



Enzyme replacement therapy for Mucopolysaccharidosis Type I among patients followed within the MPS Brazil Network

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Abstract

Mucopolysaccharidosis type I (MPS I) is a rare lysosomal disorder caused by deficiency of alpha-L-iduronidase. Few clinical trials have assessed the effect of enzyme replacement therapy (ERT) for this condition. We conducted an exploratory, open-label, non-randomized, multicenter cohort study of patients with MPS I. Data were collected from questionnaires completed by attending physicians at the time of diagnosis (T1; n = 34) and at a median time of 2.5 years later (T2; n = 24/34). The 24 patients for whom data were available at T2 were allocated into groups: A, no ERT (9 patients; median age at T1 = 36 months; 6 with severe phenotype); B, on ERT (15 patients; median age at T1 = 33 months; 4 with severe phenotype). For all variables in which there was no between-group difference at baseline, a delta of $\geq \pm 20\%$ was considered clinically relevant. The following clinically relevant differences were identified in group B in T2: lower rates of mortality and reported hospitalization for respiratory infection; lower frequency of hepatosplenomegaly; increased reported rates of obstructive sleep apnea syndrome and hearing loss; and stabilization of gibbus deformity. These changes could be due to the effect of ERT or of other therapies which have also been found more frequently in group B. Our findings suggest MPS I patients on ERT also receive a better overall care. ERT may have a positive effect on respiratory morbidity and overall mortality in patients with MPS I. Additional studies focusing on these outcomes and on other therapies should be performed.

Key words: enzyme replacement therapy, Laronidase, Mucopolysaccharidosis Type I, alpha-L-iduronidase.

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Introduction

Mucopolysaccharidoses (MPS) constitute a group of lysosomal disorders caused by 11 distinct enzyme deficiencies. In mucopolysaccharidosis type I (MPS I; OMIM 607014, 607015 e 607016), deficient activity of the enzyme alpha-L-iduronidase (EC 3.2.1.76) leads to incomplete cleavage of the glycosaminoglycans dermatan and heparan sulfate, which build up in several organ systems: respiratory, nervous, musculoskeletal, gastrointestinal (spleen and liver), and cardiovascular. Patients are affected to varying degrees and have a shortened life expectancy (Neufeld and Muenzer, 2001). From a clinical standpoint, MPS I may be divided into two phenotypes: severe, with major mental disability, and attenuated, with little or no cognitive impairment. Nevertheless, these subtypes are merely extremes of a continuous spectrum of the same condition, and there are clinical heterogeneity even within the subgroup (Moore *et al.*, 2008).

Prevalence estimates of MPS I have varied widely among studies, ranging from 0.69 to 1.66 per 100,000 population (Lowry *et al.*, 1990; Nelson, 1997; Meikle *et al.*, 1999; Baehner *et al.*, 2005; Moore *et al.*, 2008; Boy *et al.*, 2011); global data suggest the severe phenotype is the most common phenotype found (Nelson, 1997; Moore *et al.*, 2008). However, a recent study suggests that attenuated phenotype is the most prevalent in Latin America (Muñoz-Rojas *et al.*, 2011).

Management of patients with MPS I involves a multidisciplinary team of experts (Neufeld and Muenzer, 2001; Pastores and Meere, 2005; Pastores *et al.*, 2007, 2008; Muenzer *et al.*, 2009; Turra and Schwartz, 2009), and includes therapeutical strategies such as hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) with Laronidase, a polymorphic variant of the human enzyme alpha-L-iduronidase produced by DNA recombinant technology in CHO (chinese hamster ovary) cells. HSCT is indicated mainly for patients under 2 years old who present Intelligence Quotient (IQ) over 70 (Muenzer *et al.*, 2009; Giugliani *et al.*, 2010b). Laronidase is usually indicated for symptomatic patients of any age and who present at least one clinical manifestation that is known to be improved with ERT (Muenzer *et al.*, 2009; Giugliani *et al.*, 2010a,b). Laronidase was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2003, and by the Brazilian counterpart (ANVISA) in 2005. Patients for whom ERT is indicated should receive it weekly and indefinitely. However, several doubts remain as to the efficacy of this therapy (Kakkis *et al.*, 2001; Sifuentes *et al.*, 2007; Wraith *et al.*, 2007; Clarke *et al.*, 2009).

