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Enzyme replacement therapy in patients with Type 1 Gaucher's disease – A single center experience

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Gaucher's disease (GD) is a liposomal storage disorder inherited in an autosomal-recessive pattern. The underlying cause of the disease is mutation within the gene that encodes enzyme glucocerebrosidase. Accumulation of glucocerebrsidase in macrophages in the liver, spleen, bone marrow, rarely in the lungs and other organs, occurs due to deficiency of enzyme synthesis, lack or disorder of enzyme function, or deficiency of saposin C (enzyme activator). Clinical classification of GD is based on the absence (type 1) or presence (types 2 and 3) of central nervous system manifestations. Levels of β – glucocerebrosidase in leukocytes, as well as the levels of serum chitotriosidase are measured in order to make the definitive diagnosis of Gaucher's disease. Accumulation of glucocerebrsidase causes numerous multi-organ complications (anemia, thrombocytopenia, hepatomegaly, splenomegaly, skeletal and neurological changes). Since 1991 enzyme replacement therapy (ERT) has been used for treating Gaucher's disease. Show the treatment results in patients with Type 1 Gaucher's disease by administering ERT taliglucerase alfa at the Clinic of Hematology, Allergology and Clinical Immunology, University Clinical Center Niš. In the period from January 2016 to January 2025 taliglucerase alfa was used in treating 5 patients with Type 1 Gaucher's disease who did not respond to previous treatment or because the drug donation was discontinued. All our patients responded to treatment well and there were no adverse effects (administration of taliglucerase alfa results in significant regression of anemia, thrombocytopenia and organomegaly, along with bone status improvement).

Key words: Gaucher's disease, enzyme replacement therapy, taliglucerase alfa

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Primena enzimske supstitucione terapije kod pacijenata sa Gošeovom bolešću tip 1- iskustva jednog centra

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Gošeova bolest (GB) je lipozomalna bolest nakupljanja koja se nasledjuje autozomno-recesivno, u čijoj osnovi je mutacija gena koji kodira enzim glukocerebrozidazu. Do nagomilavanja glukocerebrozida u makrofazima jetre, slezine, koštane srži, redje u plućima i drugim organima dolazi usled smanjene sinteze enzima, nedostatka ili poremećaja funkcije enzima ili deficita sapozina C (aktivatora enzima). Klinička podela GB zasniva se na odsustvu (tip 1) ili prisustvu (tip 2 i 3) manifestacija od strane centralnog nervnog sistema. Nivo β -glukozocerebrozidaze u leukocitima, kao i vrednost hitotriozidaze u serumu odredjuje se u cilju postavljanja definitivne dijagnoze Gošeove bolesti. Nagomilavanje glukocerebrozida izazviva brojne multiorganske komplikacije (anemiju, trombocitopeniju, hepatomegaliju, splenomegaliju, skeletne i neurološke promene). Od 1991. godine lečenje Gošeove bolesti vrši se enzimskom supstitucionom terapijom (EST). Prikazati rezultate lečenja pacijenata sa Gošeovom bolešću tip 1 primenom EST taligluceraze alfa u Klinici za hematologiju, alergologiju i kliničku imunologiju UKC Niš. U periodu od januara 2016. godine do januara 2025. godine primenom taligluceraze alfa lečeno je 5 pacijenta sa Gošeovom bolešću tip 1

kod kojih je na prethodne terapijske linije izostao odgovor ili usled prekida donacije leka. Svi naši pacijenti su na terapiju odgovorili dobrim terapijskim odgovorom i nije bilo neželjenih efekata (primena taligluceraze alfa dovodi do značajnog smanjenja anemije, trombocitopenije i organomegalije uz poboljšanje koštanog statusa).

Ključne reci: Gošeova bolest, enzimska supstituciona terapija, taligluceraza alfa

INTRODUCTION

Gaucher's disease – Morbus Gaucher (GD) is a liposomal storage disorder inherited in an autosomal-recessive pattern, with the underlying cause being mutations within the gene which encodes enzyme glucocerebrosidase (1,2,3,4,5).

