MEDICAL PRACTICE

Enzyme replacement therapy for mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): experience in Hong Kong

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Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) is a very rare inherited lysosomal storage disease. We evaluated the efficacy and safety of weekly infusions of recombinant human arylsulfatase B as enzyme replacement therapy for two patients in whom this condition was advanced. The primary outcome variables were the distance walked in a 6-minute walk test, forced vital capacity, and ejection fraction. The secondary outcome variables were the number of stairs climbed in a 3-minute stair climbing test, joint mobility, urinary glycosaminoglycan excretion, auto–continuous positive airway pressure study and liver size. After 24 weeks of treatment, patient A walked 40 m (36%) and patient B walked 66 m (58%) more in the walk test than at baseline. After 48 weeks, in patient A the corresponding improvements were 142 m (129%) in the walk test and 33 stairs (60%) in the 3-minute stair climbing test, and in patient B the respective improvements were 198 m (174%) and 77 stairs (140%). There was a significant decline in urinary glycosaminoglycan excretion and improvement in range of motion of joints in both patients. The auto–continuous positive airway pressure study revealed improvements in patient A, while other efficacy variables remained static. There were no drug-related adverse events or allergic reactions reported during and after the infusions of recombinant human arylsulfatase B. Recombinant human arylsulfatase B significantly improves endurance and reduces urinary glycosaminoglycan excretion. The drug is generally safe and well tolerated.

Key words
Enzyme replacement therapy; Mucopolysaccharidosis VI; N-acetylgalactosamine-4-sulfatase; Recombinant proteins; Walking

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Introduction

Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome) is a lysosomal storage disease caused by deficient activity of the enzyme N-acetylgalactosamine 4-sulfatase (arylsulfatase B). The stepwise degradation of the glycosaminoglycan (GAG) dermatan sulfate is impaired and partially degraded GAG accumulates intracellularly in lysosomes, causing a chronic progressive disorder with multi-organ dysfunction.[1] This disease is a heterogeneous condition. The rapidly advancing form is characterised by growth failure, skeletal and joint deformities, coarse facial features, upper airway obstruction, and recurrent ear infections. Other clinical manifestations include hepatomegaly, cardiopulmonary disease, blindness, hydrocephalus and spinal cord compression. Affected individuals often become wheelchair bound or bedridden and die in the second decade or third decade from infections, complications related to surgical procedures or cardiopulmonary diseases. Individuals with the slowly progressive form may live longer. In both forms, the disease inevitably leads to significant functional impairment and reduced lifespan, although intelligence is usually preserved.[2]

Being a very rare metabolic disease, MPS VI is inherited in an autosomal recessive pattern, with an estimated frequency of 1 in 238 095 to 1 in 1 300 000 live births. In Taiwan the estimated frequency is 1:833 000.[3] In the past, there was no satisfactory treatment for MPS VI, so most patients received symptomatic treatment as their only form of care although a few benefited from bone marrow transplantation.[4,5] With the successful completion of clinical trials on enzyme replacement therapy (ERT) for MPS VI, Naglazyme (galsulfase; BioMarin Pharmaceutical Inc., Novato [CA], US) received marketing approval from the United States Food and Drug Administration and European Medicines Agency for the treatment of MPS VI patients in 2005 and 2006, respectively. It has been granted orphan drug designation in the US and internationally. Human clinical studies have demonstrated that weekly infusion of 1 mg/kg body weight (BW) of Naglazyme were well tolerated, produced a rapid reduction in urinary GAG levels, improved endurance based on walking and stair climbing tests, increased the range of joint movement (ROM) and improved respiratory function test.[6-9] This has generated hope for future MPS VI patients.

