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Review

Laronidase for treating mucopolysaccharidosis type I

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ABSTRACT. Mucopolysaccharidoses are a group of inherited metabolic diseases caused by the absence or deficiency of the lysosomal enzymes that are needed for breaking down glycosaminoglycans (GAGs). Over time, GAGs collect in cells, blood and connective tissues, and increased amounts are excreted in the urine. The result is permanent and includes progressive cell damage that affects the individual's appearance, physical abilities, organ and system functioning and, in certain cases, mental development. Enzyme replacement therapies are currently in use or are being tested for at least three different subtypes (I, II and VI). The aim of the present study was to evaluate the effectiveness and safety of laronidase for treating mucopolysaccharidosis type I. A systematic review of the literature was conducted. A computerized electronic search was then conducted using the CENTRAL, Pubmed, EMBASE, and LILACS databases, to identify any randomized controlled trials. The last date of the search was June 2006. There was no possibility

of combining the results, because only one study was included. In the pivotal placebo-controlled trial conducted over a 26-week period, there was a reduction in the urinary excretion of GAGs among treated patients. Regarding adverse events, there were no laronidase-related serious adverse events or deaths. Laronidase seems to be a promising agent for treating mucopolysaccharidosis type I, as shown by the reduction in the urinary excretion of GAGs and the associated improvements in vital capacity and in the performance of defined physical tasks.

Key words: Mucopolysaccharidosis type I, Hurler syndrome, Iduronidase

INTRODUCTION

Mucopolysaccharidosis type I (MPS-I; α-L-iduronidase deficiency) is one of a series of inherited metabolic disorders that involve a class of complex carbohydrates called mucopolysaccharides (also known as glycosaminoglycans or GAGs) which end up being deposited in body tissues of affected individuals who lack the specific enzyme responsible for its catabolism. MPS-I is a progressive, debilitating and life-threatening disease. People with MPS-I have an inherited disorder caused by a deficiency of α-L-iduronidase (Hartung et al., 1999; Yogalingam et al., 2004; Wraith, 2005). The deposition of mucopolysaccharides in several tissues leads to damage and distortion, and results in the stunting of children's growth and development, limitations in joint movement and, in some (but not all) types of MPS, the development of mental retardation.

Hurler syndrome is the most severe of the MPS-I subtypes. Developmental delay is evident by the end of the first year, and patients usually reach a plateau in their development between the ages of two and four years. This is followed by progressive mental decline and loss of physical skills (Scott et al., 1995). Language may be limited due to hearing loss and an enlarged tongue. In time, the clear layers of the cornea become clouded and the retina may begin to degenerate. Carpal tunnel syndrome (or similar compression of nerves elsewhere in the body) and restricted joint movement are also common.

Although no studies have been conducted to determine the frequency of MPS-I in the United States, studies in British Columbia have estimated that one in 100,000 babies born has Hurler syndrome. The estimate for Scheie syndrome (an attenuated clinical variant) is one in 500,000 births, and for Hurler-Scheie syndrome (the intermediate form) it is one in 115,000 births (Meikle et al., 1999; Wikipedia, 2007).

The underlying cause of this group of disorders is an inability to break down and store mucopolysaccharides (primarily heparan and dermatan sulfate), which are the main components of connective tissues. As a consequence, excessive amounts of GAGs pass into the blood circulation and are stored throughout the body, with some excreted in the urine. There are many different kinds of GAGs and numerous different enzymes are needed to break them down. Thus, there are different types of MPS; each one caused by a specific defect in the gene which encodes a particular enzyme involved the sequential degradation pathway of GAG metabolism.

Enzyme replacement therapy, first administered to patients with Gaucher disease in 1991, has also been developed for MPS-I, starting in 2001. Treatment for one year with the recombinant enzyme (laronidase) given to an α-L-iduronidase-deficient patient was found to "ameliorate some clinical manifestations of the disease".

