Medical Costs Related to Enzyme Replacement Therapy for Mucopolysaccharidosis Types I, II, and VI in Brazil: A Multicenter Study

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ABSTRACT

Background: Mucopolysaccharidosis (MPS) type I (MPS I), MPS type II (MPS II), and MPS type VI (MPS VI) are lysosomal storage disorders for which enzyme replacement therapy (ERT) is available. Objective: The objective of this study was to evaluate the frequency of medical interventions in a cohort of patients with MPS I, II, and VI on ERT to estimate the impact of direct medical costs associated with the treatment of MPS and compare its frequency with that observed among patients not on ERT. Methods: This was a multicenter study using a retrospective design including a convenience sampling of Brazilian patients with MPS I, II, and VI. Data on the number and type of medical appointments, hospital admissions, medications used, and surgical procedures performed per patient were obtained through a review of medical records, as were data on ERT. These variables were then compared between patients undergoing ERT and those not on ERT. Results: Thirty-four patients (27 on ERT) were included in the study. Overall, between-group differences were found in median absolute frequencies of hospital admissions and surgical procedures per year, both of which were higher in the non-ERT group. Furthermore, we observed a high rate of failure to record medication dosage regimens. Conclusions: Our findings suggest that Brazilian patients with MPS I, II, and VI who are on ERT undergo fewer medical interventions, which can lead to a reduction in direct medical costs to the publicly funded health care system. The cost of ERT, however, is extremely high and probably outweighs this reduction. Keywords: enzyme replacement therapy, health technology assessment, mucopolysaccharidosis type I, mucopolysaccharidosis type II, mucopolysaccharidosis type VI, rare disorders.

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Introduction

Mucopolysaccharidoses (MPSs) are a group of lysosomal storage disorders caused by deficient activity of enzymes involved in the degradation of glycosaminoglycans (GAGs). These disorders are characterized by intralysosomal buildup and increased urinary excretion of GAGs, which ultimately leads to cell, tissue, and organ dysfunction [1]. The GAG catabolism pathway involves different enzymes; deficiency of each of these 11 enzymes is associated with a specific type of MPSs [2] (see Appendix Table in Supplemental Material found at http://dx.doi.org/10.1016/j.vhri.2015.08.002). From a clinical standpoint, the MPS share many features, and so enzyme assays or DNA analyses are required for diagnostic confirmation. All are progressive disorders, characterized by childhood onset, and usually lead to death at an early age; the severity of clinical presentation is extremely variable, but predominantly comprises complications due to the buildup of GAGs in the respiratory system (recurrent respiratory tract infections, obstructive sleep apnea, restrictive lung disease), heart (valve disease), and joints/bone (dysostosis multiplex, decreased joint range of motion). Neurological involvement, is common; mucopolysaccharidosis type IV-A (MPS IV-A) and mucopolysaccharidosis type VI (MPS VI) were originally believed to be “protected” from cognitive involvement, but an article suggests that it may occur even in MPS VI [3]. Mucopolysaccharidosis type III-D, mucopolysaccharidosis type IV-B, mucopolysaccharidosis types VII, and mucopolysaccharidosis type IX are the rarest types. Mucopolysaccharidosis type I (MPS I) is the leading type of MPSs in the United Kingdom [4], mucopolysaccharidosis type II (MPS II) is the most common type in Brazil [5] and Japan

Conflict of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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and MPS III-A is the most common type found in Germany [7]. According to the São Paulo State MPS Association (Associação Paulista de MPS), as of 2012, there were 645 patients living with MPSs in Brazil: 160 with MPS I, 191 with MPS II, 33 with MPS III, 79 with MPS IV, and 182 with MPS VI (Nilton Próspero, personal communication, 2012). MPS II is the only form that presents an X-linked recessive pattern of inheritance; hence, it is found almost exclusively in male patients [6].