醫治黏多糖貯積症VI型（馬洛托–拉米氏症）的酶替代療法：香港經驗

黏多糖貯積症VI型（馬洛托－拉米氏症，簡稱MPS）屬溶酶體貯積病，是一種罕見的遺傳性疾病。本港有兩名黏多糖貯積症VI型重型患者，每星期接受人類重組芳基硫酸酯酶B（rhASB）注射的替代療法。本文評估此療法的效用及安全性，量度的主要結果變量有六分鐘行走測試、用力肺活量及射血分數。次要結果變量有三分鐘登樓測試、關節靈活性、尿液糖胺聚糖、自動持續正壓通氣測試及肝臟的大小。六分鐘行走測試結果方面，兩名病人接受治療24星期後，病人甲較基值多走40米（36%），病人乙則多走66米（58%）；48星期後，病人甲較基值多走142米（129%），病人乙則多走198米（174%）。三分鐘登樓測試方面，病人接受治療48星期後，病人甲較基值多登33樓級（60%），病人乙則多登77樓級（140%）。兩名病人的尿液糖胺聚糖水平均顯著回落，關節靈活性亦有所改善。病人甲的自動持續正壓通氣測試有改善，而其他療效指標亦保持穩定。病人於治療過程中及治療後都沒有出現與藥物有關的不良或敏感反應。rhASB明顯改善病人的持久力及減低尿液糖胺聚糖水平，這種藥物大致上安全，病人耐受性亦良好。

Methods

Patients

Two Chinese male patients with MPS VI who had clinical manifestations of the disease were studied. Their diagnoses were confirmed by mutational analysis for patient A[10] and enzyme study for patient B, and they were considered to be suffering from the rapidly progressive form. They were considered not suitable for bone marrow transplantation, because of the advanced stage of the disease at presentation (patient A) and there being no suitable donor (patient B). Patient A was blind due to optic atrophy and hence corneal transplant was not indicated. Patient B had a craniectomy and C1-C3 laminectomy (for cord compression) performed 2 months before the initiation of ERT. Their demographic data and associated morbidities are summarised in Table 1. The study was approved by the hospital Ethics Committee and written consent was obtained from the parents of the patients before enrolment.

