Molecular Genetics and Metabolism 121 (2017) 138–149

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Efficacy of laronidase therapy in patients with mucopolysaccharidosis type I who initiated enzyme replacement therapy in adult age. A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 24 January 2017
Received in revised form 7 April 2017
Accepted 7 April 2017
Available online 9 April 2017

Keywords:
Enzyme replacement therapy
Muchopolysaccharidosis Type I
MPS-I
Adult
Laronidase
Systematic review

ABSTRACT

Background: The efficacy of starting enzyme replacement therapy (ERT) in adults with Muchopolysaccharidosis Type I (MPS-I) is controversial. Evaluating the benefits reported by patients initiating ERT with laronidase at adult age might help physicians decide whether the use of ERT in these patients is worthwhile from a clinical point of view.
Objective: To assess every effectiveness variable modified in MPS-I patients who initiated laronidase at adult age.
Methods: A systematic search of the literature, from inception to July 2016, was conducted using MEDLINE, EMBASE, CENTRAL and LILACS to identify randomized trials or observational studies including ≥1 MPS-I patients with ERT initiated in adult age (≥18 years) and evaluating ERT efficacy. A meta-analysis of studies evaluating the same effectiveness outcome was performed and the evidence was rated according to GRADE criteria. Heterogeneity was assessed by the Chi-squared test and the I-squared statistic. Case reports were excluded from meta-analysis but their main outcomes were separately evaluated. The decrease in urine glycosaminoglycans (uGAGs) levels as patient percentage with reduction in uGAGs and with normalization was the primary outcome.
Results: Nineteen clinical studies and 12 case reports were selected. ERT decreased uGAG levels (high evidence) and liver volume (high), improved 6-min walking test (6MWT) (moderate) and increased blood anti-ERT antibody levels (high). There was no conclusive results (low or very low evidence) regarding improvement/stabilization of respiratory function, change in shoulder flexion, cardiac improvement/stabilization, improvement in symptoms of nocturnal hypoventilation and sleep apnea, improvement in quality of life, visual acuity, otolaryngologic function, bone mineral density or effectiveness of intrathecal therapy.
Limitations: Excluding case reports, there was no study conducted specifically in the target population (ERT ≥18 years). Data were from subgroup analyses of selected studies. There was a great heterogeneity between designs and clinical outcomes evaluated.
Conclusions: ERT improves uGAGs and liver volume in MPS-I patients initiating therapy as adults, although the putative clinical benefit associated to these improvements is unclear. Moderate evidence was shown for improvement in 6MWT.
Systematic review registration number (PROSPERO): 42,016,041,306

Abbreviations: ERT, enzyme replacement therapy; MPS-I, Muchopolysaccharidosis Type I; GAG, glycosaminoglycan; uGAGs, urine glycosaminoglycans; 6MWT, 6-min walking test; HSCT, hematopoietic stem cell transplantation; FVC, forced vital capacity; VA, visual acuity; NHA, nocturnal hypoventilation/sleep apnea; SRT, speech recognition threshold; BMD, bone mineral density; BMI, bone mineral index; MRI, magnetic resonance imaging; SCC, spinal cord compression; JOA, Japanese Orthopedic Association; CSF, Cerebrospinal fluid; CHAQ, Childhood Health Assessment Questionnaire; HAQ, Health Assessment Questionnaire; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

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http://dx.doi.org/10.1016/j.ymgme.2017.04.004
1096-7192/

1. Introduction

Mucopolyssacharosidosis-I (MPS-I) is a lysosomal storage disease inherited in an autosomal recessive pattern, characterized by α-L-iduronidase deficiency, which leads to the abnormal storage of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate in the cell [1]. It is a rare disease with an estimated prevalence in Europe between 0.22 and 4.05 cases per 100,000 births [2–6].

Patients have traditionally been classified into three MPS-I syndromes (Hurler syndrome, Hurler-Scheie syndrome, or Scheie syndrome) based on severity and age at onset [7,8]. However, clinical manifestations overlap and more recently, patients are being classified in just two groups: those with the severe form of the disease or Hurler syndrome and those with attenuated forms.

Infants with *severe MPS-I or Hurler syndrome* show nonspecific early manifestations, such as umbilical or inguinal hernia and/or frequent upper respiratory-tract infections; coarsening of the facial features, which becomes apparent at one year of age; corneal clouding, starting at 2 years of age; decreased growth, evident at age 3 years; frequent hearing loss, and progressive skeletal dysplasia (dysostosis multiplex), cognitive impairment and upper airway disease leading to obstructive sleep apnea; and death, typically caused by cardiorespiratory failure, that usually occurs within the first ten years of life [1,7].

Attenuated MPS-I onsets at age 3–10 years and the disease severity and course are very variable, with the following signs/symptoms among the most common ones: hepatomegaly, dysostosis multiplex, corneal clouding, sleep disturbance/snoring, cardiac valve abnormalities, hernia, joint contractures, carpal tunnel syndrome and hearing loss; although cognitive impairment is rare, learning disabilities can be present [1,8]. Depending on the severity and rate of disease progression the patient may live up to a normal life span [1].