Currently in Brazil, there are no public policies for MPS disorders, and even the tests necessary for diagnosis are not available through the public health system. Therefore, in 2004, the Brazilian MPS Network (*Rede MPS Brasil*) was established. It is an integrated network of Bra-

zilian genetics centers designed to facilitate community access to diagnostic modalities and provide information on the management and treatment of MPS. The Network provides diagnostic services as requested, requiring only that samples submitted for analysis be accompanied by a signed informed consent form (obligatory) and by a completed standardized form containing clinical information on the patient (optional), which are available online at http://www.ufrgs.br/redempmsbrasil/documentos/ficha_registro_pt_br.pdf. From 2004 through July 2009, the MPS Network diagnosed 83 Brazilian patients with MPS I.

The objective of the present work was to identify clinical outcomes of ERT for MPSI, in order to establish its real benefits to patients, and to develop a better panorama of ERT for MPSI in Brazil

Subjects and Methods

This was an exploratory, open-label, non-randomized, multicenter cohort study of patients with MPS I diagnosed by the MPS Brazil Network (*Rede MPS Brasil*). The study was approved by the Hospital de Clínicas de Porto Alegre (HCPA) Research Ethics Committee, and current standards for Good Clinical Practice were followed throughout.

Between 2004 and 2009, completed standardized clinical forms from MPS Network were only submitted for 34/83 Brazilian patients. Data collected from these forms constituted the baseline dataset for patients included in this study at the time of diagnosis (time point 1, T1).

The physicians in charge of care of each of these 34 patients were invited to complete a second form which comprised the follow-up dataset for the purposes of this study (time point 2, T2, a median time of 2.5 years after T1). This form was similar to the first, except for including additional questions regarding concomitant therapies (type, frequency, etc.). Overall, the physicians of 24 patients complied with this request. The 10 patients for whom T2 data was not available were not included in the comparative analysis.

At T2, patient charts were divided into two groups: Group A (n = 9) comprised patients who had not been on ERT, whereas Group B (n = 15) comprised patients who were on ERT. The criterion for subjecting patients to ERT was the physician's treatment choice based on the details of each case, which were not available for analysis.

The severity of the clinical phenotype (severe or attenuated) was defined as per the attending physician's impression of the neurological involvement/cognitive status of the patient (severe = abnormal; attenuated = normal). Age at diagnosis was defined as the age at the time of collection of the sample sent for analysis at T1. For patients who died during the study period, the last data available were used for analysis.

Data were entered into a Microsoft Excel spreadsheet. Categorical variables were expressed as absolute and

relative frequencies. Normally distributed continuous variables were expressed as means and standard deviations, whereas asymmetrically distributed continuous variables were expressed as medians and interquartile ranges (IQR). Kaplan-Meier estimates were used for survival analysis.

Comparative analysis was limited to patients for whom both assessments (T1 and T2) were available and to variables for which data were available at T1 and T2 in at least 60% of patients, namely: physical examination findings (anthropometric parameters, presence of joint contractures, hepatosplenomegaly, corneal opacities, and gibbus deformity); developmental delay (specified as language delay, motor delay, and sphincter control delay); history of seizures; chronic medication use; death; history of surgical procedures; history of and reason for hospital admissions; and reported presence of sleep apnea and hearing loss.

As defined *a priori* by the authors, a difference of $\geq 20\%$ between Groups A and B at T1 (B-A) and a delta of $\geq \pm 20\%$ between Groups A and B at T2 as compared with T1 [$\text{delta}\% = (\%T2 \text{ in Group B} - \%T1 \text{ in Group B}) - (\%T2 \text{ in Group A} - \%T1 \text{ in Group A})$] were considered clinically relevant. This cutoff is conservative and was established after a consensus meeting based on the borderline effect of Laronidase in the improvement of Forced Vital Capacity (about 10%), which is considered clinically relevant (Wraith *et al.*, 2004), as well as in the absence of other objective parameters to define clinical relevancy in this disorder. Clinical improvement was defined as a delta of $\leq -20\%$ between groups. In patients who met this criterion for clinical improvement, disease was considered stable when there were no changes between T1 and T2 in Group B, but only in Group A. Clinical deterioration was defined as a delta of $\geq +20\%$ between groups. For parameters in which a clinically significant between-group difference was already present at baseline (T1), the delta required for determination of clinical relevance on comparison between T2 and T1 was increased to $\pm 40\%$. These criteria were adopted due to the exploratory nature of the study and to the small sample size, which precluded formal statistical assessment.