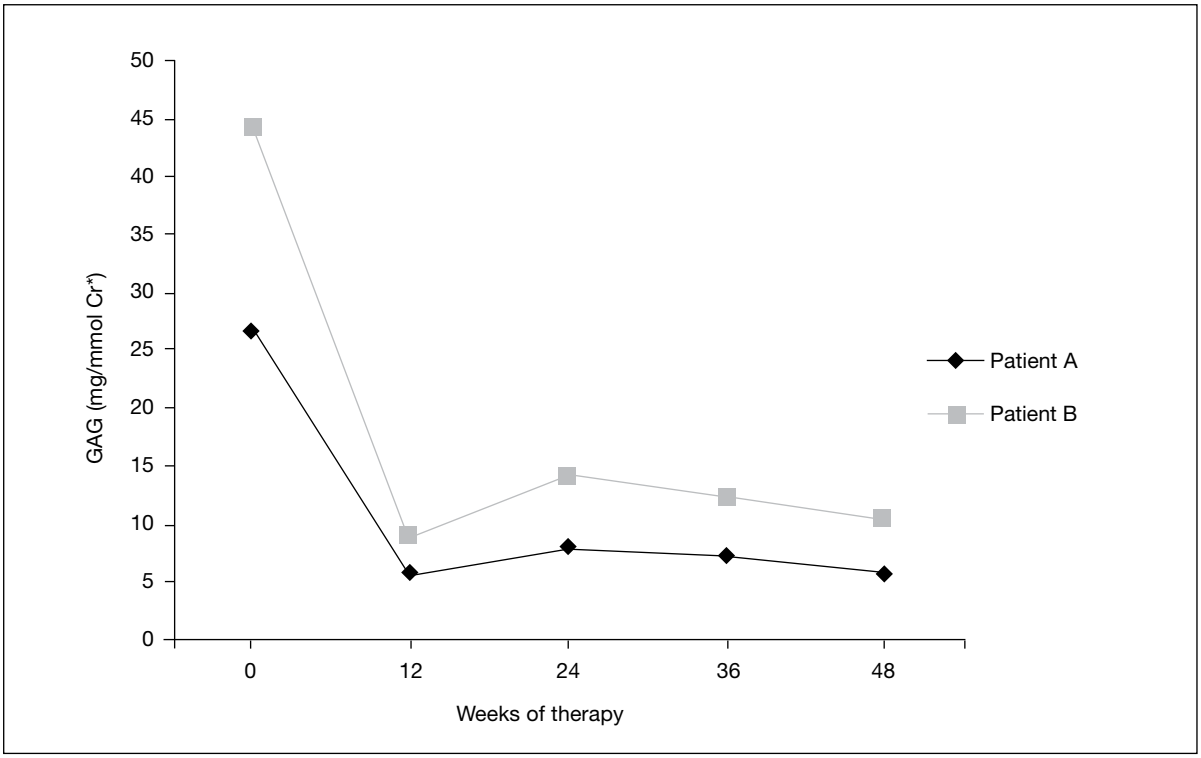
Study design

This was a prospective evaluation of the efficacy and safety of recombinant human arylsulfatase B (rhASB) in patients with rapidly progressive MPS VI disease. After initial assessment, each patient received weekly intravenous (1 mg/kg BW) rhASB of Naglazyme, which was provided through a 1-year sponsorship from BioMarin Pharmaceutical Inc, Novato (CA). Also, the Expert Panel on ERT for Rare Metabolic Diseases of the Hong Kong Hospital Authority endorsed this form of in-patient therapy for the two selected patients. About 30 minutes prior to the start of each

TABLE 1. Demographic data and associated morbidities of the patients

Demographics/morbidities	Patient A	Patient B
Age at initiation of enzyme replacement therapy (years)	17.2	16.8
Sex	Male	Male
Ethnicity	Chinese	Chinese
Weight (percentile) z score	37 kg (9 kg <3rd) -2.2	25 kg (20 kg <3rd) -3.3
Height (percentile) z score	115 cm (43 cm <3rd) -9.3	107 cm (50 cm <3rd) -10.7
Head circumference (percentile)	60 cm (0.5 cm >97th)	55 cm (25th)
Mutational analysis	• F399L/Y255X • Father is a carrier of Y225X • Mother is a carrier of F399L[10]	• Heterozygous for A372G, another mutation was not identified • Mother is a carrier of A372G • No mutation was identified in the father
Associated severe morbidities	• Blind since 11 years old • Bilateral hearing impairment, on hearing aids since 12 years old • Obstructive sleep apnoea syndrome, on CPAP* during sleep since 13 years old • Epilepsy on anticonvulsants since 12 years old • Painful umbilical hernia measured 6 cm in diameter, required repair at 16 years old • Arrested hydrocephalus • Asymptomatic cervical cord compression • Thickened mitral, aortic, and tricuspid valves since 12 years old	• Cervical cord compression with craniectomy and laminectomy at 16 years old • Tracheostomy in situ for upper airway obstruction and failed decannulation after general anaesthesia • Corneal clouding with corneal transplant at 18 years old • Bilateral hearing impairment (no need for hearing aids)
Intelligence	Normal	Normal

* CPAP denotes continuous positive airway pressure



* Cr denotes creatinine

FIG 1. Urinary glycosaminoglycan (GAG) excretion with recombinant human arylsulfatase B treatment in patients A and B

infusion, each patient was pre-medicated with a non-sedating antihistamine (cetirizine) and an anti-pyretic (paracetamol) to reduce infusion-associated reactions. The rhASB was diluted in 0.9% saline and administered over 4 hours; 2.5% of the dose was administered in the first hour and the remaining (97.5%) over the next 3 hours. Vital signs (heart rate, respiratory rate, oxygen saturation [by pulse oximetry], and body temperature) were monitored prior to infusion, every hour during the infusion, at infusion completion and prior to discharge.

Biochemical and clinical evaluations

Patients were assessed clinically every 12 weeks. A complete blood count, and renal and liver function tests were performed at baseline and 48 weeks. Urine was obtained every 12 weeks to determine total GAG, a surrogate marker for the extent of clearance of these compounds from lysosomal storage. The measurement was based on the reaction of the basic metachromatic dye dimethylmethylene blue (DMB) with sulfated GAGs. The colour of DMB reagent changes from blue to red-violet when mixed with sulfated GAGs in urine samples and is measured quantitatively at 520 nm by means of a spectrophotometer. The 6-minute walk test (6MWT) was performed according to the published guidelines.[11] Patients were instructed to walk unassisted as far as possible in 6 minutes but were allowed to rest when needed. The wall or handrails were allowed as guides only. The 3-minute stair climbing test (3MSC) was not a standardised test; the patients were instructed to climb as many stairs as possible in a 3-minute period and were allowed to rest or use handrails. Each of these endurance tests was performed twice during each assessment, and the better results were adopted for analysis. The ROM was measured with a goniometer. The 6MWT, 3MSC, and ROM tests were supervised by a physiotherapist at baseline and every 24 weeks.

Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were evaluated by means of standard spirometry, at baseline and every 24 weeks. Auto–continuous positive airway pressure (CPAP) titration study, standard 12-lead electrocardiography, and two-dimensional Doppler echocardiogram were performed at baseline, 24 weeks, and 48 weeks. Liver and spleen size were assessed by ultrasonography at baseline and at 48 weeks.

Results

Safety

Both patients completed 48 weeks of treatment. No adverse events or allergic reactions were reported. No significant abnormal haematology, renal or liver function tests were noted.

TABLE 2. Endurance parameters based on distance walked and number of stairs climbed with recombinant human arylsulfatase B treatment and compared with the report from Harmatz et al[7]

	Baseline	24 weeks*	48 weeks*
6-Minute walk test (m)			
Patient A	110	150 (36%)	252 (129%)
Patient B	114	180 (58%)	312 (174%)
Harmatz et al[7] (mean ± standard deviation)	152 ± 79	216 ± 109	244 ± 103
3-Minute stair climb test			
Patient A	55	55	88 (60%)
Patient B	55	55	132 (140%)
Harmatz et al[7] (mean ± standard deviation)	50 ± 30	98 ± 63	111 ± 65

* Numbers in parentheses refer to percentage increases relative to baseline

TABLE 3. Ranges of joint motion (degrees) in patients A and B at baseline, 24 and 48 weeks after starting treatment

		Patient	Baseline		24 Weeks		48 Weeks	
			Right	Left	Right	Left	Right	Left
Shoulder	Flexion	A	80	97	95	75	95	100
		B	50	60	90	95	100	100
	Abduction	A	90	100	85	80	100	100
		B	65	55	100	90	105	100
	Lateral rotation	A	70	65	45	45	90	90
		B	-	-	45	40	60	45
	Medial rotation	A	30	75	50	50	50	60
		B	-	-	70	90	70	90
Elbow	Flexion - extension	A	105-35	105-20	105-35	105-20	105-10	85-10
		B	90-30	100-35	110-20	110-30	120-10	120-15
Forearm	Supination	A	90	45	80	45	90	90
		B	-	-	45	45	90	45
	Pronation	A	0	80	45	80	80	80
		B	-	-	80	80	80	80
Hip	Flexion	A	45	60	90	90	90	100
		B	100	100	90	90	110	110
Knee	Flexion - extension	A	80-0	85-0	100-0	90-0	100-0	90-0
		B	110-0	110-0	100-0	110-0	110-0	110-0

Efficacy

Urinary GAG excretion levels (mg/mmol creatinine [Cr]) over the 48 weeks are shown in Figure 1. In patient A, at baseline the value was 26.7 and dropped to 5.5 at 12 weeks, and in patient B corresponding values were 44.3 and 8.9. Thus, urinary GAG excretion had decreased significantly (>80% in both patients) by 12 weeks. Moreover, the extent of excretion remained low though slightly above the reference range (<4.9 mg/mmol Cr), after 24 and 48 weeks of treatment.

The results of the 6MWT, 3MSC, and ROM tests are presented in Tables 2 and 3. At baseline, patient A could walk 110 m and patient B could walk 114 m in 6 minutes, and after 24 weeks of treatment they could walk 40 m (36%) and 66 m (58%) more, respectively. Additional improvements were evident after receiving 48 weeks of rhASB; patient A walked 142 m (129%) more than at baseline, while patient B walked 198 m (174%) more. The stair climbing test had been used historically as an integral part of preoperative assessment to guide residual lung function in patients who underwent lung resection. Both patients could climb 55 stairs in 3 minutes at baseline and after 24 weeks of ERT. After 48 weeks, patient A could climb 33 stairs (60%) more and patient B 77 stairs (140%) more. A comparison with the results of the phase 2