This dual classification distinguishes between the form with (Hurler) and without neurological involvement (attenuated) and leads to different treatment indication at diagnosis, since the first group will benefit from early hematopoietic stem cell transplantation (HSCT), although ERT may be used previous to HSCT or when the graft fails, and the second one from early start of enzyme replacement therapy (ERT) [9].

Clinical trials with intravenous ERT showed that treatment during 26 weeks and, in the extension study, up to 3.5–4 years, results in improvement and/or stabilization of several disease symptoms/signs [urinary GAGs levels, liver volume, distance in the six-minute walking test (6MWT), apnea/hypopnea index in patients with sleep apnea, shoulder flexion in patients with great baseline impairment, and percent predicted forced vital capacity (FVC)], while improving pain and activities of daily living [10,11]. These results were confirmed in the long term [12].

FVC stabilization data and the baseline lower FVC data with increasing age in patients older than 25 years, in the extension study, suggested that early treatment would help stabilize pulmonary function to higher levels [11]. Several other studies have also suggested that early initiation of ERT in attenuated MPS-I may delay or prevent the onset of the major clinical signs, and might be essential to prevent irreversible functional defects, including valve disease, since the symptoms/signs improvements observed in these studies are limited in older as compared to younger patients [12–17].

Having this in mind, the start of ERT at adult age has been controversial, especially from a cost-benefit point of view [18]. Therefore, it was of interest to assess the effectiveness of ERT in MPS-I patients who initiate treatment at adult age, by reviewing previous studies assessing the evolution of signs and symptoms, as well as quality of life, in this subpopulation of patients. This was attempted by means of a meta-analysis whose aim was to find out the evidence level for ERT's effectiveness when treatment is initiated in adult patients with MPS-I, taking into account the difficulty to perform this type of analysis in diseases with such few patients. In addition, we wanted to find out which were the main outcomes analyzed in case reports and if the results were in line with those of the meta-analysis.

2. Methods

2.1. Data sources and searches

A comprehensive search of journal articles and congress communications containing information on effectiveness of ERT for adult patients (≥18 years) with mucopolysaccharidosis type I (Hurler-Scheie syndrome and Scheie's syndrome) up to July 2016 was carried out on EMBASE, MEDLINE, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register and Health Technology Assessment Databases) and on the Latin American and Caribbean Literature on Health Sciences (LILACS). The search strategy retrieved citations for databases containing the subject headings: Mucopolysaccharidosis I, MPS I, Hurler-Scheie, Scheie, enzyme replacement therapy, ERT, laronidase and aldurazyme. The search terms were adapted to be used with different bibliographic databases (Table 1).

There was no restriction of dose, treatment duration, administration via (intravenous or intrathecal), type of study design or language. All published studies up to July 21st, 2016 were included in the search.

2.2. Study selection

The initial selection of the studies obtained by the syntax search in the literature databases was assessed from reading the title and/or abstract. The original papers of those trials, which seemed eligible, according to their title/abstract, were obtained and reviewed to select those meeting the following inclusion criteria: a) Studies conducted in patients with MPS-I; b) initiation of ERT in adult age (≥18 years); c) analysis of ERT efficacy and/or safety. The only exclusion for the meta-analysis criterion was being a case report.

2.3. Data extraction and quality assessment

The level of uGAGs has been the most studied variable, and, when reviewing the literature it, thus, had the most available data. Therefore, and although the associated clinical benefit is questionable, the primary outcome was the reduction of glycosaminoglycan levels in urine in terms of:

(A) Percentage of patients with reduction in baseline glycosaminoglycan levels.

(B) Percentage of patients with normalization of glycosaminoglycan levels.

Table 1
Search syntax. Up to date July 21st, 2016.

Data base	Search syntax	No. articles
PUBMED	("Mucopolysaccharidosis I"[all] OR "mps I"[all] OR Hurler-Scheie[*all*] OR Scheie[*all*]) AND ("enzyme replacement therapy"[all] OR ERT[*all*] OR laronidase[*all*] OR Aldurazyme[*all*])	235
COCHRANE CENTRAL	(Mucopolysaccharidosis OR mps OR Hurler-Scheie OR Scheie) AND (enzyme replacement therapy OR ERT OR laronidase OR Aldurazyme)	3 2 45 8
- All Cochrane review - Other reviews - Trials - Technology assessments		
LYLACS	(Mucopolysaccharidosis or hurler or scheie or hurler-scheie) AND (enzyme replacement therapy or Aldurazyme or laronidase)	11
EMBASE	("Mucopolysaccharidosis AND I" OR Hurler OR Scheie OR "Hurler Scheie") AND (laronidase OR aldurazyme)	336