Laronidase is indicated for enzyme replacement therapy in patients with a confirmed diagnosis of MPS-I, for treating non-neurological manifestations of the disease (i.e., unrelated to the brain or the nerves). The non-neurological symptoms of MPS can include an enlarged liver, joint rigidity (thereby making movement difficult), obstructive pulmonary disease, heart disease, and ocular disease. Laronidase forms a colorless to pale yellow solution for intravenous administration.

The aim of the present study was to evaluate the effectiveness and safety of laronidase compared to placebo or other interventions for treating MPS-I.

MATERIAL AND METHODS

Studies selected

We included randomized and quasi-randomized controlled trials (both blind and non-blind, and without language restriction), to evaluate the effectiveness and safety of laronidase in patients of all ages with a diagnosis of MPS-I. The following comparisons were considered: laronidase (α-L-iduronidase) compared with other interventions or no intervention or placebo, and different doses of laronidase.

The following outcomes were sought in the studies included: mortality; morbidity; decreases in complications (such as compression of the spinal cord leading to loss of nerve function, deformities of the extremities, visual impairment due to corneal clouding, blindness, cardiomyopathy, heart valve disease, respiratory complications, sleep apnea/hypopnea, etc.); quality of life; hormonal parameters, and adverse events.

A computerized electronic search was then conducted using the Cochrane Central Register of Controlled Trials (CENTRAL; Cochrane Library, 2006), Pubmed (1966-2006), EMBASE (1980-2006), and *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS; 1982-2006), to identify randomized controlled trials. Because we searched with both subject headings and free text words, it was expected that all studies on MPS would be identified. The words used to identify the clinical situation and the intervention were 'mucopolysaccharidosis*', α-L-iduronidase and α L iduronidase.

Additional searches were performed on websites such as http://www.controlled-trials.com, http://clinicaltrials.gov/ct/gui, and http://www.cancernet.nci.nih.gov/pdq.htm, http://www.eortc.be, http://www.ctg.queensu.ca, http://www.CenterWatch.com. The reference lists of the relevant studies identified were also scrutinized.

Data extraction and methodological quality assessment

Two reviewers (RED and GMP) independently assessed the titles and abstracts of all reports. Full-text hard copies were obtained for studies that appeared via the selection criteria, and for studies for which there was some doubt whether they fulfilled the selection criteria. The authors also independently assessed the report quality of the studies included. The criteria described by Schulz et al. (1995) were used to assess the methodological quality. These criteria consisted of the following items: allocation concealment, double blinding and reported withdrawals and dropouts.

Statistical analysis

For dichotomous variables, the relative risks and risk differences with 95% confidence intervals were calculated by means of the random-effect model (DerSimonian and Laird, 1986).

When the overall results were statistically significant, the number-needed-to-treat and the number-needed-to-harm were calculated using the inverse of the risk difference.

The heterogeneity was quantified using the chi-square test for heterogeneity and the I^2 = [(Q - d.f.) / Q] x 100% test, where Q is the chi-square test and d.f. stands for degrees of freedom. This illustrates the percentage variability in effect estimates that results from heterogeneity rather than from sampling error (Higgins et al., 2003; Higgins and Green, 2005). Meta-analyses with I^2 greater than 25% were considered to be heterogeneous.

RESULTS

Description of the studies

A total of 1290 titles were identified through the search strategy in the electronic database (Figure 1). Following the verification of 44 whole articles, four of them were considered for inclusion in this review. Three studies were excluded (Kakkis et al., 2001; Grewal et al., 2005; Sardón et al., 2005) because they were case series or phase II clinical trials that only evaluated the pharmacokinetics of the medication (Table 1). Only one study fulfilled all the inclusion criteria of this review (Wraith et al., 2004).