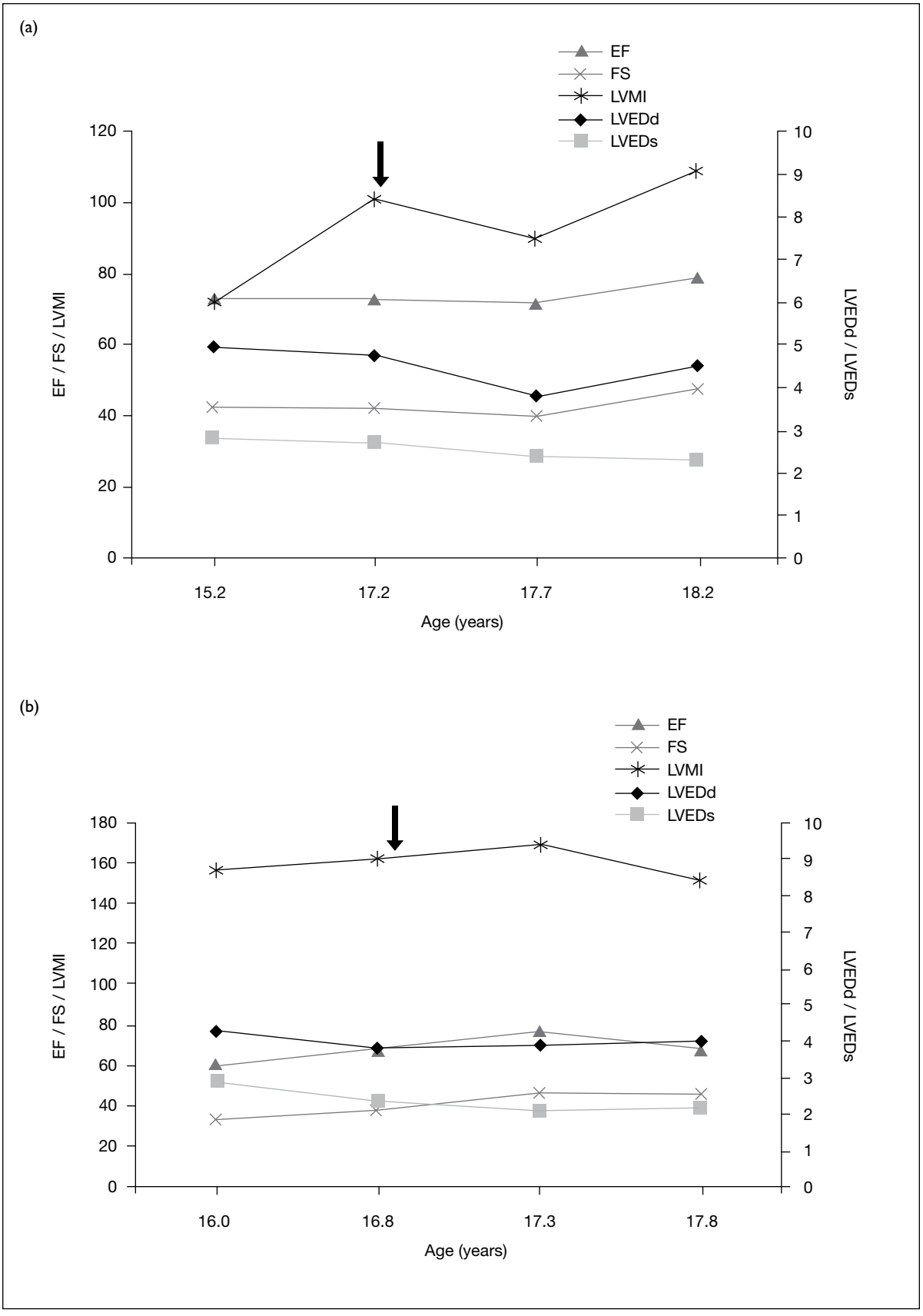


FIG 2. Echocardiographic findings of (a) patient A and (b) patient B; arrows denote initiation of recombinant human arylsulfatase B treatment

EF denotes ejection fraction (%), FS fractional shortening (%), LVMI left ventricular mass index (g/m^2), LVEDd left ventricular end diastolic diameter (cm), and LVEDs left ventricular end systolic diameter (cm)

clinical trial[7] are also shown in Table 2. Improvements in ROM were evident in both patients as shown in Table 3.

