Progression of organ manifestations upon enzyme replacement therapy in a patient with mucopolysaccharidosis type I/Hurler

Saadet Mercimek-Mahmutoglu, Christopher Reilly, Derek Human, Paula J. Waters, Sylvia Stoeckler-Ipsiroglu

Vancouver, Canada

Background: **Enzyme replacement therapy (ERT) has been increasingly used as an interim treatment in severe mucopolysaccharidosis type I (MPSI)/Hurler patients prior to hematopoietic stem cell transplantation (HSCT).**

Methods: **We present the outcome of a patient with MPSI/Hurler after 14 months of ERT prior to HSCT.**

Results: **Urinary glucosaminoglycan excretion decreased by 70% after one month of ERT. Liver volume decreased by 14% of baseline after 12 months of ERT. Pre-existing thoracolumbar kyphosis progressed to thoracolumbar dislocation with complete displacement of facets after 12 months of ERT. New development of mitral valve thickening was found by echocardiography and mild hearing loss progressed to severe sensorineural hearing loss after 13 months of ERT.**

Conclusions: **ERT over a period of 14 months did not prevent progression of organ manifestations in our patient. Patients should be monitored every 6 months for cardiac, skeletal and audiological involvement on ERT.**

World J Pediatr 2009;5(4):319-321

Key words: **Hurler disease; laronidase; mucopolysaccharidosis type I**

Author Affiliations: Division of Biochemical Diseases, Department of Pediatrics, British Columbia Children's Hospital, Vancouver, Canada (Mercimek-Mahmutoglu S, Stoeckler-Ipsiroglu S); Department of Orthopedics, British Columbia Children's Hospital, Vancouver, Canada (Reilly C); Division of Cardiology, Department of Pediatrics, British Columbia (Human D); Biochemical Genetics Laboratory, Department of Pathology and Laboratory Medicine, British Columbia Children's Hospital, Vancouver, Canada (Waters PJ)

Corresponding Author: Saadet Mercimek-Mahmutoglu, MD, FCCMG, British Columbia Children's Hospital, Division of Biochemical Genetic Diseases, Room K3-208, ACB, 4480 Oak Street, Vancouver, B.C., Canada V6H 3V4 (Tel: 604-875-2628; Fax: 604-875-2349; Email: smahmutoglu@cw.bc.ca)

doi:10.1007/s12519-009-0062-x

Introduction

Mucopolysaccharidosis type I (MPSI) is an autosomal recessively inherited lysosomal storage disorder (OMIM: 607014, 607015, 607016) caused by a deficiency of alpha-L-iduronidase (IDUA) (EC 3.2.1.76). The disorder is characterized by a progressive multisystem disease with coarse facial features, progressive dysostosis multiplex, joint contractures, cardiac valve changes, upper airway obstruction, hepatosplenomegaly, corneal clouding and various degrees of central nervous system (CNS) involvement. The clinical spectrum ranges from severe MPSI/Hurler with progressive neuro-cognitive deterioration to attenuated forms.[1]

Hematopoietic stem cell transplantation (HSCT) is the treatment of choice for patients with severe disease prior to CNS involvement.[2] Enzyme replacement therapy (ERT) with recombinant human IDUA (Laronidase) has been shown to be effective in improvement of upper airway obstruction, joint mobility and reduction of hepatosplenomegaly.[3] ERT is increasingly used as an interim treatment in Hurler patients prior to HSCT.[4] We report the outcome of a patient with Hurler after 14 months of ERT prior to HSCT.

Case report

This 34-month-old boy is the first child of non-related healthy Mexican parents. Pregnancy, birth and early development were unremarkable. At the age of 3 months he underwent an elective bilateral inguinal hernia repair. At the age of 10 months he was noted to have coarse facial features, bilateral corneal clouding, hepatomegaly and thoracolumbar kyphosis. His liver was 5 cm palpable below the right costal margin with no palpable spleen. His developmental milestones were age-appropriate. MPSI was diagnosed by elevated urinary glucosaminoglycan (GAG) excretion and undetectable IDUA activity in white blood cells. Mutation analysis of the *IDUA* gene

showed homozygosity for a known missense mutation, p.P533R (c.1598C>G) which is associated with severe phenotype.[5]

At the age of 15 months, ERT with laronidase was started (0.58 mg/kg weekly). As social difficulties and rare typing resulted in a protracted time frame prior to transplantation, ERT was continued for 14 months, until a matched umbilical cord blood stem cell transplant found. Shivering, chills, and "fussy behavior" occurred at the 3rd, 6th and 43rd weeks of ERT infusion despite premedication with diphenhydramine and ibuprofen.