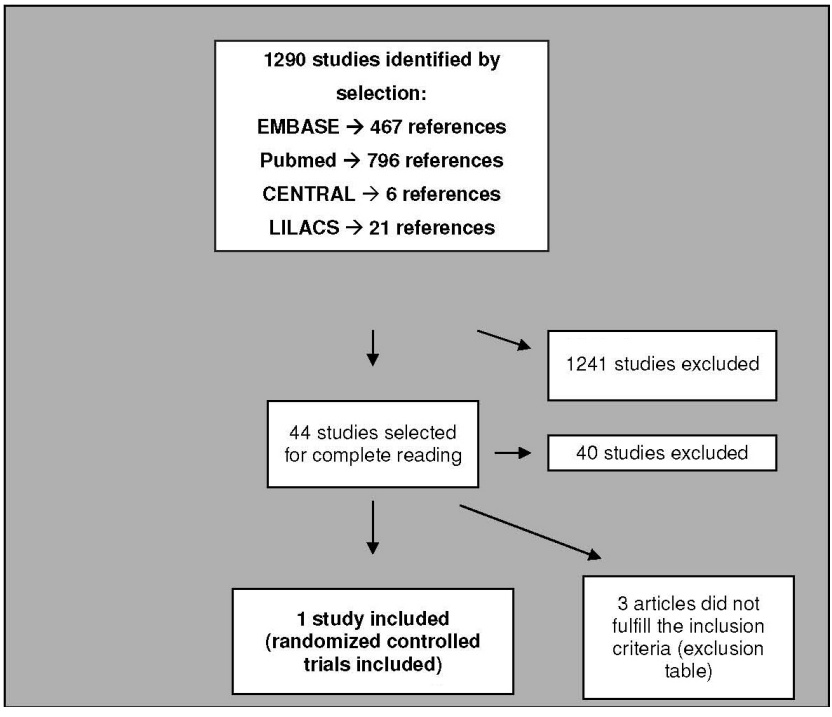

Figure 1. Trial flow diagram.

Table 1. Characteristics of excluded studies.

Study	Reason for exclusion
Grewal et al., 2005	Case series
Sardón et al., 2005	Case series
Kakkis et al., 2001	Case series

Wraith et al. (2004) evaluated 45 patients with a diagnosis of MPS-I and investigated the effects of laronidase at 100 U/kg (0.58 mg/kg) (N = 22) versus placebo (N = 23), administered intravenously on a weekly basis.

Methodological quality of the studies included

The study included was classified as B according to the Cochrane Collaboration Handbook (Schulz et al., 1995). This designation was based on the absence of descriptions of the randomization process. In other words, the authors did not report how the allocation concealment or allocation generation was performed. Moreover, the blinding process in relation to the outcome to be evaluated was not reported. With regard to descriptions of losses from follow-up and patients who withdrew, Wraith et al. (2004) reported these details. Wraith et al. (2004) reported that all the participants completed the follow-up and underwent the final evaluations.

There was no possibility of combining the results, because only one study was included and reported its data in a proper manner for inclusion in quantitative analysis using the RevMan software. Thus, we only performed representations of a meta-analysis, using a single study.

Figure 2 shows the representation of a meta-analysis using a single study (Wraith et al., 2004) that compared laronidase 0.58 mg/kg versus placebo, where the expected outcomes considered were vital capacity in the 26th week after the treatment and the mean difference between the initial evaluation and the 26th week visit. There was a statistically significant difference in the subcategory of mean difference between the initial evaluation and the 26th week (weighted mean difference, WMD = 5.60 [95%CI: 1.25, 9.96]), and also in relation to the total for these subcategories (WMD = 4.62 [95%CI: 0.64, 8.59]).