Both patients had restrictive airway diseases. At baseline, patient A's FVC and FEV_1 were 0.75 L (54% of predicted FVC) and 0.50 L (40% of predicted FEV_1), respectively; his FEV_1/FVC ratio was 67%, suggestive of obstructive airway disease. Patient B's FVC and FEV_1 were 0.45 L (66% predicted FVC) and 0.38 L (62% predicted FEV_1), respectively; his FEV_1/FVC ratio was 85%. Both also suffered from obstructive sleep apnoea diagnosed by sleep studies and required CPAP during sleep. The sleep study in patient A (aged 12 years) revealed an Apnoea Index of 5.5, an Apnoea Hypoxic Index of 18.8, and a desaturation index of 25.4 with a minimal oxygen saturation (SaO_2) of 62%. For patient B, his sleep study (aged 14 years) showed corresponding values of 4.8, 9.0, and 37.6 with a minimal SaO_2 of 78%. In patient A, the FVC and FEV_1 remained static throughout the assessment periods while the auto-CPAP study showed a decrease by 21.6% (19.9 mm Hg at baseline vs 14.5 mm Hg at 24 weeks and 15.6 mm Hg at 48 weeks). Lung function tests and sleep study could not be performed in patient B after ERT because of failure of decannulation, following cervical cord decompression and the presence of a tracheostomy tube.

Both patients had valvular heart diseases and hypertrophic cardiomyopathy. The left ventricular mass index (LVMI) was 101 g/m^2 and 163 g/m^2 for patient A and B, respectively. Despite this, their cardiac contractility was good with normal ejection fraction (EF) and fractional shortening (FS). After 48 weeks of treatment, there were no significant changes in EF, FS, left ventricular end diastolic diameter, left ventricular end systolic diameter, and LVMI (Fig 2).

The livers and spleens of both patients were considered normal in size by ultrasonography although in both patients the livers were palpable 6 cm below the right costal margin at baseline. Clinically and by ultrasonographic assessment, the liver and spleen sizes of both patients had remained static at 48 weeks.

Discussion

The ability to walk for a distance is a quick, easy, and inexpensive way to assess an individual's physical function. It is also an important component of quality of life as it reflects the ability to undertake daily activities.[12] The 6MWT has been frequently used to measure outcomes before and after treatment in patients with moderate-to-severe heart and lung diseases, and has been shown to accurately predict morbidity and mortality in cardiopulmonary diseases.[13] With regard to impaired endurance, our patients were very similar to those enrolled in earlier phase 2 and 3 clinical trials. Both patients could walk unaided at least 1 m but less than 250 m in 6 minutes. Height-specific reference values for heights of 120 to 180 cm for the 6MWT in healthy children aged between 7 and 16 years are available for comparison. However, comparisons with normal healthy children were not appropriate for our patients as both were shorter than 120 cm.[12] Regarding the 3MSC as a measure of endurance, Bolton et al[14] had demonstrated a strong relationship of 3MSC to pulmonary function tests, including FVC and FEV_1, although the test was also affected by other parameters, including cardiovascular status, cooperation, and determination. The 6MWT and 3MSC were considered the most clinically meaningful and sensitive measures of functional improvement, and the results of our study indicated that there were significant functional improvements after ERT. Greater improvement was observed in patient B than in patient A (174% vs 129% for 6MWT and 140% vs 60% for 3MSC, after 48 weeks of treatment). The improvement in exercise endurance seen in patient B could also be attributed to successful cervical cord decompression performed just before initiation of ERT.

A survey of 121 patients with MPS VI showing high urinary GAG values (>22.6 mg/mmol Cr) were associated with an accelerated clinical course that comprised endurance, pulmonary function, growth, and ROM. The results also showed that most MPS VI individuals with urinary GAG levels higher than 11.3 mg/mmol Cr do not live beyond the age of 20 years.[15] Both of our patients were suffering from the rapidly progressive form and had high urinary GAG excretion values before treatment. Thus, they were unlikely to live beyond the age of 20 years without specific treatment. With ERT, their urinary GAG levels decreased rapidly and after 48 weeks of treatment remained within 2-3–fold of the reference range.

The auto-CPAP titration study performed was not manually titrated and might carry some limitations. For example, leakage of air around the mask required a higher pressure generated by the computer.

Several other measurements obtained in the course of this study did not show any clinically meaningful improvement within 48 weeks of treatment. In terms of FVC and FEV_1, lung function remained static in patient A, which might be due to the small lung volumes, the profound short stature, and malformed skeletal system. Another study also showed that FVC and FEV_1 showed little change from baseline during the first 24 weeks of ERT, but after 96 weeks they had increased by 11% and 17%, respectively.[16] The livers were palpable in both patients but were of normal size by ultrasonography. This might be explained by the small thorax and abdomen;

no further deterioration in these parameters despite a progressive disease may already indicate treatment effectiveness. Optimally, a quality-of-life score could also be included as one of the efficacy variables.