There is no curative treatment for MPSs. Currently available treatment options include interventions that target the clinical phenotype (supportive care or symptomatic therapy) and those that target the mutant protein (specific treatments, such as hematopoietic stem cell transplantation [HSCT] and enzyme replacement therapy [ERT]) [8]. Growing research interest in MPSs from a health technology assessment standpoint is explained by the advent of ERT for MPS I, II, IV-A, and VI, a high-cost treatment indication for visits), and on the use of medical devices, including eyeglasses, hearing aids, wheelchairs, and continuous positive airway pressure/bilevel positive airway pressure devices. For patients on ERT, a separate data collection sheet was specifically designed to record the date and number of infusions performed, the number of infusions lost, the number of vials used (dose calculated according to body weight), premedication, and infusion duration. Throughout 2011, one of the investigators (F.H.B.) reviewed the records of all the patients included in the study and completed the data collection instrument.

### Sample
A convenience sampling strategy was used. Four Brazilian MPS treatment centers were included in this study: the Medical Genetics Service of Hospital Clínicas de Porto Alegre, state of Rio Grande do Sul (SGM-HCPA); the Department of Medical Genetics of Universidade Estadual de Campinas, state of São Paulo; Pontifícia Universidade Católica de Campinas, state of São Paulo; and the Department of Pediatrics at Universidade Estadual do Rio de Janeiro, state of Rio de Janeiro. These centers were chosen because all kept high-quality patient records, all are part of the SUS, all are affiliated with universities in the south or southeast regions of Brazil, and all monitored both patients who were on ERT and those not on ERT (the exceptions were Department of Medical Genetics of Universidade Estadual de Campinas, state of São Paulo, which followed patients only on ERT, and Pontifícia Universidade Católica de Campinas, state of São Paulo, which monitored only those on ERT). Furthermore, all are led by medical geneticists. This would ensure good record-keeping and a measure of consistency with respect to follow-up protocols. It bears noting that of the four participating centers, only one (SGM-HCPA) had electronic medical records.

### Patient Inclusion/Exclusion Criteria
The patient inclusion criteria were as follows:

1. Diagnosis of MPS I, II, or VI confirmed by enzyme assay in plasma/leukocytes or fibroblasts and/or DNA analysis;
2. Not being on a clinical trial involving ERT;
3. No history of HSCT;
4. Treatment duration, according to presence or absence of ERT:
   a. Patients in the ERT group were required to undergo regular follow-up and to be on ERT for at least 12 months before the start of data collection (January 2011).
   b. Patients in the no ERT group were required to undergo regular follow-up for at least 12 months before the start of data collection (January 2011).

For purposes of analysis, patients aged 18 years or older were considered adults. All others were classified as children/adolescents.

### Methods

#### Study Design
This was a retrospective, hospital-based, cohort study designed to collect data on variables of interest to a pharmacoeconomic assessment of ERT for MPS I, II, and VI. MPS IV-A was not included because ERT with elosulfase alfa was not approved at the time of the study. The study was approved by all involved ethics committees.

#### Data Collection Instrument
The data collection instrument (available on request) consisted of 15 questions organized in two sections. The first section was designed to obtain general data on each patient: center of origin, severity of phenotype (with or without cognitive involvement, according to the registries), ERT status, history of HSCT, date of birth, date of diagnosis, date of first medical geneticist appointment, date of first infusion (in case of ERT), and date of death (when applicable). The second section of the instrument was designed to collect data on variables directly associated with the cost of MPS treatment. Data recorded included the date, specialty, and reason for each medical appointment; the date, type, and indication for each test; the date, type, and length of stay for each surgical procedure; the type, cause, and length of stay for each hospital admission; and the type, dosage regimen, duration of use, and indication for each medication prescribed. Data were also collected on ancillary therapies, such as physical therapy, speech and language therapy, occupational therapy, social services, and psychology or counseling (duration, frequency, and indication for visits), and on the use of medical devices, including eyeglasses, hearing aids, wheelchairs, and continuous positive airway pressure/bilevel positive airway pressure devices. For patients on ERT, a separate data collection sheet was specifically designed to record the date and number of infusions performed, the number of infusions lost, the number of vials used (dose calculated according to body weight), premedication, and infusion duration. Throughout 2011, one of the investigators (F.H.B.) reviewed the records of all the patients included in the study and completed the data collection instrument.
Assessment of the Study Instrument and Data Collection Method

The data collection instrument was designed by the multidisciplinary team of study investigators, which comprises physicians, pharmacists, health technology assessment experts, and economists.