Accumulation of glucocerebrsidase in macrophages in the liver, spleen, bone marrow, rarely in the lungs and other organs, occurs due to deficiency of enzyme synthesis, lack of or enzyme function disorder, or deficiency of saposin C (enzyme activator). Accumulation of glucocerebrsidase causes numerous multi-organ complications (anemia, thrombocytopenia, hepatomegaly, splenomegaly, skeletal and neurological changes) (1,6,7,8,9,10).

Clinical classification of GD is based on the absence or presence of central nervous system manifestations and it is differentiated into type 1 (characterized by the absence of central nervous system manifestations) and types 2 and 3 (characterized by the presence of central nervous system manifestations) (1,10).

Type 1 GD is the most common type and clinical manifestations may vary from asymptomatic forms to forms with severe complications in the childhood or adulthood. It is manifested with hepato-splenomegaly,

leukopenia, thrombocytopenia, skeletal changes and pulmonary disease (1).

Type 2 is characterized as an acute and lethal neuronopathic form involving the nervous system, while type 3 GD is chronic neuronopathic form involving visceral organs, bones and the heart.

Levels of β – glucocerebrosidase in leukocytes are measured in order to make the definitive diagnosis of Gaucher's disease. However, a broad spectrum of pathological features observed in Gaucher's disease is not merely a consequence of accumulation and mechanical activity of glucocerebrosidase, but a consequence of macrophage activation and cytokine secretion as well.

In the serum of patients with Gaucher's diseases the levels of interleukin-1β, interleukin-6, THF-alfa, soluble interleukin-2 receptor, and CD14 are elevated. What is specific for patients with Gaucher's disease is elevation of chitotriosidase activity in serum originating from the Gaucher cells and it is considered to be a marker of macrophage activation and immune response induction. Chitotriosidase levels serve as a surrogate marker for total amount of accumulated glucocerbrosidase and for assessing Enzyme replacement therapy (ERT) intervention as well (1,11,12,13,14,15,16,17,18).

The presence of the Gaucher cells in the bone marrow and other tissues is not pathognomonic of Gaucher's disease, but it can be seen in a number of

other diseases (thalassaemia, acute and chronic lymphoproliferative disease, granulocytic leukemia).

Since 1991 ERT has been used for treating Gaucher's disease by substituting β-glucocerebrosidase with the enzyme produced by recombinant technology (alglucerase, imiglucerase, velaglucerase, taliglucerase alfa). The therapy has been shown to achieve effective results, corrects the anaemia, thrombocytopenia, organomegaly, improves bone status, and adverse effects are scarce (10,20,21,22,23,24) .

AIM OF THE PAPER

The aim of the paper is to show the treatment results in patients with Type 1 Gaucher's disease by administering ERT taliglucerase alfa at the Clinic of Hematology, Allergology and Clinical Immunology.

MATERIAL AND METHODS

In the period from January 2016 to January 2025 at the Clinic of Hematology, Allergology and Clinical Immunology taliglucerase alfa was used in treating 5 patients with Type 1 Gaucher's disease who did not respond to previous treatment or because the drug donation was

discontinued. One patient underwent splenectomy. Since 2016 the patients were treated at the expense of the National Health Insurance Fund.

ERT taliglucerase alfa is administered at a dose of 30U/kg body weight every other week as a 60-120 minutes intravenous infusion. The dosage of taliglucerase alfa is adjusted on an individual basis to achieve adequate therapeutic response (absence of thrombocytopenia and anaemia syndrome, reduced spleen and liver volume, as well as reduction in chitotriosidase levels and improvements in skeletal system) (20,21,22,23,25,26)

The treatment started after the definitive diagnosis of type 1 Gaucher's disease was made; diagnostic procedure included bone marrow biopsy, confirmation of the Gaucher cells presence, assessment of chitotriosidase levels, measurement of spleen and liver volume and identification of genotypes based on PCR and direct gene sequencing, while the gold standard for making the diagnosis of Gaucher's disease is to determine the β-glucocerebrosidase levels in leukocytes (1,11,12,13,14,15,16,17,18,19,20).