Results

Overall sample (T1; n = 34)

Thirty-four Brazilian patients with MPS I (32 unrelated families) were included in the study. Parental consanguinity was present in eight of the 32 families (25%). Of the 34 patients, 17 were from the Southeast region of Brazil, eight from the Northeast, seven from the South and two from the North of the country. Sixteen patients were male (47%), and median age at enrollment was 4.1 years (range, 10.4 months-38.1 years; IQR, 18-118 months). There was substantial heterogeneity in presenting symptoms, which included gibbus deformity (n = 10), articular complaints

(n = 8), hepatosplenomegaly (n = 5), hernia (n = 5), and respiratory tract infections (n = 5). The median age at symptom onset was 8.5 months (range, 0-120 months; IQR, 3.75-27 months). Twenty-four patients exhibited their first symptoms of MPS I during the first year of life; nine experienced symptom onset between the ages of 1 and 5 years, and one patient experienced symptom onset at age 10.

Seven patients died between T1 and T2: five with the severe form of MPS I (four off ERT, one on ERT) and two with the attenuated phenotype (one off ERT, one on ERT) (Table 1). Overall, at 2.5 years of follow-up after diagnosis, 17 of the 24 patients (70.5%) who completed T1 and T2 assessment were alive, with only five of having the severe phenotype.

Baseline profile of Groups A and B (n = 24)

Patients from Groups A (n = 9) and B (n = 15) at T1 are described in Tables 2 and 3. Groups A and B were dissimilar at T1: the severe phenotype of MPS I was more common in Group A, whereas hepatomegaly, a history of hernia repair, and hospitalization for lower respiratory tract infections (LRTI) were more common in Group B, as shown in Table 3. No patient from group B underwent HSCT, while one patient from group A has been submitted to this procedure (Table 1), and for him, the data was collected up to the moment of the procedure.

Profile of Groups A and B at T2 (Table 3, n = 24)

Median age at onset of ERT was 50.8 months (IQR, 16-247 months), 17.8 months after diagnosis. There was a difference between Groups A and B regarding the median time elapsed between T1 and T2 (Group A, 11 months; Group B, 41 months). Kaplan-Meier analysis showed that the likelihood of survival at 7 years after symptom onset was 41.7% in Group A vs. 83.9% in Group B. Median duration of ERT was 3 years (IQR, 1.6-3.6 years). Median age at T2 was 76 months (6 years) in Group A and 86 months (7 years) in Group B.

Concomitant interventions

Patients also received other interventions during the study. Most drugs were prescribed for cardiovascular and ophthalmic complaints, and vitamin supplements were also common (Table 3). Other therapies, which were found to be more common in Group B than in Group A in T2, included physical therapy, speech therapy, hydrotherapy, and occupational therapy (data not shown).

Discussion

This is an exploratory, retrospective study of a cohort of patients who present a rare disorder (MPS I) treated through a novel therapy (ERT with Laronidase). Its main limitations are the relatively small sample size, the method we used for data collection (a retrospective filling out, by the attending physician, of a relatively long questionnaire)

Table 1 - Characteristics of patients with mucopolysaccharidosis type I who died during the study period (n = 7/24).

Phenotype	Genotype	Age at symptom onset (months)	Presenting symptom	Age at diagnosis (months)	Age at death (months)	Cause of death	Age at ERT onset (years)	Time on ERT (years)
1 Severe	??	11	Gibbus deformity	11	62.4	Post-HSCT*	-	-
2 Severe	p.W402X/W402X	4	Cardiomyopathy	13.9	45.6	LRTI	1.4	1
3 Severe	p.W402X/W402X	1	Inguinal hernia	16.7	20.4	CHF	-	-
4 Severe	p.W402X/W402X	8	Macrocephaly	14.4	21.6	LRTI	-	-
5 Attenuated	p.P533R/P533R	53	Cardiomyopathy	50.6	91.2	RF	-	-
6 Severe	??	12	Umbilical hernia	36.4	75.6	RF	-	-
7 Attenuated	p.W402X/?	12	Gibbus deformity	26.3	72	Complications of anesthesia	2.4	3.6
Overall (median)		11		16.7	45.6			

*Respiratory infection after immunosuppression. Data collected up to transplantation.

