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Original scientific paper

RESULTS OF ENZYME REPLACEMENT THERAPY IN BULGARIAN PATIENTS WITH A SEVERE FORM OF HUNTER SYNDROME: A 42-MONTH FOLLOW-UP

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Hunter syndrome (Mucopolysaccharidosis type II, MPS II) is a rare X-linked disease caused by a deficiency of the enzyme iduronate-2-sulphatase (IDS), which results in the lysosomal accumulation of the undegraded glycosaminoglycans (GAGs) dermatan and heparan sulfate in various tissues and organs. Enzyme replacement therapy (ERT) with recombinant iduronate-2-sulphatase is the first disease-specific treatment for Hunter syndrome. Clinical trial data for the use of idursulfase to treat severe Hunter patients are limited and controversial. Our study analyzes therapeutic responses after ERT over 42 months of five Hunter patients and further expanding the knowledge of benefits and disadvantages of such therapy. Five boys with the severe form of MPS II (age range, 5−17 years) were treated with idursulfase for a minimum period of 8 months to a maximum period of 42 months. ERT with idursulfase in patients with the severe form of MPS II was associated with improvements in urinary GAG excretion and spleen size, stabilization of cardiac disease, and not effective on joint contractures, and on liver volume. MPS II is a progressive disease and response to ERT is influenced by the severity of the phenotype at treatment initiation.

Keywords: Enzyme replacement therapy, hunter syndrome, idursulfase, mucopolysaccharidosis II, severe form.

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INTRODUCTION

Hunter syndrome (Mucopolysaccharidosis type II, MPS II, OMIM 309900) is a rare X-linked disease caused by a deficiency of the enzyme iduronate-2-sulphatase (IDS), which results in the lysosomal accumulation of the undegraded glycosaminoglycans (GAGs) dermatan and heparan sulfate, in various tissues and organs (ARCHER *et al*., 2014). To date, more than 300 mutations have been described in the *I2S* gene encoding the IDS (GIUGLIANI *et al*., 2014). The estimated incidence of MPS II is 1.3 in 100.000 male newborns (BECK *et al*., 2012). Hunter syndrome is a progressive condition with a wide spectrum of clinical manifestations and a variable age of presentation. However, the disease is formally divided into two major phenotypes. The early-onset severe form begins in late infancy and is associated with progression to profound mental retardation. Approximately two thirds of the MPS II patients have central nervous system (CNS) involvement (MANARA *et al*., 2011). The attenuated form is characterized by a slower progression and a lack of neurological symptoms. The clinical presentation of Hunter syndrome includes coarse facial features, hepatosplenomegaly, cardiomyopathy and valvular disease, airway obstructions, skeletal abnormalities, hearing loss, joint contractures, inguinal and/or umbilical hernia (TOMANIN *et al*., 2014). Enzyme replacement therapy (ERT) with recombinant iduronate-2-sulphatase (idursulfase, Elaprase® Shire Human Genetic Therapies, Cambridge, MA, USA), is the first disease-specific treatment for Hunter syndrome. The ERT does not cross the blood–brain barrier however it improves somatic presentations of the disease (PARINI *et al*., 2015). This study analyzes therapeutic responses after ERT with idursulfase over 42 months of five Hunter patients.

MATERIAL AND METHODS

Five boys with MPS II were treated with idursulfase (Elaprase® Shire Human Genetic Therapies, Cambridge, MA, USA) at a dose of 0.5 mg/kg weekly intravenously. All patients were with typical clinical features of Hunter syndrome. Four out of five were with mental retardation. Two of them had seizures. All patients were with mitral and/or aortic insufficiency, and one patient had a thrombocytopenia prior to ERT. The diagnosis has been confirmed by enzyme and DNA analysis in all cases. Different mutations were found in the *I2S* gene – three missense, a large deletion, and an inversion. Two of the mothers are non-carriers. The age at diagnosis ranged from 6 months to 6 years. The age at beginning of ERT was between 5.6 and 17.4 years. The duration of therapy was from 8 to 42 months. The clinical, biochemical and molecular genetic characteristics of the patients are shown in **Table 1**. Antihistamines and nonsteroidal anti-inflammatory drugs were administered in all cases to prevent infusion-related adverse reactions (IARs). Clinical status, blood count, liver and spleen dimensions, and urinary GAGs excretion were assessed every 6 months. Cardiac disease was evaluated through echocardiography. Liver and spleen size was measured via palpation and through abdominal ultrasound (US). Midclavicular (MCL), anteroposterior (AP) dimensions measurements have been used in US to estimate the liver size. The splenic length was measured on longitudinal coronal image from dome to tip through the hilum. The joint range of motion (JROM) was evaluated by kinesiotherapist. Informed consent was not requested as all tests were part of the regular follow-up procedures.