RESULTS

ERT Taliglucerase alfa was used to treat 5 patients with type 1 Gaucher's disease, 3 male patients (60%) and 2 females (40%) (Figure 1).

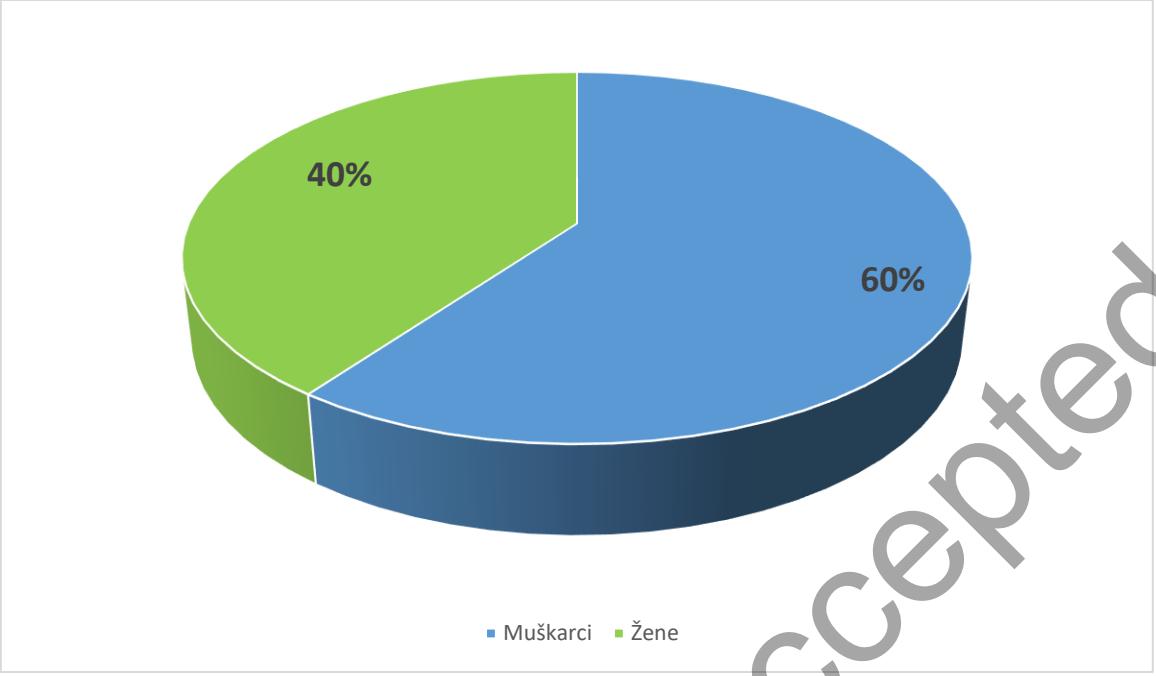

Figure 1. Patients with Gauchers disease by gender

Mean age of all the patients at the time of initiating taliglucerase alfa therapy was 39.2 years. The youngest patient was 17 and the oldest one 63 years old. Two patients previously used 1 therapeutic line (imiglucerase within donation programme), one patient received 3 therapeutic lines (recombinant glucocerebrosidase within the clinical study, Protalix from humanitarian aid, imiglucerase), and two patients were treated with taliglucerase alfa in the first therapeutic line.

The time period between establishing Gaucher's disease diagnosis and initiation of ERT with taliglucerase alfa was 44.4 months (range 1-132) (Figure 2).

