Deleterious effects of interruption followed by reintroduction of enzyme replacement therapy on a lysosomal storage disorder

ANA PAULA SCHNEIDER, URSULA MATTE, GABRIELA PASQUALIM, ANGELA MARIA VICENTE TAVARES, FABIANA QUOOS MAYER, BARBARA MARTINELLI, GRAZIELA RIBAS, CARMEN REGLA VARGAS, ROBERTO GIUGLIANI, and GUILHERME BALDO

PORTO ALEGRE, BRAZIL

Temporary interruption of enzyme replacement therapy (ERT) in patients with different lysosomal storage disorders may happen for different reasons (adverse reactions, issues with reimbursement, logistic difficulties, and so forth), and the impact of the interruption is still uncertain. In the present work, we studied the effects of the interruption of intravenous ERT (Laronidase, Genzyme) followed by its reintroduction in mice with the prototypical lysosomal storage disorder mucopolysaccharidosis type I, comparing to mice receiving continuous treatment, untreated mucopolysaccharidosis type I mice, and normal mice. In the animals which treatment was temporarily interrupted, we observed clear benefits of treatment in several organs (liver, lung, heart, kidney, and testis) after reintroduction, but a worsening in the thickness of the aortic wall was detected. Furthermore, these mice had just partial improvements in behavioral tests, suggesting some deterioration in the brain function. Despite worsening is some disease aspects, urinary glycosaminoglycans levels did not increase during interruption, which indicates that this biomarker commonly used to monitor treatment in patients should not be used alone to assess treatment efficacy. The deterioration observed was not caused by the development of serum antienzyme antibodies. All together our results suggest that temporary ERT interruption leads to deterioration of function in some organs and should be avoided whenever possible. (Translational Research 2016;176:29–37)

Abbreviations: MPS = mucopolysaccharidosis; ERT = enzyme replacement therapy; GAG = glycosaminoglycan

Guilherme Baldo, PhD, *is an assistant professor in the Department of Physiology at the Federal University of Rio Grande do Sul in Brazil. Dr. Baldo is now focusing on developing better treatments for lysosomal storage disorders, including gene therapy and improvements in enzyme replacement therapies. He is working on gene editing studies using the CRISP-Cas9 system to allow autologous stem cell transplantation of genetically modified cells in selected disorders, such as Hurler and Hunter syndromes. He is also studying mechanisms by which these disorders lead to multisystemic features, aiming to find out new disregulated pathways and potential new treatments based on modulation of these alterations.*

From the Centro de Terapia Gênica- HCPA, Porto Alegre, Brazil; Programa de Pós-Graduação em Genética e Biologia Molecular, UFRGS, Porto Alegre, Brazil; Programa de Pós-Graduação em Ciência Biológicas: Fisiologia, UFRGS, Porto Alegre, Brazil; Serviço de Genética Médica-HCPA, Porto Alegre, Brazil.

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Reprint requests: Ursula Matte, Centro de Terapia Gênica-HCPA, Ramiro Barcelos, 2350, Porto Alegre 90035-903; e-mail: umatte@hcpa.edu.br.

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AT A GLANCE COMMENTARY

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Background

This article deals with the deleterious effects of interrupting enzyme replacement, the main therapy for lysosomal storage disorders, on an animal model of the multisystemic disease mucopolysaccharidosis type 1 (MPS I). This is highly important since we frequently observe treatment interruption in patients due to several reasons, and for years anecdotic cases have tried to show which disease parameters can or cannot be reversed after treatment reintroduction.

Translational Significance

Based on the results, we demonstrate that some organs (such as the brain and the aorta) may be irreversibly impaired due to ERT interruption. We also show that the main biomarker used to follow patients does not reflect disease status after treatment withdrawal. We hope these results will have a high impact on dealing with patients in cases where treatment is discontinued.

INTRODUCTION

The lysosomal storage disorders (LSDs) are a group of genetic diseases, usually caused by the deficient activity a lysosomal enzyme due to mutations in the specific codifying gene, leading to the intracellular storage of undegraded or partially degraded substrates.[1] Many of these disorders can be now treated using different approaches, depending on the characteristics of the disease. Potential approved treatments for selected LSDs include hematopoietic stem cell transplantation, substrate reduction therapy, and enzyme replacement therapy (ERT).

ERT is already available for several LSDs, including Gaucher disease, Fabry disease, Pompe disease, and MPS types I, II, IV, and VI, and Pompe disease. Although effective for several aspects of the MPS (especially organomegaly and respiratory problems), ERT is only partially effective considering the multisystemic features of the diseases.[2] For example, alterations in the heart valves, aorta, bones, and especially the brain are not completely corrected[3–5] probably due to the poor inaccessibility of the enzyme to these tissues when applied intravenously. Together with the treatment limitations, the high cost of these treatments (varying from U$150,000–500,000/year/patient) is an important point to be considered from a public health perspective.[6]

It is not uncommon to find reports in the literature about ERT interruption/withdrawal in the LSDs. Reasons for that include reimbursement issues (difficulties in obtaining the high-cost medication from the health system), medical recommendation (adverse reactions to infusions, pregnancy), and logistic problems (difficulties to travel or to skip school/work to have the infusion, for example). Also, shortage of the recombinant enzyme due to production problems may occur.[7,8] In these cases, some level of deterioration in the patient condition is usually reported. However, due to differences in phenotypes across diseases and even within the same disease, it is hard to obtain accurate data on which organs/systems are more or less affected when treatment is interrupted, and how to monitor any potential deterioration. Therefore, in the present work, we aimed to study the effects of ERT withdrawal followed by reintroduction in an animal model of MPS type I, as a prototypical multisystem lysosomal storage disorder.

MATERIALS AND METHODS

Experimental design. MPS I mice were produced by insertion of a neomycin resistance gene that interrupts the IDUA gene and therefore produces no enzyme, leading to a multisystemic disease that resembles the phenotype of Hurler syndrome in humans and affects all major organs in the body.[9] Furthermore, in a previous study,[3] we have shown that treatment with ERT from birth corrects most of MPS I symptoms, which allows a direct comparison of treated animals with or without interruption in the present study.

The article conforms to the relevant ethical guidelines for human and animal research. All animal studies were approved by our local Ethics Committee and complied with National Guidelines on Animal Care. MPS I mice on a C57BL/6 background (kindly donated by Dr Elizabeth Neufeld, UCLA) were used.

Animals with treatment interruption (ERT-stop group) were submitted to the following protocol: animals were injected intravenously with 1.2 mg/kg of Laronidase (Genzyme) every 2 weeks from birth up to 2 months of age. At 2 months, treatment was interrupted until mice were 4 months old. Finally, treatment was reintroduced and mice were sacrificed at 6 months of age for analyses.

These mice were compared with normal mice (Normal group), untreated MPS I mice (MPS I group), and mice treated from birth without interruption (ERT-neo), as previously described.[3] All animals were sacrificed at 6 months of age, 2 weeks after the last injection, in case of treated animals. At the time of sacrifice, mice were anesthetized with isoflurane, serum was

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