The data collection allowed the evaluation of the study instrument regarding its layout. The quality of data records was appraised qualitatively and quantitatively by analysis of the number of missing variables in the instrument (due to missing data or inadequate record-keeping) and of the quality of information obtained. For the variables medical appointments, tests, hospital admissions, and surgical procedures, records were considered adequate if they contained information on the type of intervention, the date of intervention, the duration or frequency of the intervention, and the indication(s) for the intervention. Records were considered adequate for ancillary therapies if they contained information on the type, frequency, and duration of therapy; for medications (pharmacotherapy), if they contained data on the active pharmaceutical ingredients used, duration, dosage regimen, and indications for each medication; for chronic-use medical devices, if they contained information on the date of use of each device was started; and finally, regarding ERT, records were considered adequate if they contained data on time on ERT, number of vials used, number of scheduled infusions, and number of completed infusions.

Estimation of the Effect of ERT, Cognitive Involvement, and Duration of the Disease on the Frequency of Medical Interventions

All data were collected by a chart review.

The following data were taken into account for this analysis: date of birth, age at diagnosis, presence of cognitive involvement (according to medical records, even in the absence of IQ testing), date ERT was started, and frequency of medical interventions (number and type of hospital admissions, tests, surgical procedures, medical appointments, and medications prescribed/used) performed between January and December 2010.

Medications used as part of ERT (laronidase, idursulfase, or galasulfase, premedications and medications used in the treatment of infusion adverse reactions) and those not directly related to MPS management (such as oral contraceptives) were not tallied. For the purposes of this study, the number of medications used as part of ERT was defined as the number of different active pharmaceutical ingredients used during the study period; for example, if a patient received two courses of plain amoxicillin and one course of amoxicillin/clavulanate, these would be tallied as “two medications used during the study period.”

Tests were tallied as a single instance when performed on the same day; for example, complete blood cell count alone or complete blood cell count plus platelet count were both counted as a single test for statistical purposes as long as both tests were performed at a single visit. This practice was used for hematology and biochemistry tests alike, including urea, creatinine, bilirubin, Alanine transaminase (ALT), aspartate transaminase (AST), Gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase, cholesterol, glucose, sodium, potassium, chloride, magnesium, calcium, phosphorus, albumin, globulins, and total protein. Conversely, imaging tests of different body segments were counted separately even when performed on the same day.

Variables (medians) were initially assessed with regard to disease duration (equivalent to the age of the patient; in this analysis, data only from patients in the non-ERT group were taken into account) and presence/absence of cognitive involvement. To assess the influence of time on ERT on the variables of interest, data from the ERT group were included.

Statistical Analysis

Databases were constructed in Microsoft Office Excel 2010, and statistical analyses were performed in the SPSS 20.0 software environment. Descriptive data were described as frequencies, means and SDs, and medians and quartiles.

For evaluating the effect of the duration of disease on the frequency of medical intervention, a Pearson correlation was performed. The influence of the presence of cognitive involvement on other variables was then assessed using the Kruskal-Wallis test. The Mann-Whitney U test was used for comparison of the median number of medications, medical appointments, hospital admissions, tests, and surgical procedures in the ERT and non-ERT groups. To assess the influence of time on ERT on the variables of interest, data from the ERT group were included and Pearson correlation coefficients were calculated.

For all analyses, P values of less than 0.05 were considered statistically significant.