Clinical and biochemical parameters and their changes after the months of ERT are shown in Tables 1, 2 and in Fig. Urinary GAG excretion decreased by 70% after one month of ERT. After 12 months of ERT, his liver volume decreased by 14% of baseline. Progressive communicating hydrocephalus required a right ventricular peritoneal shunt after 3 months of ERT. An umbilical hernia occurred after 3 months of ERT and was repaired after 6 months of ERT. Pre-existing thoracolumbar kyphosis progressed to thoracolumbar dislocation with complete displacement of facets and translation requiring thoracolumbosacral orthosis after 12 months of ERT. He developed mild mitral valve thickening after 12 months of ERT. Mild hearing loss progressed to severe sensorineural hearing loss in the mid and high frequency range after 13 months of ERT. Developmental assessments revealed age appropriate developmental milestones prior to ERT and HSCT.

At the age of 30 months (after 14 months of ERT), our patient received unrelated donor umbilical cord stem cell transplantation. He showed a full donor chimerism (97%), normal IDUA activity and normalization of urinary GAG excretion 3 months post-transplantation (Fig.). ERT was discontinued 3 months after HSCT.

Discussion

We had the opportunity to study the effects of ERT in a severely affected MPSI patient in the early stage of the disease for 14 months prior to HSCT. We observed progression of pre-existing disease related complications and development of new clinical manifestations between the age of 15 months and 29

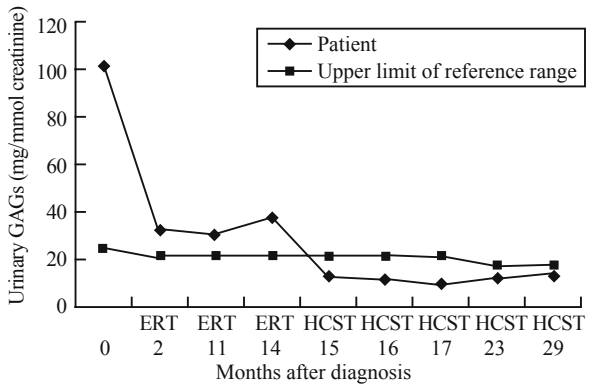

Fig. Follow-up of urinary GAGs at diagnosis, upon ERT and following HSCT. GAGs: glycosaminoglycans; ERT: enzyme replacement therapy; HSCT: hematopoietic stem cell transplantation.

Table 1. Follow-up of organ manifestations at diagnosis and after 12 to 14 months of ERT

Organ systems	Baseline investigations at diagnosis	Investigations after months of ERT (months of ERT)
Central nervous system	Communicating hydrocephalus	Progressive communicating hydrocephalus, VP shunt (3 months)
Developmental assessment	Age appropriate by BSIDS	Age appropriate by VABS (11 months)
Skeletal	Thoracolumbar kyphosis Cobb angle of 30 degrees	Thoracolumbar kyphosis Cobb angle of 35 degrees (12 months)
Cardiac	Normal ECHO	Mild mitral valve thickening in ECHO (12 months)
Visceral	Liver volume 1.4 times increased in MRI Spleen volume 2.9 times increased in MRI	Liver volume 1.2 times increased (12 months) in MRI Spleen volume 3.1 times increased (12 months) in MRI
Audiology	Mild hearing loss by AS, IT & AR	Severe sensorineural hearing loss by BA (13 months)

ERT: enzyme replacement therapy; VP: ventricular peritoneal; BSIDS: Bailey scale of infant development score; VABS: Vineland Adaptive Behavior Scales; ECHO: echocardiography; MRI: magnetic resonance imaging; AS: auditory stimuli; IT: immittance test; AR: acoustic reflexes; BA: behavioral audiometry.

Table 2. Follow-up of biochemical investigations at diagnosis and after 12-14 months of ERT including IDUA activity, serum α-L-iduronidase IgG antibodies, neutralizing antibody and urinary GAGs

Biochemical investigations	At diagnosis	After 14 months of ERT	Reference range
Urinary GAGs (mg GAG/mmol creatinine)	101	31	<25 at the age of 10 months <22 at the age of 27 months
IDUA enzyme activity nmol/hr/mg protein	Undetectable	0.3	4.5-14.1 (mean: 8.4)
Serum α-L-iduronidase IgG antibodies	Not performed	6400	Not detectable
Neutralizing antibody	Not performed	<298	Not detectable

ERT: enzyme replacement therapy; GAGs: glucosaminoglycans; IDUA: alpha-L-iduronidase.

months. Our patient developed mitral valve deposits, umbilical hernia, and sensorineural hearing loss and had deterioration of preexisting thoracolumbar kyphosis, and communicating hydrocephalus.