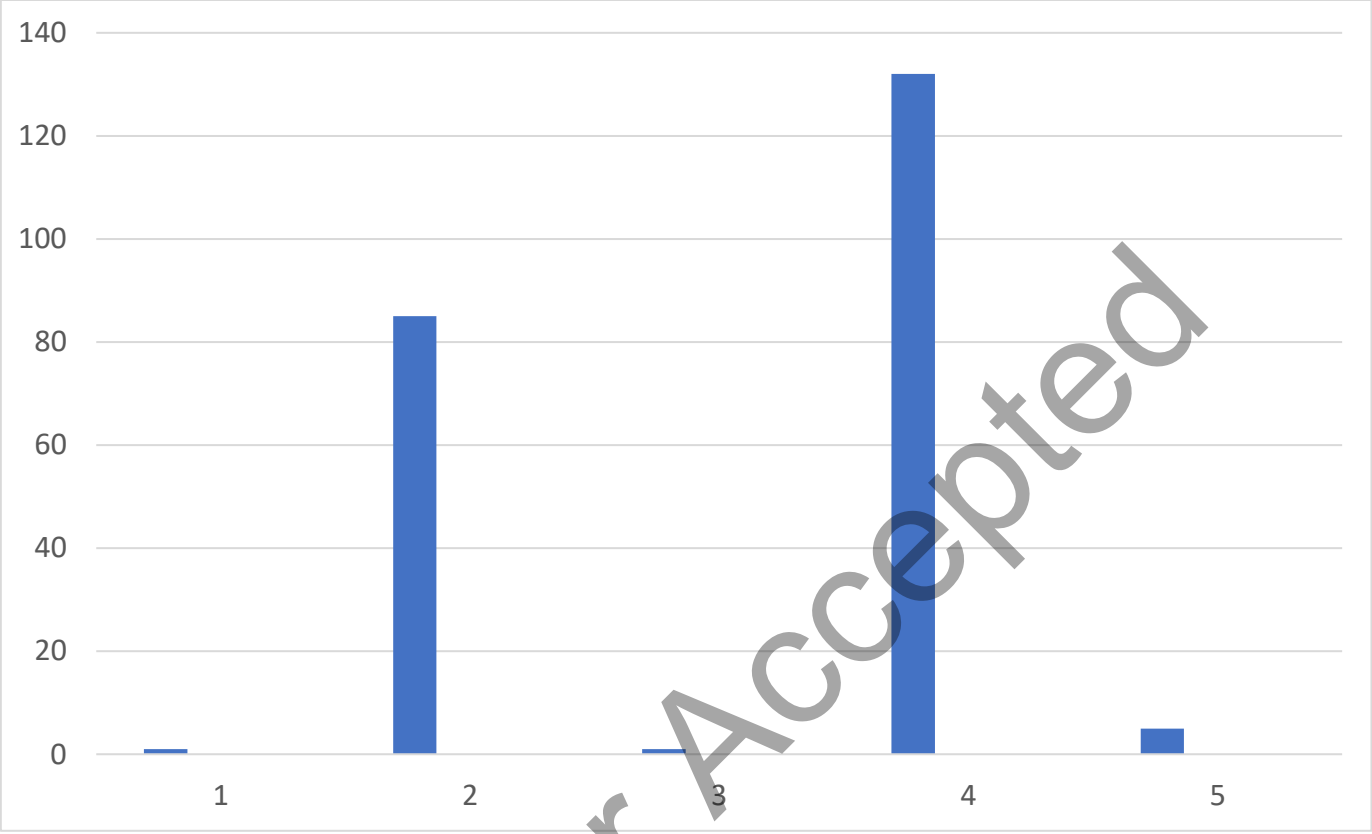

Figure 2. Time period in months from diagnosis of GD to initiation of ERT

The time period needed for treatment response after initiation of ERT taligluceraze alfa was 6 -12 months.

The average duration of treatment with Taliglucerase alfa was 61.6 months (range 13-83 months), and average chitotriosidase level for that period was 3937.5 nmol/h/ml (range 481.4-8299.5 nmol/h/ml).