All monetary values that are expressed in pounds sterling were obtained through the exchange rate provided by the Central Bank of Brazil (Banco Central do Brasil) on July 15, 2014. Because the data collected are prior to 2010, the monetary values determined may have suffered variations because of annual inflation rates in Brazil (around 6%).

Results

Forty-three patients with MPSs (I = 15, II = 23, VI = 5) were alive and registered at the four participating centers in 2010. Of these, only 35 met the inclusion criteria because 8 did not have any appointments in 2010 (e.g., they were not regularly seen at the center). The medical records of one patient were not available for review. Therefore, the sample comprised 34 patients: 27 on ERT (“ERT group”) and 7 receiving supportive care only (“non-ERT group”). The reasons why patients from the non-ERT group were not receiving ERT were not clearly stated in medical records.

Table 1 describes the profile of the patients included in the sample.

Appraisal of the Data Collection Instrument

Table 2 lists the variables associated with the cost of MPS treatment and describes our appraisal of the adequacy of record-keeping of these variables in patient charts.

Data on the chronic use of medical devices and information on ancillary therapies are presented in Table 3.

Influence of Disease Duration on the Variables of Interest

There were no significant correlations between length of disease and any of the variables of interest (data not shown).

Comparison between the ERT and Non-ERT Groups

There were significant between-group differences in the median number of hospital admissions and surgical procedures, both of which were higher in the non-ERT group (Table 4). There were no significant between-group differences when only children and adolescents were taken into account (data not shown). Because there were no patients older than 18 years in the non-ERT group, no such analysis could be conducted for adult patients.
A correlation was found between time on ERT and the median number of hospital admissions \( (r = -0.504; P = 0.007) \). Time on ERT did not correlate with any other variables (data not shown).

When only patients younger than 18 years were considered, there was also a correlation between time on ERT and the median number of hospital admissions \( (r = -0.674; P = 0.004) \). No such correlation was found in adult patients.

**Discussion**

The importance of this article is based on the worldwide scientific, economic, and social relevance of rare diseases and orphan drugs. The present study used an exploratory and retrospective design and was based exclusively on data contained in patient records before the implementation of Ordinance No. 199, January 30, 2014, from the Brazilian Ministry of Health, which establishes the National Policy on Comprehensive Care for People with Rare Diseases in the SUS. The policy forecasts the incorporation and use of technologies for the promotion, prevention, and comprehensive care, including drugs and nutritional formulas as specified in the SUS, which will change the panorama of rare diseases in the county. For purposes of this ordinance, a disease that affects up to 65 people in every 100,000 individuals, or 1.3 people per 2000 individuals [16], is considered a rare disease.

Unfortunately, most participating centers did not have electronic medical records. Furthermore, some centers use different records or forms for different departments or sectors in which patients are seen over the course of their treatment, thus making data collection a complex, extensive, and eventually incomplete endeavor.

However, one of the advantages of chart review studies is that medical records provide very precise information on the date and type of medical appointments, surgical procedures, hospital admissions, and tests performed at the hospital in which patients receive follow-up, as well as the type and duration of pharmacotherapy.
At least in this study, however, data on use of medical devices and ancillary therapies by Brazilian patients with MPS I, II, and VI.

<table>
<thead>
<tr>
<th>Medical devices/Ancillary therapies</th>
<th>No. (%) of patients with intervention reported in medical records</th>
<th>No. (%) of patients with adequate records</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical devices for long-term use</td>
<td>16/34 (47.0)</td>
<td>13/16 (81.2)</td>
</tr>
<tr>
<td>Eyeglasses</td>
<td>6/5</td>
<td></td>
</tr>
<tr>
<td>Hearing aid</td>
<td>5/3</td>
<td></td>
</tr>
<tr>
<td>CPAP</td>
<td>3/2</td>
<td></td>
</tr>
<tr>
<td>BiPAP</td>
<td>1/0</td>
<td></td>
</tr>
<tr>
<td>Walker</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>Wheelchair</td>
<td>1/0</td>
<td></td>
</tr>
<tr>
<td>Leg orthosis</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>Neck brace</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>Ancillary therapies</td>
<td>15/34 (44.1)</td>
<td>9/34 (60)</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>10/4</td>
<td></td>
</tr>
<tr>
<td>Speech-language pathology</td>
<td>4/1</td>
<td></td>
</tr>
<tr>
<td>Occupational therapy</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>Social services</td>
<td>4/4</td>
<td></td>
</tr>
<tr>
<td>Psychologist/counselor</td>
<td>0/0</td>
<td></td>
</tr>
</tbody>
</table>