HSCT, hematopoietic stem cell transplantation. CHF, congestive heart failure. ERT, enzyme replacement therapy. LRTI, lower respiratory tract infection. RF, respiratory failure.

and the clinical heterogeneity between the groups which received or not ERT. The discrepancies between the two groups regarding the prevalence of the severe form of the disease prevent us from drawing stronger conclusions regarding the effect of ERT. Unfortunately, due to the small sample size, we were not able to perform certain important subgroup analyses, such as the follow-up per phenotype, which could have added useful information to our work. Even so, we have been able to generate some interesting new data on the issue.

The inclusion of ERT in routine treatment regimens for MPS I is still recent practice in Brazil (Giugliani *et al.*, 2010a). Nevertheless, the proportion of patients on ERT in this study (62.5%) was similar to that reported in previous studies conducted in the country (78% and 88% respectively) (Turra and Schwartz, 2009; Boy *et al.*, 2011). Regarding indications for HSCT, due to the logistical and clinical challenges posed by this procedure in Brazil or by delayed diagnosis of MPS I in Latin America (Giugliani *et al.*, 2010b; Muñoz-Rojas *et al.*, 2011), few patients appear to pursue it as a treatment modality, although it is the first-line therapy of choice for young children with the severe phenotype.

The earlier median age at diagnosis in our sample (49 months) as compared with that reported by another Brazilian study (72 months) (Vieira *et al.*, 2008) may have been associated with greater awareness of MPS I by the Brazilian physicians, and to the establishment of the MPS Network. Nevertheless, diagnosis is still delayed, as the vast majority of patients exhibited symptoms as early as the first year of life. The symptoms presented and the age at symptom onset were consistent with previous reports (Vijay and Wraith, 2005; Vieira *et al.*, 2008). The presence of early clinical manifestations in the first year of life is associated with the severe form of MPS I, as reported elsewhere (Pastores *et al.*, 2007; Vieira *et al.*, 2008). Although the severe form of MPS I is the most frequent one considering worldwide data (Nelson, 1997; Moore *et al.*, 2008; Muñoz-Rojas *et al.*, 2011), our sample was mostly composed of patients with the attenuated phenotype (60%), as is to be expected in Latin America (Muñoz-Rojas *et al.*, 2011).

Mean survival was longer than previously described (Moore *et al.*, 2008), which may be attributed, at least partly, to duration of ERT and to the greater prevalence of patients with the attenuated phenotype in our sample. Nevertheless, some patients died at an early age, possibly due to marked vital-organ involvement or to absence or insufficient duration of ERT, which stresses the need for early institution of specific treatment in these patients. The leading cause of death were respiratory system problems. Both patients who died in the ERT group had the severe phenotype and died of complications associated with the underlying disease (pneumonia and complications of anesthesia). The higher mortality rate of Group A was clinically significant, and the presence of more severely ill patients and the ab-

Table 2 - Comparison between Groups A and B at T1 (diagnosis) (n = 24).

Variable	Group A* (n = 9)	Group B* (n = 15)	Clinically relevant difference
Median age, months (IQR)	36 (13-179)	33 (18-139)	No
Male sex, n (%)	5 of 9 (55%)	8 of 15 (53%)	No
Severe phenotype, n (%)	6 of 9 (66%)	4 of 15 (26%)	Yes
Median age at symptom onset, months (IQR)	11 (3-36)	8 (3-18)	No
Median weight, kg (IQR)	14.1 (9-36)	13.9 (11-30)	No
Median height, cm (IQR)	92 (76-138)	98 (79-116)	No
Median HC, cm (IQR)	51.3 (49-53)	51 (49-55)	No
Hernia repair required, n (%)	2 of 9 (22%)	7 of 15 (46%)	Yes

*Group A, no ERT between T1 and T2; Group B, ERT between T1 and T2.
ERT, enzyme replacement therapy; HC, head circumference; IQR, interquartile range.

Table 3 - Enzyme replacement therapy for mucopolysaccharidosis type I: comparative analysis of clinical variables between T1 and T2 (n = 24).