Chitotriosidase is an enzyme belonging to the family of chitinases, that has a role in innate immunity and it is a marker of macrophage activation. Activated macrophages secrete chitotriosidase. Chitotriosidase activity level

drops 3-6 months after initiation of ERT, and increases 20 weeks after ERT cessation.

Extremely elevated chitotriosidase activity level originating from the Gaucher cells is registered in the plasma of Gaucher's patients. A direct correlation between chitotriosidase concentration and total amount of non-degraded glucocerebroside substrate has been established. That is why one of the parameters of treatment success is still serum chitotriosidase level.

The amount of glucocerebrosidase in patients with Gaucher's disease is increased 10-1000 times and can make up to 2% body weight of the patient.

The analysis of chitotriosidase average value upon introducing ERT Taliglucerase alfa showed the following trend: for the first patient average chitotriosidase value was 9007,2 nmol/ml/h (range 4202-21226,3); for the second patient the average chitotriosidase value was 4709,3 nmol/ml/h (range 2992,5-8299,5); for the third patient the average chitotriosidase value was 683.3 nmol/ml/h (range 534-1137); for the fourth patient the average chitotriosidase value was 970.7 nmol/ml/h (range 657,4-1443,6); for the fifth patient the average chitotriosidase value was 3402,8 nmol/ml/h (range 749.7-6056). Patients responded well to the therapy from its initiation and during its course, except two patients who responded at the level of stable disease, meaning that chitotriosidase level was maintained, as well as the volume of the liver and spleen in the previous two years.

There were no adverse effects during the administration of the drug (Table 1).

Table 1. Effect of ERT taliglucerase alfa in patients with Gaucher disease

Patients with GD	Chitotriosidase value before ERT administration	Chitotriosidase value after EST application	Side effects
1.	21226,3 nmol/ml/h	4202 nmol/ml/h	No
2.	8229,5 nmol/ml/h	2992,5 nmol/ml/h	No
3.	1137 nmol/ml/h	534 nmol/ml/h	No
4.	1443,6 nmol/ml/h	657,4 nmol/ml/h	No
5.	6056 nmol/ml/h	749,7 nmol/ml/h	No

Apart from assessment of chitotriosidase levels, our small group of patients was regularly radiologically monitored by performing whole-body NMR imaging for a year (measurements of spleen and liver volume, as well as regular monitoring of skeletal system status) .

The most common clinical manifestation of type 1 Gaucher's disease is painless splenomegaly, mostly detected accidentally. The spleen is sometimes palpated a few centimeters below the left rib arch, or it can be enlarged throughout the abdomen. The liver is slightly enlarged and portal hypertension is rare.

Magnetic Resonance Imaging of the abdomen performed a year after the initiation of ERT Taliglucerase alfa revealed a reduction in the spleen size in two patients, in one for 32% after a year of ERT Taliglucerase alfa administration, reduction from 201mm to 136mm, while in one patient the spleen volume was reduced from 134mm to 130mm. In one patient the spleen was of regular size at the time of diagnosis and at the check-up by abdomen NMR imaging, while in one patient the liver and spleen size was maintained despite the administered therapy, and one patient underwent splenectomy before establishing the diagnosis. The control magnetic resonance imaging was performed every year aiming at detecting any changes in the liver and spleen volume, and skeletal system as well.

The presence of anemia and thrombocytopenia is one of the criteria for establishing the diagnosis of Gaucher's disease. Our group of patients had regular laboratory analyses follow-up to assess the efficacy of ERT. At the time of diagnosis two patients had severe anemia syndrome, two patients had moderate thrombocytopenia, and one patient had both anemia and thrombocytopenia.

The analysis of average number of platelets upon the introduction of ERT Taliglucerase alfa showed the following: for the first patient the average number of platelets was 122.8 x 10^9/L (range 84-149); for the second patient the average number of platelets was 233.2 x 10^9/L (range 220-244); for the third patient the average number of platelets was 149x10^9/L (range

125-180); for the fourth patient the average number of platelets was 271.6x 10^9/L(range 210-330); for the fifth patient the average number of platelets was 115x 10^9/L (range 62-209).