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; MPS I, mucopolysaccharidosis type I; MPS II, mucopolysaccharidosis type II; MPS VI, mucopolysaccharidosis type VI.

+ Adequate record-keeping was defined as the presence of information pertaining to the type of device and date device use began (for medical devices) or duration, frequency, and type of therapy (for ancillary therapies).
+ Three patients used more than one device.
+ Three patients were undergoing more than one type of therapy.

Inadequate record-keeping, we found that very few patients actually used these interventions—fewer than expected. Children with severe MPS I, for instance, have limited development of language skills [1] and monitoring by a speech-language pathologist is essential. From a behavioral standpoint, children with MPS I tend to be placid, whereas those with MPS II tend to exhibit aggressive behavior [2]; therefore, psychological treatment can play a very important role. Hearing loss is quite common in MPS I, and many patients require hearing aids. Obviously, the low rate of use of these services and devices in our sample may be secondary to failure to record these interventions in patient charts, or may reflect difficulty obtaining access to these therapies. Brazilian MPS treatment centers do not always make ancillary therapies available to all patients; when provided, they are often extramural, which may explain, at least partly, why their use was not reported in patient records. Previous studies by our group [19,20] suggest, however, that many patients with MPS actually did not have access to ancillary therapies. Turra and Schwartz [18] conducted a multicenter study including 78 Brazilian patients with MPS (17 presenting with mental retardation) who underwent an interview with a speech and language therapist and physical examination. Of these patients, only 18 were undergoing speech therapy intervention at the time of the study [18]. In 2012, Guarany et al. [19] conducted a prospective, longitudinal study of 21 Brazilian patients with MPSs. Of these, only seven reported that they have been treated at rehabilitation clinics or institutions; physical therapy, speech therapy, and psychotherapy were among the treatments provided.

In 2012, Wyatt et al. [17] conducted a pioneering study of the costs of MPS I and MPS II treatment in the United Kingdom. All cost estimates in their investigation were based on data collected by means of questionnaires designed to obtain information on the last 12 months of patient follow-up. Questionnaires were administered directly to patients whenever possible or to their caregivers otherwise. One of the advantages of this mode of data collection is that patients and their caregivers are more likely to have reliable information on ancillary therapies, such as physical therapy, speech and language pathology, and occupational therapy, as well as on the duration of use of medical devices. Therefore, we suggest that future studies on this topic use both designs and data collection methods, so as to ensure collection of reliable data.

We detected a high rate of missing data in relation to the reasons or indications for medical appointments and tests. Although this circumstance hinders assessment of the natural history of MPS, it has little impact on pharmacoeconomic analysis of the treatment of MPS. Missing data pertaining to medication dosage regimens, however, will certainly affect the calculation of MPS treatment costs in subsequent stages of our project. Another point worth considering concerns collection of data on chronic use of medical devices and use of ancillary therapies, as mentioned above. In addition to the issue of