	No-ERT group (A) N = 9		ERT group (B) N = 15		Delta (%)*
	T1	T2	T1	T2	
Developmental delay	5 of 9 (55%)	7 of 9 (77%)	7 of 12 (58%)	9 of 12 (75%)	-5%
Language delay	4 of 9 (44%)	5 of 9 (55%)	3 of 11 (27%)	5 of 11 (45%)	+7%
Motor delay	4 of 10 (44%)	6 of 9 (66%)	4 of 12 (33%)	5 of 11 (41%)	-14%
Joint contractures	5 of 6 (83%)	6 of 6 (100%)	13 of 15 (86%)	15 of 15 (100%)	-3%
Seizures	0 of 9 (0%)	0 of 9 (0%)	0 of 14 (0%)	3 of 14 (21%)	+21%
Splenomegaly	2 of 6 (33%)	3 of 6 (50%)	6 of 14 (42%)	4 of 14 (28%)	-31%
Thoracolumbar gibbus deformity	3 of 6 (50%)	5 of 6 (83%)	10 of 14 (71%)	10 of 14 (71%)	-33%
Hepatomegaly**	3 of 6 (50%)	5 of 6 (83%)	10 of 14 (71%)	6 of 14 (42%)	-62%
Chronic medication use	4 of 9 (44%)	5 of 9 (55%)	4 of 14 (28%)	4 of 14 (28%)	-11%
Death	0 of 9 (0%)	5 of 9 (55%)	0 of 15 (0%)	2 of 15 (13%)	-42%
Surgical procedures	6 of 9 (66%)	2 of 9 (22%)	9 of 15 (60%)	5 of 15 (33%)	+17%
Corneal opacities	4 of 6 (66%)	5 of 6 (83%)	8 of 14 (57%)	9 of 14 (64%)	-10%
Reported:					
Sleep apnea	2 of 8 (25%)	4 of 8 (50%)	5 of 15 (33%)	13 of 15 (86%)	+28%
Hearing loss	2 of 9 (22%)	3 of 9 (33%)	4 of 12 (33%)	8 of 12 (66%)	+22%
Hospital admission, all-cause	5 of 9 (55%)	6 of 9 (66%)	9 of 15 (60%)	4 of 15 (26%)	-45%
Hospital admission, RTI	3 of 7 (42%)	3 of 7 (42%)	7 of 15 (46%)	3 of 15 (20%)	-26%
LRTI**	2 of 7 (28%)	3 of 7 (42%)	7 of 15 (46%)	1 of 15 (6%)	-40%
URTI	1 of 7 (14%)	0 of 7 (0%)	2 of 15 (13%)	2 of 15 (13%)	+14%

*Delta = [(Group B at T2 - Group B at T1) - (Group A at T2 - Group A at T1)]. A delta of $\geq \pm 20\%$ between groups A and B was considered clinically relevant.

**A delta of $\geq \pm 40\%$ was considered clinically relevant for these variables, due to the presence of a significant between-group difference at T1 (see Methods section).

ERT, enzyme replacement therapy. RTI, respiratory tract infection. LRTI, lower respiratory tract infection. URTI, upper respiratory tract infection.

sence of ERT or other therapies in this group might help to explain its higher mortality rate.

The length of follow-up was shorter in Group A than in Group B, which can be explained by the greater number of deaths in Group A. This, in turn, may have contributed to the absence of specific treatment in this group. As Laronidase is not included in the list of medicines provided free of charge by the Brazilian government, most patients

with MPS I in the country can only secure access to it by pursuing legal action; this may have been a contributing factor to the delayed onset of ERT (in our sample, treatment was initiated, on average, 1.5 years after diagnosis, and the median time of follow-up for Group A was 11 months). Disease severity may also have limited provision of ERT, as most patients in Group A had the severe phenotype, and there is some controversy in the literature regarding the use

of ERT in terminally ill patients. We should also point out that the adherence to the treatment was not evaluated in our study; it is possible that many patients, for different reasons (*e.g.*, no easy access to the infusion center) have not received all the infusions scheduled for the period.

We observed improvement in some efficacy outcomes at T2, even though the duration of ERT in our sample cannot be considered long in view of the chronic nature of MPS I. Nonetheless, we cannot attribute this improvement solely to ERT, as there is a higher prevalence of severe patients in group A (which are therefore likely to show a worse outcome), whereas patients in group B also more frequently received “adjunct” therapies. The higher concomitance of ERT and other therapies is an interesting finding, which suggests that patients on ERT are also provided with a better overall care or have more access to information. Unfortunately, we were not able to perform any further analysis regarding this variable since we did not have any data in this respect at diagnosis.