Table 1 Clinical and laboratory characteristics of the MPS II patients included in the study.

Patients	Phenotype	Age at diagno-sis	Age at starting ERT	I2S activity*	Mutation	Mother
1	Coarse facial features, megacephaly, joint contractures, dysostosis multiplex, hepatosplenomegaly, valvular heart disease, cloudy cornea, deafness	6y	17y	0	K227M	carrier
2	Coarse facial features, megacephaly, joint contractures, dysostosis multiplex, hepatosplenomegaly, valvular heart disease, mental retardation, subcutaneous deposits	4y	8y	0	D334G	carrier
3	Coarse facial features, megacephaly, joint contractures, dysostosis multiplex, hepatosplenomegaly, valvular heart disease, mental retardation, epilepsy, thrombocytopenia	6mo	13y	0	inv *IDS*	carrier
4	Coarse facial features, megacephaly, joint contractures, dysostosis multiplex, hepatosplenomegaly, valvular heart disease, mental retardation, epilepsy	2y6mo	7y	0	R468W	non-carrier
5	Coarse facial features, megacephaly, joint contractures, dysostosis multiplex, hepatosplenomegaly, valvular heart disease, mental retardation	5y6mo	5y8mo	0	Deletion of 1-9 exons of *IDS* gene	non-carrier

* Iduronat-2-sulfatase normal range 50-650 nmol/4h/ml

RESULTS

Fig.1 shows the decrease of urinary glycosaminoglycans from baseline during ERT. Patient 4 had been treated by ERT for 5 years in other country, before starting treatment in our hospital, and no significant change in urinary GAG excretion was observed. In all children who started ERT in our clinic, urinary GAG levels were elevated at baseline and rapidly reduced during the first 6 months of treatment. They continued to decrease slowly and were approaching the normal range in two patients, and fluctuated in one patient throughout the rest of the period.

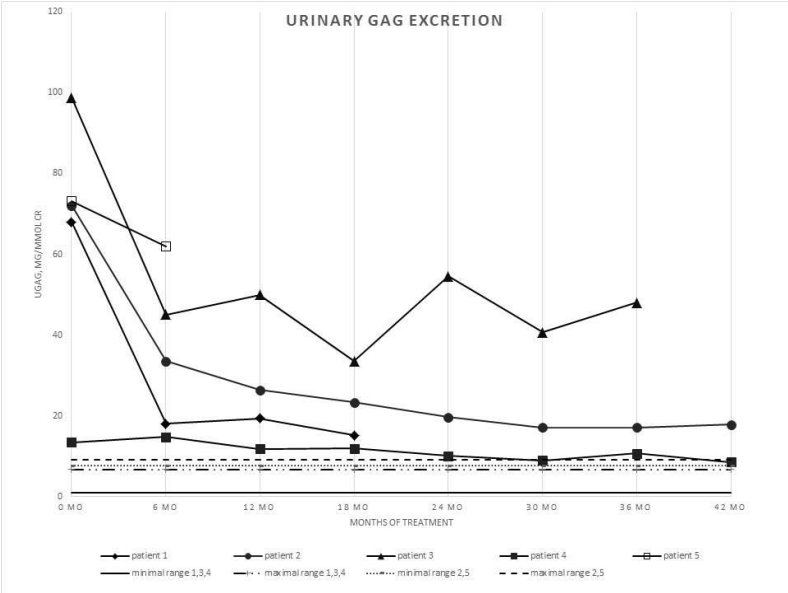

Figure 1. Urinary GAG excretion during ERT

No significant improvements were evidenced for hepatomegaly in all cases analysed (Fig.2). The AP hepatic diameter fluctuated in patients 2 and 3, and increased in patient 4. In our group an enlargement of the spleen in 3 patients at 12 months of ERT was followed by reduction, and at 18 months of treatment the splenic length of these patients was smaller compared to baseline. All patients had normal spleen size at the end of the study (Fig.3). During follow-up cardiac status remained stable in all cases except for patient 5 who developed progressive pulmonary hypertension and heart failure. Patient 3 had thrombocytopenia prior to ERT. The platelet count normalized within 2 weeks of initiating idursulfase infusions. Patient 2 had subcutaneous deposits that decreased significantly during the treatment. Based on performed goniometries of our patients we cannot report a significant overall change in parameters. The follow-up of flexion-extension and adduction-abduction contractures, based on about six arthrometric evaluations, showed uncertain improving or worsening in range of movements of the assessed joints. In all patients the ankyloses of ankles joints severely progressed. Two out of five patients experienced IARs during the course of ERT. Patient 3 developed generalized skin rash at fourth infusion. Patient 5 had generalized urticarial rash at third infusion and cheek