Long-term follow up of patients on ERT showed a deterioration of aortic and/or mitral valve function in 4 out of 5 patients with MPSI/Hurler-Scheie and MPSI/Scheie phenotypes.[6] Monitoring of cardiac function in 3 patients who received ERT with advanced stages of MPSI/Hurler also revealed progression of preexisting cardiac valvular involvement.[7-9] Our patient is the first to demonstrate *de novo* development of cardiac GAG deposits while receiving ERT.

One MPSI/Hurler patient has been reported with non-progressive sensorineural hearing loss, and in another patient conductive hearing loss had improved after 3 years of ERT.[8] The deterioration of preexisting sensorineural hearing loss in our patient suggests that ERT might not be effective in preventing this manifestation in patients with MPSI/Hurler.

Skeletal manifestations were not included as primary outcome parameters in the ERT phase 3 studies; however, in the subsequent open label trial progressive vertebral wedging accompanied by extreme kyphosis and lateral subluxation of the femoral heads was observed in 1 out of 5 MPSI/Hurler-Scheie patients after 6 years of ERT.[6] In 2 reported patients with MPSI/Hurler, ERT was started at the age of 5 years and failed to prevent the development of spinal cervical cord compression.[8,9] These findings together with the findings in our patient indicate that skeletal disease is poorly responsive to ERT, particularly when significant disease is present at commencement of treatment.

The clinical studies of ERT effectiveness have been performed in patients with attenuated disease. The currently recommended ERT dose might not be sufficient to reduce tissue GAG accumulation and thus prevent progression of the disease in severely affected patients. Serum α-L-iduronidase IgG antibodies were detected between 6 to 26 weeks of infusions in up to 90% of patients on ERT. Although patients seem to develop immune tolerance after 6 to 12 months of ERT with decreasing antibody titers, the presence of antibodies could affect tissue distribution and thus effective function of substituted enzyme.[10] The deterioration of disease seen in our patient may be related to either insufficient dosing of ERT in the face of severe disease or ineffectiveness of ERT related to immune response.

In summary, ERT over a period of 14 months did not prevent disease progression in this young MPSI/Hurler patient. HSCT should be the first choice of treatment in MPSI/Hurler patients with a suitable donor and should be performed as early as possible. Patients should be monitored every 3 to 6 months for cardiac, skeletal and audiological involvement in the first 3 to 12 months of ERT.

Acknowledgements

We thank Dr Eduard Paschke for sequencing DNA of the patient, Dr. Lorne A. Clarke and Dr. Y. Lillquist for comments and critical reading of the manuscript, and Dr. Jeff Davis for performing HSCT.

Funding: None.
Ethical approval: Not needed.
Competing interest: None declared.
Contributors: Mercimek-Mahmutoglu S wrote the main body of the article under the supervision of Stoeckler-Ipsiroglu S. Reilly C provided data on skeletal manifestations, Human D on cardiac manifestation, and Waters PJ on biochemical findings.

References

1 Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic & molecular bases of inherited disease. New York: McGraw-Hill, 2001: 3421-3452.
2 Peters C, Balthazor M, Shapiro EG, King RJ, Kollman C, Hegland JD, et al. Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. Blood 1996;87:4894-4902.
3 Wraith JE, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). J Pediatr 2004;144:581-588.
4 Grewal SS, Wynn R, Abdenur JE, Burton BK, Gharib M, Haase C, et al. Safety and efficacy of enzyme replacement therapy in combination with hematopoietic stem cell transplantation in Hurler syndrome. Genet Med 2005;7:143-146.
5 Scott HS, Litjens T, Nelson PV, Brooks DA, Hopwood JJ, Morris CP. alpha-L-iduronidase mutations (Q70X and P533R) associate with a severe Hurler phenotype. Hum Mutat 1992;1:333-339.
6 Sifuentes M, Doroshow R, Hoft R, Mason G, Walot I, Diament M, et al. A follow-up study of MPSI patients treated with laronidase enzyme replacement therapy for 6 years. Mol Genet Metab 2007;90:171-180.
7 Braunlin EA, Berry JM, Whitley CB. Cardiac findings after enzyme replacement therapy for mucopolysaccharidosis type I. Am J Cardiol 2006;98:416-418.
8 Tokic V, Barisic I, Huzjak N, Petkovic G, Fumic K, Paschke E. Enzyme replacement therapy in two patients with an advanced severe (Hurler) phenotype of mucopolysaccharidosis I. Eur J Pediatr 2007;166:727-732.
9 Thomas JA, Jacobs S, Kierstein J, Van Hove J. Outcome after three years of laronidase enzyme replacement therapy in a patient with Hurler syndrome. J Inherit Metab Dis 2006;29:762.
10 Kakkis ED, Muenzer J, Tiller GE, Waber L, Belmont J, Passage M, et al. Enzyme-replacement therapy in mucopolysaccharidosis I. N Engl J Med 2001;344:182-188.

Received November 5, 2008
Accepted after revision April 15, 2009