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Short Communication

Long-term effects of enzyme replacement therapy for Taiwanese patients with mucopolysaccharidosis IVA

Hsiang-Yu Lin [a,b,c,d,e,1], Chih-Kuang Chuang [c,f,g,1], Yu-Yuan Ke [h], Chia-Chi Hsu [h], Pao Chin Chiu [i], Dau-Ming Niu [j], Fuu-Jen Tsai [k], Wuh-Liang Hwu [l], Ju-Li Lin [m], Shuan-Pei Lin [a,b,c,n,*]

[a] *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*
[b] *Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*
[d] *Mackay Junior College of Medicine, Nursing and Management, Taipei, Taiwan*
[e] *Department of Medical Research, China Medical University Hospital, China Medical University, Taichung, Taiwan*
[f] *Medical College, Fu-Jen Catholic University, Taipei, Taiwan*
[g] *Institute of Biotechnology, National Taipei University of Technology, Taipei, Taiwan*
[h] *Department of Pediatrics, Taichung Veterans General Hospital, Taichung, Taiwan*
[i] *Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[j] *Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan*
[k] *Department of Pediatrics, China Medical University Hospital, Taichung, Taiwan*
[l] *Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan*
[m] *Department of Pediatrics, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan*
[n] *Department of Infant and Child Care, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan*

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1. Introduction

Mucopolysaccharidosis IVA (MPS IVA; Morquio A syndrome; OMIM 253000) is a rare autosomal-recessive inherited disorder caused by *N*-acetylgalactosamine-6-sulfatase (GALNS) deficiency which leads to excessive lysosomal storage of glycosaminoglycans (GAGs), keratan sulfate (KS) and chondroitin-6-sulfate in various tissues and organs. The clinical manifestations include corneal clouding, hearing loss, valvular heart disease, systemic skeletal chondrodysplasia, malformation of the thorax that impairs respiratory function, short stature, joint abnormalities with limitations in mobility and endurance, odontoid hypoplasia and ligamentous laxity, cervical spinal instability and potentially cord compression.[1,2] The reported birth incidence of MPS IVA varies among different populations from 0.14 to 0.45 cases per 100,000 live births. In Taiwan, the birth incidence of all types of MPS was 2.04 per 100,000 live births, including 0.33 per 100,000 live births for MPS IV, accounting for 16% of all cases of MPS in Taiwan.[3] Elosulfase

* Corresponding author. Department of Pediatrics, Mackay Memorial Hospital, No.92, Sec. 2, Chung-Shan North Road, Taipei 10449, Taiwan. Fax: +886 2 2543 3642.
E-mail address: 4535lin@gmail.com (S.-P. Lin).
[1] These authors contributed equally to this work.

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alfa (Vimizim®; BioMarin Pharmaceutical Inc., Novato, CA, USA) is a recombinant human GALNS associated with increased endurance, reduced urine KS and acceptable safety profile, and it has been approved as enzyme replacement therapy (ERT) for MPS IVA.[4,5] However, information regarding the long-term outcomes of ERT with elosulfase alfa for Taiwanese patients with MPS IVA is limited.

2. Case series

We reviewed six Taiwanese patients with MPS IVA (four males and two females; age range, 1.4—25.8 years) treated with weekly intravenous infusions of elosulfase alfa (2.0 mg/kg) at Mackay Memorial Hospital, Taipei, Taiwan. A set of biochemical and clinical assessments were performed to evaluate the safety and efficacy of ERT every 3 months (Supplementary Table 1). The age at a confirmative diagnosis in these six patients ranged from 0.4 to 4.5 years. After ERT for 4.0—6.5 years, a mean reduction in urinary GAGs of 26% (μg/mg creatinine) (226.7 vs. 168.0) and a 60% reduction in urinary KS (μg/mL) (142.3 vs. 57.1) were recorded in the six patients.[6] The mean height *z* score at baseline was −7.2 compared with −8.0 after ERT. The mean 6-minute walk test (6MWT) distance of four patients increased from 201.1 to 259.0 m, and the mean 3-minute stair climb test (3MSCT) increased from 78.8 to 129.5 stairs. Pulmonary function tests of four patients showed both stabilized forced vital capacity (FVC) (0.68 ± 0.15 vs. 0.68 ± 0.08 L) and forced expiratory volume in 1 s (FEV_1) (0.59 ± 0.12 vs. 0.62 ± 0.10 L). After ERT, echocardiography of the six patients showed a decrease in mean left ventricular mass index (LVMI) *z* score from 1.14 to 0.77, a decrease in mean interventricular septum thickness in diastole (IVSd) *z* score from 1.95 to 1.88, and a decrease in mean left ventricular posterior wall thickness in diastole (LVPWd) *z* score from 0.33 to −0.35. For two patients who started ERT at a younger age (1.4 and 2.8 years, respectively), *z* scores for LVMI, IVSd, and LVPWd all decreased after ERT. Among these six patients, only one (No. 3) developed mild urticaria during ERT. However, with premedication with oral antihistamines and steroids, this patient was able to tolerate the ERT.

3. Discussion

This is the first report regarding the clinical benefits and safety of long-term ERT in Taiwanese patients with MPS IVA. To the best of our knowledge, these six cases are the only MPS IVA patients in Taiwan who are currently receiving ERT. Our review demonstrated both biochemical and clinical functional improvement in all six patients after 4.0—6.5 years of ERT. In our series, elosulfase alfa reduced urinary GAGs and KS, improved endurance as measured by the 6MWT and 3MSCT, stabilized pulmonary function, and had an acceptable safety profile. MPS IVA has a chronic progressive nature. Hendriksz et al.[5] reported that ERT with elosulfase alfa improved endurance over 120 weeks. Compared with the gradual decline in corresponding subpopulations of untreated patients in the MorCAP natural history study, the improvement and subsequent stabilization of 6MWT and 3MSCT results showed significant alterations in the expected natural course of these patients. In our study, elosulfase alfa also appeared to be effective in reducing cardiac hypertrophy, and may have led to better results when started at a younger age.[7] The age at a confirmative diagnosis of these six patients ranged from 0.4 to 4.5 years. However, ERT with elosulfase alfa was not available until they were 1.4—25.8 years old. As the patients grew older, GAG accumulation in all tissues and organs may have resulted in irreversible damage refractory to ERT. Since an early diagnosis and timely ERT may contribute to a better clinical outcome, understanding and identifying the early manifestations of this disease is of major importance.

Conflict of interest

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

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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.2018.08.005.

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