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Long-term galsulfase enzyme replacement therapy in Taiwanese mucopolysaccharidosis VI patients: A case series

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ABSTRACT

Background: Information regarding the long-term outcome of enzyme replacement therapy (ERT) with recombinant human *N*-acetylgalactosamine 4-sulfatase (rhASB, galsulfase, Naglazyme®, BioMarin Pharmaceutical Inc.) for Taiwanese patients with mucopolysaccharidosis (MPS) VI is limited.
Methods: Nine Taiwanese patients with MPS VI (4 males and 5 females; age range, 1.4 to 21.1 years) treated with weekly intravenous infusions of galsulfase (1.0 mg/kg) in 5 medical centers in Taiwan were reviewed. A set of biochemical and clinical assessments were evaluated annually.
Results: After 6.2 to 11.2 years of galsulfase treatment, 6 patients experienced improvement over baseline in the 6-minute walk test by a mean of 150 m (59% change over time), and 3 patients also increased the 3-minute stair climb test by a mean of 60 steps (46%). In a manual dexterity test, 3 patients decreased the time required to pick up 10 coins and put the coins into a cup by 15 s (33%). Shoulder range of motion in all 9 patients improved, and Joint Pain and Stiffness Questionnaire scores improved by 0.42 points (21%). Four patients showed improved pulmonary function. Five patients had positive effects on cardiac-wall diameters. Four patients had improved cardiac diastolic function. Liver and spleen sizes as measured by abdominal ultrasonography remained the same or decreased in all 9 patients. However, the severity degree of valvular stenosis or regurgitation did not show improvement despite ERT. A mean overall 69% decrease in urinary glycosaminoglycan (GAG) excretion indicated a satisfactory biomarker response.
Conclusions: Long-term ERT was beneficial and safe for Taiwanese patients with MPS VI. This treatment reduced urinary GAG and had positive effects on a wide range of clinical functional assessments including endurance, mobility, joint function, pulmonary function, liver and spleen size, cardiac hypertrophy and diastolic dysfunction.

Abbreviations: MPS, mucopolysaccharidosis; ASB, *N*-acetylgalactosamine 4-sulfatase; GAG, glycosaminoglycan; ERT, enzyme replacement therapy; Galsulfase, recombinant human *N*-acetylgalactosamine 4-sulfatase; *Z* score, standard deviation score; 6MWT, 6-minute walk test; 3MSCT, 3-minute stair climb test; FVC, Forced vital capacity; FEV_1, forced expiratory volume in 1 s; E/A, ratio between early and late (atrial) ventricular filling velocity; LVMI, left ventricular mass index; IVSd, interventricular septum thickness in diastole; LVPWd, left ventricular posterior wall thickness in diastole; LVM, left ventricular mass; BMD, bone mineral density; HAZ, height-for-age; DXA, dual energy x-ray absorptiometry; PTA, pure-tone audiometry; AC, air conduction; BC, bone conduction; HAQ, Health Assessment Questionnaire; CHAQ, Childhood Health Assessment Questionnaire.

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1. Introduction

Mucopolysaccharidosis VI (MPS VI; OMIM #253200, Maroteaux-Lamy syndrome) is an autosomal recessive disorder caused by lysosomal enzyme *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B, or ASB) deficiency with a clinical spectrum of mild to severe phenotypes. Decreased ASB enzyme activity leads to impaired degradation of the glycosaminoglycan (GAG) dermatan sulfate. The resulting GAG accumulation in the lysosomes of connective tissue causes a chronic progressive disorder characterized by significant functional impairment and shortened lifespan. Patients with rapidly progressing disease often have coarse face, short stature, joint and skeletal deformities, corneal clouding, recurrent respiratory and ear infections, compromised cardiovascular and pulmonary function, spinal cord compression, and ultimately become wheelchair-bound or bedridden with early mortality in the late teens to early twenties. Although patients with MPS VI typically do not have neurocognitive impairment, their learning and development could be affected by physical limitations, particularly with vision deficit and hearing loss [1,2]. MPS VI is an ultra-rare genetic disorder with a reported incidence of 0.14–0.38/100,000 live births [3]. Previous human clinical trials have demonstrated that enzyme replacement therapy (ERT) for MPS VI with recombinant human *N*-acetylgalactosamine 4-sulfatase (rhASB; galsulfase; Naglazyme®) significantly improves physical endurance, reduces urinary GAG, and has an acceptable safety profile [4–8]. Giugliani et al. [9] conducted a Resurvey Study of MPS VI patients to obtain 10-year follow-up data that included medical histories and clinical assessments ($n = 59$), and survival status over 12 years ($n = 117$). They reported that long-term ERT resulted in improvements in pulmonary function and endurance, stabilized cardiac function and increased survival. However, information on the long-term effects of ERT in Asian MPS VI patients is limited. In this study, we report our findings on the long-term effects of galsulfase treatment in 9 Taiwanese MPS VI patients.