erythema at seventh infusion. All reactions were treated successfully by corticosteroids. In patient 3 seizures appeared during follow-up. He had progressive upper airway obstruction leading to tracheostomy and gastrostomy tube placement after 42 months of treatment. Patient 5 suffered from recurrent airway obstructions, and died from progressive heart failure 12 months after starting ERT. Patient 1 was referred to an adult clinic after 8 months of enzyme intake.

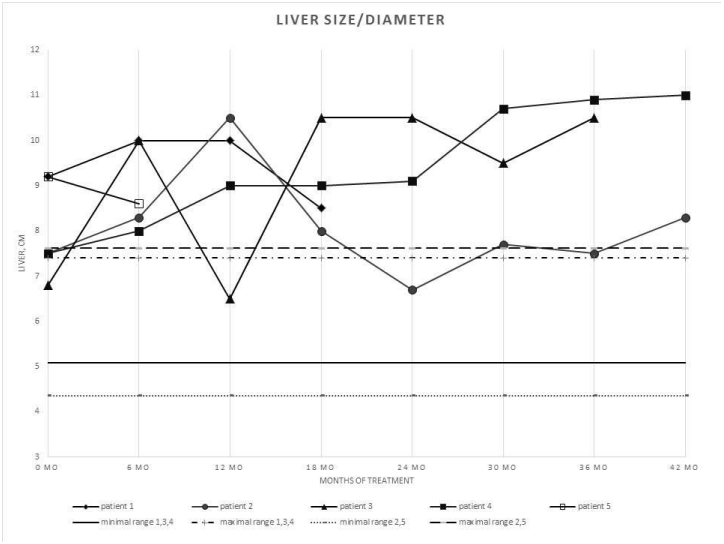

Figure 2. Midclavicular anteroposterior hepatic diameter during ERT

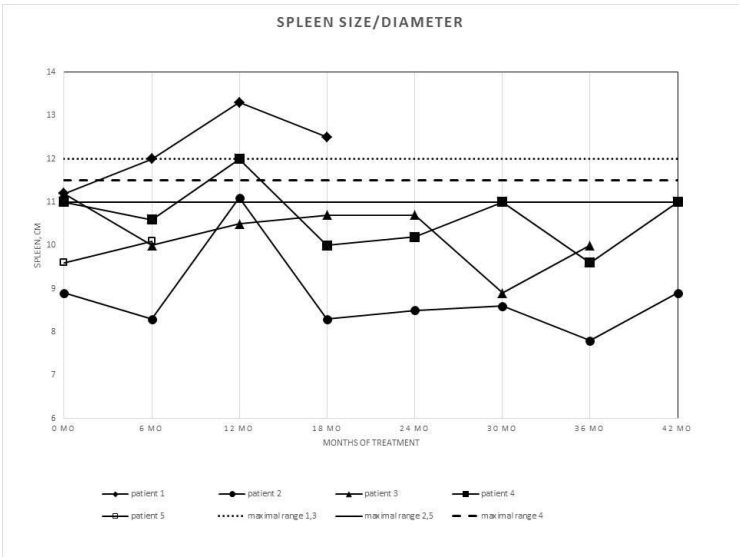

Figure 3. Spleen size during ERT

DISCUSSION

Clinical trial data for the use of idursulfase to treat severe MPS II are limited and controversial. Some of them concluded that somatic symptoms were improved in the majority of cases (PARINI *et al*., 2015; LAMPE *et al*., 2014) while in other studies no significant changes were found from baseline (TOMANIN *et al*., 2014). This report provides data reflecting our experiences with treating 4 patients with neuropathic MPS II and one patient with severe somatic involvement with ERT for 8 to 42 months. Three of them started ERT in 2012 when the reimbursement of idursulfase in Bulgaria has begun. One of patients (patient 4) had started the treatment 5 years earlier in other country. Patient 5 started at a later date as soon as the diagnosis was made. In four out of five cases there was a long period of time between diagnosis establishment and start of treatment (**Table** 1). Urinary GAGs are a useful mark in order to observe the biochemical effects of ERT. In children who started ERT in our clinic urinary GAG excretion was significantly reduced even in the more severe cases. This improvement was mainly during the first six months and sustained at 42 months of therapy. However our data show that not always a decrease of urinary GAG corresponds to an improvement of other clinical symptoms. According to most existing clinical trials the majority of treated patients experienced reductions in liver and/or spleen size (PARINI *et al*., 2015; LAMPE *et al*., 2014). Analyses of splenomegaly and hepatomegaly were performed separately in our study. In our patients the splenomegaly decreased progressively after 12 months of ERT, while the results were below expectations in terms of hepatomegaly, which slowly progresses in all cases. Similarly, the recent study did not detect any significant reduction of organomegaly in a large group of Hunter patients (WYATT *et al*., 2012). Unfortunately, anti-idursulfase antibodies were not measured. They could partly explain why the liver size does not decrease. Progressive joint contractures is a typical sign of MPS II and result in significant restrictions in mobility and gradual disability (LINK *et al*., 2010). Measurement techniques were not standardized, however, an increase in joint range of motion of at least 10° was considered an improvement. Goniometries performed in our group at baseline showed a severe involvement of upper and lower limbs in all patients. Joint range of motion stabilized/worsened in all cases while no improvements were described. Later started treatment and lack of appropriate