practice was performed in 2008 in 884 children with type 1 GD. In 49% of the cases, GD1 was diagnosed before the age of 10 years, in 17% of the cases – at the age of 11-20 years. The study included evaluation of hemoglobin level, platelet count, size of spleen and liver, mineral bone tissue density (Z-score), bone manifestations (ostealgia and bone crises) and growth parameters. Improvement of clinical parameters of an overwhelming majority of the patients was observed after 8 years of therapy: hemoglobin level normalized in 100% of the patients, platelet count, liver and spleen volume – in 95% of the patients; mineral bone density normalized after 6.6 years (initial Z-score median – -1.4, end median - -0.34); no bone manifestations (ostealgia, bone crises) were observed as soon as after 2 years [14].

Several studies evaluated ERT effect on separate clinical parameters. Analysis of growth parameters revealed that ca. 25% of children with GD were shorter than expected. Eight out of nine patients, who were at or below the 5th percentile in the beginning of the study, featured normal growth rate after 4-36 months of ERT. Thus, children managed to attain the population-average growth parameters in the setting of ERT. Retrospective study of 212 patients with Gaucher's disease dedicated to evaluation of life quality by means of SF-36 Health Survey Questionnaire demonstrated lower physical activity and total well-being in persons with Gaucher's disease than in the general population; it also demonstrated improvement of these parameters in the setting of ERT. One of the clinical studies, which involved 9 children with type 1 GD and 2 children with type 3 GD and follow-up observation for 6 years, demonstrated hemoglobin level normalization after 2 years of imiglucerase ERT, platelet count normalization after one year in 7 patients, hemorrhagic syndrome termination after 6 months and 10-20-fold chitotriosidase level decrease [15]. Another study of ERT effect on bone tissue condition in children and adolescents demonstrated Z-score improvement in comparison with the initial data in 19 patients: from -1.38 to -0.73 (8-9 years of treatment); similar tendency was observed in 23 adolescents: from -2.16 to -1.13 (10 years of treatment) [16].

CONCLUSION

Clinical studies demonstrated that enzyme replacement therapy is effective, safe, highly tolerable and has low rate of side effects. Early Gaucher's disease diagnosis and timely imiglucerase (Cerezyme) therapy launch are important for attaining therapeutic objectives.

Introduction of enzyme replacement therapy into clinical practice allowed considerably reducing the number of unsubstantiated palliative interventions; in appropriate dosage, it helps to normalize hemoglobin and platelet parameters; decrease liver and spleen size; reduce ostealgia, frequency of bone marrow crises, bone marrow infiltration with Gaucher's cells; normalize bone mass, growth parameters; considerably improve life quality of patients and their families.

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