2. Patients and methods

2.1. Selection of subjects

Data from 9 patients with MPS VI (4 males and 5 females) who received, or are currently receiving, ERT with galsulfase (1.0 mg/kg/week intravenously) between March 2004 and December 2015 in 5 medical centers in Taiwan, were retrospectively reviewed. Medical institutions included Mackay Memorial Hospital, China Medical University Hospital, National Cheng Kung University Hospital, Changhua Christian Hospital, and National Taiwan University Hospital. The patients' ages at which treatment was begun ranged widely from 1.4 to 21.1 years, and the duration of therapy ranged from 6.2 to 11.2 years. We routinely assessed a set of biochemical and clinical responses each year during treatment. Written informed consent for ERT was obtained from a parent for children and from patients over 18 years. The study was approved by the ethics committee of Mackay Memorial Hospital, Taipei, Taiwan.

2.2. Baseline and follow-up biochemical and clinical evaluation

All patients had clinical manifestations of MPS VI, and diagnosis was confirmed by two-dimensional electrophoresis of urinary GAGs and ASB enzyme assay in serum, leukocytes and/or fibroblasts [10]. Each patient had a mutational analysis performed [11]. Height and weight were transformed to standard deviation scores (*z* scores) on the basis of a standard growth table for the Taiwanese population [12]. Prior to each intravenous infusion, patients were pre-medicated with diphenhydramine (0.5 mg/kg body weight). Galsulfase was diluted in 0.9% saline and administered at 1.0 mg/kg over 4 h once weekly according to product label administration instructions. Urinary GAGs and white blood cell ASB levels were measured at baseline and every year during treatment. Evaluation of mobility and physical function was performed at baseline and every year subsequently. Clinical functional assessments varied somewhat by institution and may have included a 6-minute walk test (6MWT), 3-minute stair climb test (3MSCT), joint range of motion, coin picking-up test, spirometry, echocardiography, abdominal ultrasonography, bone mineral density, and hearing test. Range of motion of the shoulders was measured with a goniometer by physical therapists. The goniometer assessments included both active and passive shoulder flexion, extension, and lateral rotation, and were consistent at all centers. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were evaluated by standard spirometry techniques according to American Thoracic Society guidelines [13,14]. The cardiac ultrasound systems used were Philips Sonos 5500/7500 System (Andover, MA, USA), equipped with electronic transducers from 2 to 8 MHz. Diastolic and systolic diameters were measured using the M-mode, and the systolic function of the left ventricle was evaluated through the ejection fraction obtained by the Teichholz method [$V = 7D^3 / (2.4 + D)$, where V = LV volume and D = LV diameter] [15]. Diastolic filling was established using the E/A ratio by measuring mitral-inflow as determined by pattern-peak early filling (E) and late filling (A) velocities [16]. A reversed E/A ratio (E/A ratio < 1) was considered diastolic dysfunction. Severity of valvular stenosis and regurgitation were estimated and graded on the following scores: 0 (none), 1 (mild), 2 (moderate), and 3 (severe) based on the European Society of Cardiology/American Society of Echocardiography guidelines [17,18]. The data of left ventricular mass index (LVMI), the thicknesses of the interventricular septum diameter in diastole (IVSd), and the thicknesses of the left ventricular posterior wall diameter in diastole (LVPWd) obtained by serial echocardiographic assessments [19] were recorded. These values were compared with normal values according to the study of Kampmann et al. [20]. Left ventricular mass (LVM) was calculated according to the American Society of Echocardiography simplified cubed equation. LVM was indexed (LVMI) by $height^{2.7}$ to normalize heart size to body size. The LVMI was also calculated using the Devereux formula and indexed by body surface area with normal values according to the report of Poutanen et al. [21]. All above echocardiographic values were transformed into a *z* score derived by subtracting the mean reference value from an individual observed value, and then dividing the difference by the standard deviation from the reference value. *Z* score > 2 was considered abnormal. Abdominal ultrasonographic examinations were performed using high-resolution B-mode ultrasonography (SA-700A, Toshiba, Tokyo, Japan) with a 3.5-MHz curved array transducer. Liver size and spleen size were measured in comparison with the normal reference values for different body height of children [22]. The absolute value of bone mineral density (BMD) and height-for-age (HAZ) adjusted BMD *z* scores were evaluated by dual energy x-ray absorptiometry (DXA) as previously described [23]. The assessment of hearing loss by pure-tone audiometry (PTA) was performed as previously described [24] with the collection of the values of air conduction (AC), bone conduction (BC), and air-bone gap.

Height was used as a covariate for normal values. Joint Pain and Stiffness Questionnaire scores (Disability Index) were assessed by an analog scale based on the Health Assessment Questionnaire (HAQ) [25,26] for patients who were >18 years of age or Childhood Health Assessment Questionnaire (CHAQ) [27] completed by a parent or caregiver for younger patients. In 3 cases a manual dexterity test was performed where the patient was asked to pick up 10 coins and place them in a cup while their elbow was allowed to rest on the table; the time required to complete the task was recorded. All 9 patients were assessed using the Disability Index, with an overall score that addresses eight categories of activity, including dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Adverse events were recorded as previously described [28].

2.3. Data analysis

The latest results of examinations for these 9 patients receiving ERT were compared with baseline data. Descriptive statistics were