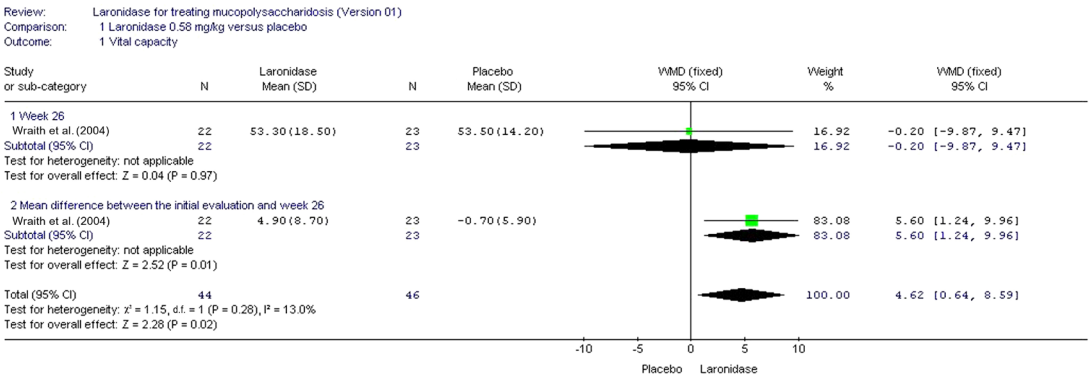

Figure 2. Representation of a meta-analysis using a single study (Wraith et al., 2004) that compared laronidase 0.58 mg/kg versus placebo. Outcome evaluated: vital capacity. WMD = weighted mean difference; 95%CI = confidence interval at 95%.

The representation of a meta-analysis using a single study (Wraith et al., 2004) that compared laronidase 0.58 mg/kg versus placebo is shown in Figure 3, in which the expected

outcomes considered were a 6-min walk test in the 26th week after the treatment and the mean difference between the initial evaluation and the 26th week visit. There were no statistically significant differences in any of the subcategories presented, or even in relation to the total for the subcategories (WMD = 27.60 [95%CI: -7.52, 62.72]).

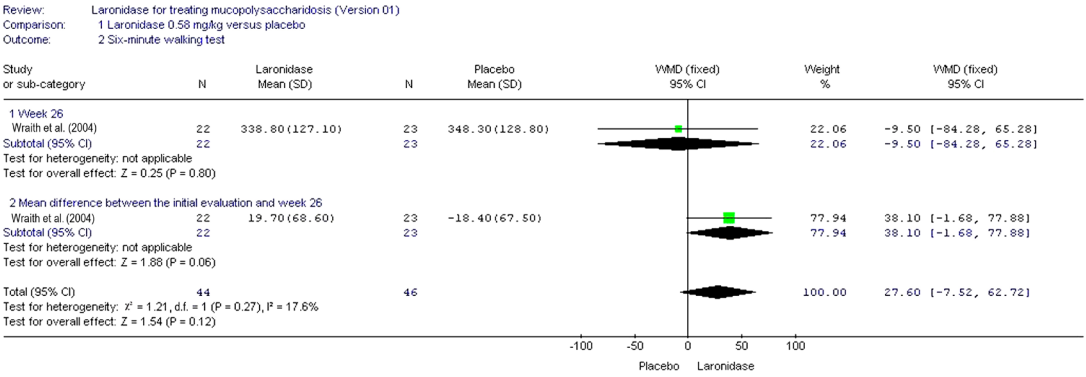

Figure 3. Representation of a meta-analysis using a single study (Wraith et al., 2004) that compared laronidase 0.58 mg/kg versus placebo. Outcome evaluated: a 6-min walk test. WMD = weighted mean difference; 95%CI = confidence interval at 95%.

The representation of a meta-analysis using a single study (Wraith et al., 2004) that compared laronidase 0.58 mg/kg versus placebo is shown in Figure 4, in which the expected outcomes considered were adverse effects (infusion-related reactions occurring in at least one laronidase-treated patient). There were no statistically significant differences in any of the subcategories presented.