Descriptive Analysis of Treatment Costs in MPS I, II, and VI

Since its establishment in 1990, the SUS has ensured the right to care—including medical appointments, tests, hospital admission, and treatment—at all affiliated health facilities to all Brazilian citizens [20]. Nevertheless, the demand for ERT is on the rise, with patient requests many times supported by court orders that conflict directly with Brazil’s National Medicines Policy and with evidence-based medicine. Furthermore, the influence of pharmaceutical industry lobbying for registration and marketing of new drugs in Brazil cannot be ruled out [21]. A Brazilian article published in 2012 showed that in the case of MPSs, litigation results from the lack of a clear policy in the health system for rare diseases in general, thereby leading to excessive expenditures for MPS treatment. The authors reviewed files from 196 court rulings ordering the Brazilian Ministry of Health to provide medicines, in addition to Ministry of Health administrative records. Overall, 195 patients sued to secure their access to laronidase, idursulfase, and galsulfase between 2006 and 2010, at a total cost of £57,112,763.76 to the public purse, distributed as follows: £2,408,375.06 for laronidase (24 patients with MPS I), £22,616,218.82 for idursulfase (68 patients with MPS II), and £32,088,170.14 for galsulfase (103 patients with MPS VI) [15].

Despite the high cost of recombinant enzymes for the treatment of MPS I, II, and VI, the current state of the evidence provides only limited information on the overall cost burden of these conditions [15]. Within this context, the present study was the first Latin American investigation to assess the economic impact of ERT on the cost burden of disease as represented by medical interventions. The only similar study in the international literature is the aforementioned investigation by Wyatt et al. [17], which consisted of a retrospective assessment of 68 patients with MPS I (20 adults and 48 children) and 39 patients with MPS II (3 adults and
36 children), recruited from several UK centers. In the MPS I group, 24 patients with no cognitive involvement (12 children and 12 adults) were on ERT, with a median time on ERT of 4.68 years, slightly higher than that found in our sample. The remaining patients in the Wyatt et al. [17] sample had undergone HSCT, whereas the other patient with MPS I in our sample was on supportive care alone. Wyatt et al. [18] estimated the annual cost of MPS I treatment to the National Health Service (NHS) and publicly funded social-care services, including the costs of hospital services (hospital admissions, medical appointments, etc.) and extramural services (occupational therapy and other therapies) at £2000 for adult patients and £5300 for children. Furthermore, the annual cost of idursulfase ERT was £37,605 for an adult patient versus £314,004 for a child with the condition.

In the Wyatt et al. [17] sample, median age at ERT onset was 18.7 years for adults and 3.38 years for children with MPS I and 16.6 years for adults and 6.96 years for children with MPS II. In our sample, onset of ERT was later in both forms of MPSs, and in children and adults alike (data not shown). Many factors may have contributed to this late onset of therapy, including delays in diagnosis and the lack of reimbursement of ERT in Brazil. A study of 113 Brazilian patients with several forms of MPSs showed a 4.8-year delay between symptom onset and diagnostic confirmation [22]. Because of the progressive course of MPSs, early diagnosis and immediate institution of therapy are paramount [23], and may even lead to a reduction in treatment costs. Case studies of nontwin siblings with MPS I, II, and VI have reported much better outcomes in siblings who are diagnosed at birth and begin ERT within the first 6 months of life [24–26].

When analysis was restricted to children and adolescents, we found no difference between the ERT and non-ERT groups in terms of the frequency of medical interventions. These results are in line with those of Wyatt et al. [17], who found that in children with MPS I, there was no association between time on ERT and total NHS and social-care costs, hospital-care costs, or nonhospital-care costs, and in children with MPS II, there was no statistically significant association between time on ERT and total NHS and social-care costs or nonhospital-care costs. The authors, however, did find an association between time on ERT and hospital costs (hospital admissions, accident, and emergency visits, etc.) (costs 3.78 times