The values of Hgb levels followed-up in patients upon ERT Taliglucerase alfa introduction were as follows: for the first patient the average HGB value was 137.8 g/l(range 128-147), for the second patient the average HGB value was 152.4g/l (range 149-157), for the third patient the average HGB value was 95.2g/l (range 81-106), for the fourth patient the average HGB value was 131.6g/l (range 109-145), for the fifth patient the average HGB value was 140g/l (range 135-148).

For the assessment of bone involvement pelvic MRI and long bones MRI were performed. One of the important features of type 1 Gaucher's diseases is skeletal system involvement, as registered in 60 % of our small group of patients. Skeletal changes are not always in direct correlation with other symptoms, bone involvement is not rare and it is often the first presenting sign of the disease. Bone involvement most commonly includes the thighbone, vertebrae, pelvis, the upper arm and forearm long bones with the development of osteoporosis, osteolysis, avascular necrosis, and pathological fractures. Episodes of bone crises are manifested as intense pain and are caused by bone microinfarction. At the time of establishing the

diagnosis, in 3 out of 5 monitored patients signal intensity changes in the bones were registered, and the regression of manifestations was observed after the administration ERT Taliglucerase alfa.

DISCUSSION

Gaucher's disease is an autosomal recessive disease, more common in females and more prevalent in Ashkenazi Jews than in general population. At the time of diagnosis patients' age ranges from birth to 81 years, mean age of 17.4 years, with almost half of the patients having the diagnosis before 10 years of age. In our small group the mean age was 39.2 years (27,28,29).

The purpose of treating Gaucher's diseases is correction of anemia syndrome, thrombocytopenia, and reduction of liver and spleen volume, along with the improvement of bone status. The effects of ERT can be seen 3 to 6 months after the initiation of the treatment, while in our group of patients the effects were seen after 6 to 12 months of treatment, which is in accordance with literature data (18,20,21,22,23,25,26).

Available literature does not favour any type of ERT, but according to current experience taliglucerase alfa exhibits less risk of immunogenicity in comparison to imiglucerase. ERT Taliglucerase alfa is well tolerated and adverse effects are mild to moderate in intensity and transient. The most common adverse effects include headache, nasopharyngitis, hypertension,

chest discomfort, nausea, vomiting, itching, pain in extremities, although no adverse effects were registered in our small group (24,29,30).

Getting IV ERT treatment every other week in hospital environment has a negative impact on patients' quality of life, considering the fact that it is a lifelong treatment (31).

All our patients had good therapeutic response, except one patient in whom there was no reduction in the liver and spleen volume in a period over a year, and treatment modality change has been considered. Taliglucerase alfa dosage was increased in two patients in proportion with their body size. According to literature data, termination of ERT results in disease progression in most patients, as well as in chitotriosidase level increase 20 weeks after treatment discontinuation (22,23).

CONCLUSION

Until the 1990 the only treatment available for Gaucher's disease was symptomatic one, such as erythrocyte transfusion, transfusion of platelets, multivitamin infusions, NSAIDs, androgen and bisphosphonate treatment, and orthopaedic procedures. Splenectomy was accompanied with transient improvement only and the disease was still progressing, especially in accelerating skeletal structures damage.

A great advancement in GD treatment was the introduction of replacement therapy with alglucerase (the placenta-derived modified form of β-glucocerebrosidase) in 1990s. A recombinant form of alglucerase – imiglucerase Cerezyme was introduced as a treatment option in the late 90s**.**

Based on previous experience, administration of taliglucerase alfa results in significant reduction of anemia, thrombocytopenia and organomegaly, as well as in bone status improvement.

Gaucher's disease is an example how modern medicine may alter the course of human life.

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