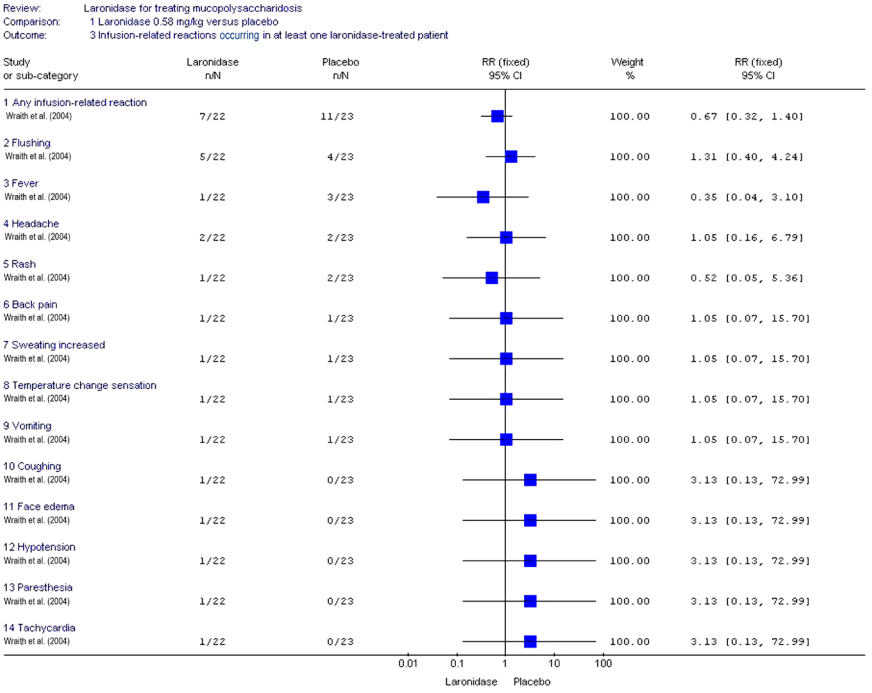

Figure 4. Representation of a meta-analysis using a single study (Wraith et al., 2004) that compared laronidase 0.58 mg/kg versus placebo. Outcome evaluated: adverse effects. RR = relative risk; 95%CI = confidence interval at 95%.

There were no laronidase-related serious adverse effects or deaths. The majority of events were associated with underlying MPS-I disease.

DISCUSSION

The results are limited, although they demonstrate a benefit in favor of laronidase, in comparison with placebo. We made two representations of meta-analyses, using data from the study by Wraith et al. (2004), which evaluated vital capacity and performance in the 6-min walk test. In the first outcome, there was a statistically significant difference in the subcategory "mean difference between the initial evaluation and the 26th week", and in relation to the total for these sub-categories.

These results were influenced by the small sample size, the lack of data described in the studies that could be used to perform a meta-analysis, the uncertainty relating to adjustments in the generation and concealment of randomization of the subjects to the two study groups, and the certainty that there was no blinding relating to the outcomes evaluated by the study investigators (which would tend to favor the treated group). Nonetheless, systematic reviews are still the best study design for answering questions about disease treatment. Even with the possible bias in the studies included, the evidence-based medicine approach indicates that it is preferable to obtain results from evidence level I (systematic reviews and meta-analyses) than to use non-controlled studies (case series and case histories), or retrospective studies (case-control studies) in which, in practice, memory bias is present and has an influence on the results of the studies, or the divergent opinions of specialists, or *in vitro* and animal research.

The study demonstrated that laronidase is effective and safe for patients with MPS-I, because after about 26 weeks of treatment there was a reduction in the urinary excretion of GAGs and an improvement in vital capacity, in comparison with findings for the placebo group (Wraith et al., 2004).

Implication for clinical practice

The evidence available at present is limited because there is only one randomized clinical trial found in the medical literature. Moreover, the sample size of the study included in this review was small, which made it difficult to detect statistical differences between the study groups. Likewise, the data from the study included were poorly reported, making more precise quantitative analysis difficult. Although the evidence found in relation to internal validity was weak (which thus influences the external validity, i.e., the applicability to clinical practice), laronidase seems to be promising for the treatment of MPS-I, with regard to improvement in vital capacity and walking distance test performance and reduction in urinary excretion of GAGs. Although adverse effects occurred more frequently in the groups that received the drug, it was found that such effects could be controlled, thus making the treatment efficient. However, the clinical decision regarding the use of this drug must be based on three matters before reaching a definitive conclusion: the physician's experience; the desire and the circumstances of the patient, and the evidence currently available, taking into consideration the degree of recommendation and, most importantly, the strength of the evidence, with clinical evaluation of the internal validity of each study.