| Table 4 – Comparison between the ERT and non-ERT groups. |
| Medical appointments | No ERT (n = 7) | ERT (n = 27) | P |
| Number/patient, median (IQR 25–75) | 8 (2–13) | 7 (3–10) | 0.915 |
| Patients who attended visits in the period, n (%) | 7 (100) | 26 (96.2) | |
| Most commonly seen specialists† | Ear-nose-throat, medical geneticists, surgeons | Geneticists, ear-nose-throat, pulmonologists | |
| Hospital admissions | | | |
| Number/patient, median (IQR 25–75) | 1 (0–2) | 0 (0–1) | 0.015 |
| Patients who were hospitalized in the period, n (%) | 5 (71) | 7 (25.9) | |
| Most common reasons for hospital admission† | Asthma, respiratory insufficiency | Respiratory insufficiency, surgery | |
| Surgeries | | | |
| Number/patient, median (IQR 25–75) | 0 (0–2) | 0 (0–0) | 0.040 |
| Patients who underwent surgery in the period, n (%) | 3 (42.8) | 3 (11.1) | |
| Most commonly performed surgeries† | Adenoidectomy, umbilical hernia repair, tonsillectomy | Adenoidectomy, inguinal hernia repair, myringotomy | |
| Tests | | | |
| Number/patient, median (IQR 25–75) | 13 (6–44) | 8 (2–13) | 0.096 |
| Patients who had tests in the period, n (%) | 7 (100) | 25 (92.5) | |
| Most commonly performed tests† | Blood counts/chemistry panels, chest X-ray, echocardiogram | Blood counts/chemistry panels, urinary GAG measurement, echocardiogram | |
| Medications† | | | |
| Number/patient, median (IQR 25–75) | 2 (0–22) | 3 (0–3) | 0.735 |
| Patients who used medications in the period, n (%) | 4 (57) | 15 (55.5) | |
| Most commonly prescribed medications† | Antibiotics, analgesics, corticosteroids | Analgesics, antibiotics, antihistamines | |

ERT, enzyme replacement therapy; GAG, glycosaminoglycan; IQR, interquartile range.
† Listed in order of frequency.
† Median refers to the number of different active pharmaceutical ingredients used during the study period.
higher) in children with MPS II. One major factor that should be taken into account is the difference in profile between the two groups of the present study: the non-ERT group was composed exclusively of children and adolescents, most with MPS II, whereas only 59.3% of the patients in the ERT group were children. Contrary to the suggestion by Wyatt et al. [17] that children with MPS II generate a lower cost burden than do adults, our data suggest higher costs for patients not on ERT; consequently, the higher cost burden of this group must be attributable to children and adolescents.

Analysis of all patients regardless of age showed that the frequency of medical interventions was essentially similar in the ERT and non-ERT groups, with the exception of surgical procedures and hospital admissions, which were less frequent in the ERT group. In our sample, the leading causes of hospitalization in both groups were respiratory tract infections and surgery. According to the SUS coding database, Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e Orteses e Próteses e Materiais do Sistema Único de Saúde (SIGTAP), the total cost (including hospital charges and provider fees) of an adenoidec- tomy, bilateral inguinal hernia repair, or umbilical hernia repair—the most common surgical procedures in both groups—is £90.53, £90.01, and £93.77, respectively [27]. Despite the cost of ERT, the impact of these costs appears to be lower in the ERT group, due to the relatively low frequency of surgical procedures and hospital admissions. According to SIGTAP, the cost of 1 day in an intensive care unit (adult or pediatric) is £96.14 [27].

Our findings also suggest that the most common medical procedures in both groups are physician appointments (medical appointments) and tests. Within the SUS, according to SIGTAP [27], the reimbursement rate for a visit to a primary care physician (e.g., to a pediatrician or general surgeon) is £0.53, whereas the rate for a specialist physician visit (e.g., geneticist or cardiologist) is £2.60. Since the creation of Ordinance No. 199, SIGTAP began to incorporate the procedure of Clinical Diagnostic Evaluation for Rare Disorders — Inborn Errors of Metabolism with a total cost of £156.00. Among the list of inborn errors of metabolism contemplated by this assessment, there are MPS I and MPS II. MPS VI, in turn, does not seem to be covered by the SUS [27]. Therefore, we believe that the costs of physician appointments will not be a major burden on the total treatment costs of patients with MPS I, II, or VI. This finding is consistent with the results reported by Wyatt et al. [17].