Hospital admissions are frequent in patients with MPS I, with respiratory tract infections being the leading cause of hospitalization other than surgery (Vijay and Wraith, 2005). The clinically relevant reduction in the rate of hospital admission observed in Group B may be indicative of a protective effect of ERT or respiratory physical therapy, or even to a higher prevalence of the severe form in Group A, as patients in Group A experienced an increase in the number of hospitalizations. A clinically significant protective effect of ERT against lower respiratory tract infections is unreported in the literature.

Regarding clinical examination findings, patients in the ERT group experienced a clinically significant reduction in the prevalence of hepatosplenomegaly, as expected (Kakkis *et al.*, 2001; Wraith *et al.*, 2004, 2005, 2007; Sifuentes *et al.*, 2007; Clarke *et al.*, 2009). It is worth stressing that, as physical examination data at the time of ERT onset were unavailable, improvement may have been underestimated, as any deterioration between the time of diagnosis and the time of treatment onset will have gone unnoticed due to the study design. The fact that weight, height, and head circumference could not be analyzed due to missing data reflects the challenges of performing retrospective studies in which data collection is based on questionnaires. Therefore, the association between anthropometric parameters and provision of ERT remains unclear, despite previous reports of a positive effect (Kakkis *et al.*, 2001; Sifuentes *et al.*, 2007; Wraith *et al.*, 2007; Clarke *et al.*, 2009).

Both groups experienced a similar change in the prevalence of joint contractures (deterioration), although the difference was not considered clinically relevant. Isolated analysis of the progression of thoracolumbar gibbus deformity could suggest that this manifestation progresses as the disease does, but can be at least partially controlled by ERT, as its frequency remained stable in the ERT group and increased in the no-ERT group. However, this finding is

most probably due to the higher prevalence of the severe form of the disease in the group A, since this form is more frequently associated to the development of gibbus. There is no information in the literature as to the effects of ERT on gibbus deformity (Pastores and Meere, 2005).

Ophthalmic complaints are exceedingly common in patients with MPS I, and corneal opacities affect virtually all patients with the condition (Caruso *et al.*, 1986; Neufeld and Muenzer, 2001; Ashworth *et al.*, 2006a,b; Pitz *et al.*, 2007; Fahnehjelm *et al.*, 2010). The prevalence of corneal opacities increased in both groups, despite ERT. There is no consensus in the literature as to the effects of ERT on this clinical manifestation (Kakkis *et al.*, 2001; Pitz *et al.*, 2007; Sifuentes *et al.*, 2007; Clarke *et al.*, 2009).

The increase in the reported rate of sleep apnea and hearing loss between T1 and T2 is probably attributable to improved follow-up of patients with MPS I, particularly in the ERT group, where this rate increase was clinically significant. Again, this finding suggests that, once diagnosed, many patients who began ERT also began other therapies, which would have provided an add-on benefit to the effects of ERT. The increased frequency of reported sleep apnea and hearing loss may also be associated with a higher prevalence of the attenuated phenotype in group B, as patients with the attenuated phenotype are usually free of cognitive deficits and consequently able to express their complaints. It is worth stressing that, as polysomnography and audiometry were unavailable to the majority of patients, the reported presence of sleep apnea and hearing loss is not sufficient to establish a diagnosis, which confirms that our findings in relation to this parameter should be viewed with caution. However, there have been reports in the literature of a potential benefit of ERT on sleep apnea syndrome (Kakkis *et al.*, 2001; Wraith *et al.*, 2005), but no reports on hearing loss. Despite the lack of a biological explanation at present, this finding could be an adverse event related to the use of Laronidase.

Finally, there is a need for greater dissemination of guidance and information on MPS I and provision of incentives for the early diagnosis of patients with this condition. ERT is still a high-cost, relatively novel treatment modality, and many patients can only secure access to it by pursuing legal action; furthermore, it must be combined with other therapeutic interventions to achieve the optimal potential for management of MPS I. Further studies focusing on the effect of ERT on respiratory morbidity and overall mortality in patients with MPS I, and on other therapies, are needed.

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