Implications for scientific research

More randomized clinical trials with sufficiently large sample sizes to detect possible statistical differences between the study groups are needed to prove the beneficial effects of laronidase. Subgroups of patients with MPS must be analyzed, to take into consideration all types of the disease (Hurler, Hurler-Scheie, Scheie syndrome). Furthermore, studies with different doses of laronidase must be conducted, so that the ideal drug dose can be determined. The outcomes must be standardized and evaluated whenever possible. This is so that data for meta-analysis can be obtained, so as to increase the sample size and, consequently, the statistical power of the analysis. Trials must prove internal and external validity, in order to have more reliable results.

Potential conflict of interest

None known.

REFERENCES

DerSimonian R and Laird N (1986). Meta-analysis in clinical trials. *Controlled Clin. Trials* 7: 177-188.

Grewal SS, Wynn R, Abdenur JE, Burton BK, et al. (2005). Safety and efficacy of enzyme replacement therapy in combination with hematopoietic stem cell transplantation in Hurler syndrome. *Genet. Med.* 7: 143-146.

Hartung SD, Reddy RG, Whitley CB and McIvor RS (1999). Enzymatic correction and cross-correction of mucopolysaccharidosis type I fibroblasts by adeno-associated virus-mediated transduction of the alpha-L-iduronidase gene. *Hum. Gene Ther.* 10: 2163-2172.

Higgins JPT and Green S (2005). Cochrane Reviewers' Handbook 4.2.5. Assessment of study quality. In: The Cochrane Library. Vol. 3. John Wiley and Sons Ltd., Chichester.

Higgins JP, Thompson SG, Deeks JJ and Altman DG (2003). Measuring inconsistency in meta-analyses. *BMJ* 327: 557-560.

Kakkis ED, Muenzer J, Tiller GE, Waber L, et al. (2001). Enzyme-replacement therapy in mucopolysaccharidosis I. *N. Engl. J. Med.* 344: 182-188.

Meikle PJ, Hopwood JJ, Clague AE and Carey WF (1999). Prevalence of lysosomal storage disorders. *JAMA* 281: 249-254.

Sardón O, Pardos CG, Mintegui J, Ruiz EP, et al. (2005). Evolución de dos pacientes com síndrome de Hurler en tratamiento con enzima recombinante humana alfa-L-iduronidasa. *An. Pediatr.* 63: 61.

Schulz KF, Chalmers I, Hayes RJ and Altman DG (1995). Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 273: 408-412.

Scott HS, Bunge S, Gal A, Clarke LA, et al. (1995). Molecular genetics of mucopolysaccharidosis type I: diagnostic, clinical, and biological implications. *Hum. Mutat.* 6: 288-302.

Wikipedia (2007). The free encyclopedia. Mucopolysaccharidosis. http://en.wikipedia.org/wiki/Mucopolysaccharidosis. Accessed January 27, 2007.

Wraith JE (2005). The first 5 years of clinical experience with laronidase enzyme replacement therapy for mucopolysaccharidosis I. *Expert. Opin. Pharmacother.* 6: 489-506.

Wraith JE, Clarke LA, Beck M, Kolodny EH, et al. (2004). Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). *J. Pediatr.* 144: 581-588.

Yogalingam G, Guo XH, Muller VJ, Brooks DA, et al. (2004). Identification and molecular characterization of alpha-L-iduronidase mutations present in mucopolysaccharidosis type I patients undergoing enzyme replacement therapy. *Hum. Mutat.* 24: 199-207.