The most common tests undergone by patients included complete blood cell counts/blood chemistry panels, chest radiographs, echocardiography, and urinary GAG quantitation. The SUS covers the costs associated with these interventions, with a reimbursement rate of £1.07 per sample for complete blood cell counts, £0.48 to £0.91 for each blood chemistry test (urea, creatinine, bilirubin, Alanine transaminase (ALT), aspartate transaminase (AST), Gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase, cholesterol, glucose, sodium, potassium, chloride, magnesium, calcium, phosphorus, albumin, globulins, and total protein), £1.79 per plain chest radiograph, and £10.38 for echocardiography [27]. We observed an increase in the frequency of urinary GAG quantitation orders in the ERT group. This is attributable to three factors. First, urinary GAG levels are used extensively in clinical trials of ERT for MPS I, II, and VI as a pharmacodynamic marker of in vivo enzyme activity and a purported surrogate biomarker of treatment response [26]. Second, because ERT is a novel treatment modality and has been the subject of relatively little study, attending physicians are understandably concerned about its effects; this leads to an increase in test orders. Third, according to the protocol for follow-up of patients with MPS I, II, and VI developed by Rede MPS Brasil (a network of Brazilian medical genetics services supported by public and private funding), GAG quantitation should be performed every 3 months [5]. Although currently the identification of urinary GAGs, as well as enzymatic assays in plasma and leukocytes for the diagnosis of EIM, is still to be covered by the SUS [27] at the time of conducting the study, urinary GAG quantitation was available only through the SUS for diagnostic purposes, with a reimbursement list rate of £0.96 per sample. In addition to not listing which assays are included in this test (toluidine blue, GAG chromatography or electrophoresis, or GAG quantification), it does not cover any form of GAG quantitation for monitoring purposes [27]. Therefore, at all participating centers, all GAG quantitation tests performed during the pre-ERT period (for diagnostic purposes) and during ERT are covered by MPS Brazil Network.

Thus far, no studies have been published on the cost of galafusert ERT in patients with MPS VI. Although the worldwide incidence of MPS VI is estimated at only 1:250,000 live births [29], it seems to be more common in Brazil. A study conducted in the southern region of the country found a high frequency of MPSs among inborn errors of metabolism, with MPS I and MPS VI being the most frequently diagnosed forms [30]. Monte Santo, a municipality in northeastern Brazil, features a markedly elevated incidence of several genetic conditions, including MPS VI. The incidence of MPS VI in the area is estimated at 1 in 5000 live births [31]. Within this context, it needs to be noted that this was the first study to address the pharmacoconomics of ERT for MPS VI.

A previous study conducted by our group assessed the effects of ERT in a sample of patients with MPS I (n = 9) throughout their follow-up at SGM-HCPA. Variables were compared between the pre-ERT and post-ERT periods within the same group of patients. Our findings suggested that ERT does not alter the natural history of MPS I (according to the medical interventions analyzed), and that—contrary to the findings of the present study—the treatment costs of patients with MPS I increase during ERT. Comparison between these two retrospective, hospital-based studies clearly shows the superior design and larger sample size of the present investigation [32]. Furthermore, the previous study was restricted to patients with MPS I, whereas the present study included patients with MPS II and MPS VI as well. In view of the sample size, we chose not to conduct subgroup analyses by MPSs type. Hence, there may be differences in terms of cost and treatment efficacy among patients with each of these three types of MPSs.

Conclusions

Our findings suggest that excluding the cost of recombinant enzymes, Brazilian patients with MPS I, II, and VI who receive disease-specific treatment undergo fewer medical interventions than do patients in supportive care. This seems to be associated with lower SUS expenditures with direct medical costs for patients with ERT. Despite some missing data, particularly regarding medication dosage and administration regimens, the study instrument appears adequate for collection of data on the costs associated with treatment of MPSs. Longitudinal studies will be useful in the evaluation of the long-term costs associated with ERT and its impact on the SUS.

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Supplemental Materials

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REFERENCES


