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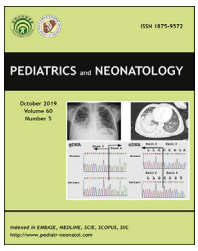

Short Communication

Long-term outcomes of enzyme replacement therapy for Taiwanese patients with Mucopolysaccharidosis I

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1. Introduction

Mucopolysaccharidosis (MPS) I is an autosomal recessive lysosomal storage disorder resulting from a deficiency in the lysosomal enzyme α-L-iduronidase, leading to the accumulation of the glycosaminoglycans (GAGs) dermatan sulfate (DS) and heparan sulfate (HS) in cells throughout the body. The clinical characteristics of MPS I include cognitive impairment (severe form), coarse facial features, corneal clouding, respiratory disorders, cardiac diseases, hepatomegaly, umbilical and inguinal hernias, skeletal abnormalities, and joint contractures. MPS I has a variable clinical severity and rate of progression, and it can be classified into three syndromes: Hurler syndrome (severe), Hurler-Scheie syndrome (intermediate), and Scheie syndrome (attenuated).[1] The reported birth incidence of MPS I is 1 in 900,000 live births in Taiwan, accounting for 6% of all cases of MPS.[2] Over the past decade, enzyme replacement therapy (ERT) with laronidase (Aldurazyme®; Sanofi Genzyme, Boston, Massachusetts), a recombinant human form of α-L-iduronidase, has been shown to improve endurance, joint mobility, and pulmonary function, and potentially to be beneficial for patients with MPS I, especially if started at a younger age.[3] However, information regarding the long-term outcomes of ERT with laronidase for Asian patients with MPS I is limited.

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2. Case series

We reviewed seven Taiwanese patients with MPS I (four with Hurler-Scheie syndrome and three with Scheie syndrome; age range, 0.7—34.9 years) treated with weekly intravenous infusions of 0.58 mg/kg/week laronidase at Mackay Memorial Hospital, Taipei, Taiwan. Biochemical and clinical responses were evaluated every year. The age at a confirmative diagnosis ranged from 0.6 to 34 years. After ERT for 2.0—8.3 years, a mean reduction in urinary GAGs of 88% (from 680.2 to 84.2 μg/mg creatinine) was observed (Supplementary Fig. 1), indicating a satisfactory biochemical response. In addition, mean reductions in urinary DS of 94% (from 204.3 to 11.2 μg/mL) and in urinary HS of 68% (from 8.4 to 2.7 μg/mL) were noted in six patients. The mean 6-min walk test distance of five patients improved from 315.9 to 321.8 m, and shoulder range of motion improved in all patients. Pulmonary function tests of four patients showed stabilized mean forced vital capacity (FVC) (2.60 vs. 2.32 L) and forced expiratory volume in 1 s (FEV_1) (1.98 vs. 1.82 L). After ERT, echocardiography of all patients showed a decrease in mean left ventricular mass index (LVMI) *z* score from 0.76 to 0.62, and a mean decrease in interventricular septal end-diastolic dimension (IVSd) *z* score from 3.58 to 2.62. For two patients who started ERT before 1.1 years of age, *z* scores for LVMI, IVSd, and left ventricular posterior wall end-diastolic dimension (LVPWd) all decreased after ERT. Ejection fraction revealed stationary after ERT (reference rage > 0.5). Due to the limitation of the patient number in this study, only urinary DS and GAGs, and 3-min stair climb showed statistically significant improvement after ERT ($p < 0.05$). Abdominal ultrasonographic assessments of the liver and spleen showed a decreased or stabilized size after ERT in all patients. One patient (No. 6) had positive antibodies to laronidase, and four patients had negative results. Cord blood transplantation was smoothly performed for patient 1 at 1.6 years of age, and then ERT was discontinued at 2.1 years of age. However, due to the detection of a chimeric status and relatively high level of urinary GAGs, ERT was resumed at 2.5 years of age. Patients No. 5, 6, and 7 are brothers and sister in the same family. No founder effect or genotype—phenotype correlations was found in this cohort. None of the patients developed allergic reactions during ERT with laronidase (Supplementary Table 1).

3. Discussion

This is the first report regarding the clinical benefits and safety of long-term ERT in Taiwanese patients with MPS I. Our results demonstrated improvements in both biochemical and clinical functions in all of the patients after 2.0—8.3 years of ERT. Laronidase reduced the levels of urinary GAGs, DS and HS, improved or stabilized endurance, mobility, joint function, pulmonary function, liver size and spleen size, and had an acceptable safety profile. MPS I has a chronic progressive nature. Our results revealed that laronidase also appeared to be effective in reducing cardiac hypertrophy, and that better results may be obtained when starting treatment at a younger age.[4] Only patient 6 had positive antibodies to laronidase, however a previous study reported that the presence of antibodies had no significant impact on clinical outcomes or the occurrence of hypersensitivity reactions.[5] The ages at a confirmative diagnosis of patients 3 and 4 were 3.1 and 11 years, respectively. However, ERT with laronidase was not available until they were 18.2 and 18.9 years old, respectively. Patient 3 died at the age of 20.2 years due to respiratory infection-induced cardiopulmonary failure,[6] and patient 4 died of cardiac failure at the age of 27.6 years. As the patients grew older, GAG accumulation in all tissues and organs may have led to irreversible damage refractory to ERT. Since timely ERT may contribute to a better clinical outcome, making an early diagnosis through screening programs for newborns or high-risk populations is very important.[7]

Conflict of interest statement

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2019.05.005.