Because Naglazyme is administered intravenously, it may not reach poorly vascularised sites such as the cornea, bone, and joint cartilage. Thus, patient B received a corneal transplant 8 months after initiation of ERT, because of impaired vision due to severe corneal clouding. Moreover, ERT may not prevent or revert neurological complications because the blood-brain barrier prevents delivery of the enzyme into the central nervous system. The management of these complications is challenging as major surgical procedures like cervical cord decompression and meticulous postoperative rehabilitation are often required. Long-term data regarding the prevention of these complications by ERT are still lacking. A recent sibling controlled study demonstrated that ERT is safe when started at an early age. It is effective at preventing the development of significant pathological changes (scoliosis) associated with MPS VI, and preserves normal joint movement range, cardiac valve function, and facial appearance.[17]

Enzyme replacement therapy is extremely expensive and requires lifetime weekly intravenous infusions. It also carries a risk of allergic reactions and may require a central venous access port for infusion, with all its inherent risks of infection including endocarditis. The risk is especially significant in patients with valvular heart disease. There is also an increased anaesthetic risk when attaining central venous access.[18] Physicians managing these patients have to balance the risks. In view of valvular disease in our two patients, we preferred access via peripheral venous catheters and we were able to administer the drug weekly. Interestingly, venous catheter insertion was very difficult in the initial period because the skin was very thick, but after 24 weeks we were able to insert peripheral venous catheters without much difficulty as the skin had become thinner.

Upon obtaining compassionate-free drug for 1 year from BioMarin Pharmaceutical Inc, our two MPS VI patients requested commencement of ERT. The Expert Panel on ERT for Rare Metabolic Diseases of the Hong Kong Hospital Authority met and discussed their applications for such support. As our patients did not satisfy some of the criteria for initiation of ERT recommended by the Expert Panel such as reasonable evidence of intact survival benefits, no or minimal major organ damage and no major debility at start of treatment as well as early presentation, it was agreed to accept the free drugs offered by the drug company. Accordingly, the two applicants were entered into this 1-year research programme using Naglazyme as an ERT, but with exit criteria. The patients had to be closely monitored during this 1-year research programme, and the treatment was to be withheld if the patients failed to attend three or more consecutive scheduled infusions without valid reasons, or were absent for more than 10% of sessions in any 6-month treatment period. Treatment with Naglazyme ERT would also be terminated according to the following criteria: (a) development of a life-threatening complication unlikely to benefit from further ERT (eg severe infusion-associated reactions not controlled by other means); (b) failure to comply with the recommended dosage regimen or follow-up requirements including investigations; (c) evidence of disease progression despite regular therapy as indicated by further deterioration in % predicted FVC, EF, and distance walked in the 6MWT, unless there was a specific complication amendable to surgery (eg cardiac valve lesion or cervical myelopathy).

Upon expiry of the 1-year research period, patients were to be reassessed for continuation of the ERT, which would be continued if found effective in preventing disease progression. This was in line with the recommendation by the Hospital Authority Clinical Ethics Committee that if patient could not afford the financial burden of the therapy, it was appropriate to provide financial support for those in whom ERT was considered beneficial. The annual financial implications would be in the order of three to four million Hong Kong dollars per patient. To meet the increasing demand of ERT for MPS and other rare diseases, the Government of the Hong Kong Special Administrative Region announced incorporation of enzyme replacement into the Hospital Authority drug formulary in its budget for 2010-2011 and allocated additional resources for this expensive medication. As this study demonstrates that Naglazyme as ERT was safe and beneficial for our patients, approval has been obtained from the Expert Panel to continue ERT for both of them. As ERT is very expensive, significant clinical improvement such as prolonged life expectancy has to be expected to justify such public funding. Being parameters for continuation of treatment, cardiopulmonary function should be closely monitored.

Conclusion

Naglazyme as ERT significantly improved endurance based on the 6MWT and 3MSC. It also reduced urinary GAG excretion within 12 weeks. There were mild-to-moderate improvements in the ROM after treatment. The drug is generally safe and well tolerated.

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Conflict of interests

BioMarin supplied the rhASB used in this study but did not have a role in the study design, collection or interpretation of data. None of the authors have received any payment from the company.

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