rehabilitation by specially trained physical therapists may be coexisting factors for the joint contracture progression. A progressive cardiac involvement is a common symptom in mucopolysaccharidoses. According to our study, valvular disease as assessed by echocardiogram was stabilized in four patients. Stabilization can be considered a benefit of treatment for a progressive disease like MPS II. Similarly, several reports suggest that ERT is effective in improving heart function in MPS II (TOMANIN *et al*., 2014; PARINI *et al*., 2015; BRANDS *et al*., 2015). Seizures are common neurologic findings in patients with Hunter disease. Two patients in our group were with preexistent epilepsy. As expected, the treatment did not show a positive effect on seizures due to the inability of ERT to cross the blood–brain barrier. Patient 3 had thrombocyte count 40 000/mm^3 proir to ERT. The platelet count normalized within two weeks of initiating idursulfase. The effect of ERT on thrombocytopenia in Hunter patients has not reported until now.

Treatment was generally well tolerated. Two of our patients experienced IARs during the first two months of treatment. The observed adverse event – skin rash - was easily controlled by temporary stopping of infusion and steroid administration.

Our data show that not much benefit is seen during the ERT in patients with severe form of MPS II but it may be that a longer time of treatment might reveal some improvements.

CONCLUSIONS

Our experience with treating severe MPS II patients with ERT for 42 months demonstrated that treatment was associated with improvements in urinary GAG excretion and spleen size, stabilization of cardiac disease, not effective on joint contractures, and on liver size, and it was generally well tolerated. MPS II is a progressive disease and response to ERT is influenced by the severity of the phenotype at treatment initiation.

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REZULTATI TERAPIJE ENZIMSKE ZAMENE KOD BUGARSKIH PACIJENATA SA OZBILJNIM OBLIKOM *HUNTER*-OVOG SINDROMA TOKOM PERIODA PRAĆENJA OD 42 MESECA

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Izvod

Hunter-ov sindrom (*Mucopolysaccharidosis type II, MPS II*) je retka bolest izazvana nedostatkom enzima iduronate-2-sulfataze (IDS), koja rezultira akumulacijom lizozoma nedegradiranih glikozaminoglukana (GAGs) sulfata u različitim tkivima i organima. Terapija zamene enzima sa rekombinantnom (ERT) iduronate-2-sulfatazom je prvi primer bolest specifičnog tretmana Hunter-ovog sindroma. Klinički podaci o upotrebi idursulfaze u terapiji pacijenata su ograničeni i kontroverzni. Naše proučavanje reakcije pacijenata posle 42 meseca primene enzimske terapije dalo je nova saznanja o njenim prednostima i nedostacima. Pet dečaka sa ozbiljnim oblikom MPS II (starosti od 5−17 godina) lečeni su idursulfazom u periodu od najmanje 8 meseci do maksimalno 42 meseca. ERT sa idursulfazomje bila povezana sa poboljšanjem urinarnog izlučivanja GAG i veličine slezine, stabilizacijom srčanih bolesti, i bez uticaja na zglobove i zapreminu jetre. MPS II je progresivna bolest i odgovor na ERT zavisi I od stanja fenotipa na početku tretmana.

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