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Enzyme replacement therapy for the treatment of Hunter disease: A systematic review with narrative synthesis and meta-analysis

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ABSTRACT

Background: In the last 10 years enzyme replacement therapy (ERT) has become an alternative for the treatment of patients with Hunter disease (HD). Nevertheless, the information regarding efficacy and safety is scarce and mainly based on the pivotal trials. This scarcity is especially evident for adults and severe forms of HD.
Methods: A systematic review of publications in the electronic databases PUBMED, EMBASE and Cochrane Central was undertaken. Clinical trials and observational studies were included. The data about efficacy and security were retrieved and analysed with Review Manager version 5.3.
Results: 677 records were found, 559 remaining after the removal of duplicates. By title and abstract review, 427 were excluded. Full reading of the rest was made (122 publications) and 42 were finally included. It was not possible to perform meta-analysis of all the endpoints due to high heterogeneity in the reporting and measuring of variables in each publication. Eight clinical trials were included, 6 with high risk of bias. The quality of the other studies was low in 12%, average in 68% and good in 21%. Main findings were: a reduction in the elimination of glycosaminoglycans (GAG) in urine in all the studies (26/26), decrease in liver and spleen size (18/18), increase of 52.59 m (95% CI, 36, 42–68.76, $p < .001$) in the 6-min walk test (TM6M), increase in forced vital capacity (FVC) of 9.59% (95% CI 4.77–14.51, $p < .001$), reduction of the left ventricular mass index of 3.57% (95% CI 1.2–5.93) and reduction in mortality (OR) of 0.44 (0.27–0.71).
Discussion: The data suggests a clear and consistent effect of ERT in HD reducing the accumulation of GAGs in the body, demonstrated by the reduction of its urinary excretion, as well as by the reduction of its deposits (spleen, liver and heart). Likewise, there is an improvement in physical and respiratory function. In addition, a reduction in mortality has been observed. Lack of studies, small size of the samples, and methodological deficiencies are the main limitations to establish definite conclusions.
Conclusions: The data suggests that ERT is effective and safe in the treatment of HD. There is a need to evaluate patient-centred outcomes and the impact on quality of life.

1. Background

Hunter disease (HD) or mucopolysaccharidosis type II (MPS II, Hunter syndrome, OMIM 309000), is a rare, multisystemic, lysosomal deposit disease caused by a deficiency of the enzyme iduronate-2-sulfatase (I2S). This produces progressive accumulation of glycosaminoglycans (GAGs) heparan sulphate and dermatan sulphate in multiple systems and organs. These accumulations give rise to skeletal malformations, organ enlargement (especially liver and spleen), mental retardation, short stature, cardiac and pulmonary disease. Two

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phenotypes have been described, the severe and the attenuated. The severe is characterized by a serious affectation of the central nervous system at early stages of life, severe respiratory difficulties, dysostosis multiplex and early death. The attenuated form is characterized by a milder involvement but in the same organs and the affected individuals usually reach adulthood without CNS impairment. The disease has an inheritance pattern linked to chromosome X. Therefore, it affects mainly males, although rare cases have been described in females due to the selective inactivation of the healthy X chromosome [1].

In the last ten years, enzyme replacement therapy (ERT) has emerged as an alternative for HD treatment. Some clinical trials and observational studies have been published with promising results [2,3]. Two molecules are available, Idursulfase alpha (IDSα) [4] and Idursulfase beta (IDSβ) [2], although the latter is not commercialized in the European Union nor in the United States. In the trials, the treatment efficacy has been measured mainly by the determination of the urine concentration of GAGs. However, it is not clear that normalization of this parameter supposes a clinical improvement. Other variables have been measured, nevertheless, the results have not been consistent. Likewise, it is not clear that the therapy affects both phenotypes equally. Other therapies still under development are hematopoietic stem cell transplant and gene therapy [5,6].

There are few literature reviews that systematically summarize and analyse the clinical impact and safety of existing ERT in HD both in clinical trials and in real life studies beyond the pivotal trials [2,4]. This scarcity is especially evident when patient-centred outcomes such as mortality and quality of life (QOL) are considered. That is why the present study is proposed, with the aim of evaluating the efficacy of ERT in HD in terms of the impact on clinical and safety variables.

2. Methods

2.1. Bibliographic search

A bibliographic search was carried out in PubMed, Embase and Cochrane Central using the key words: “Therapeutics” AND “Iduronate Sulfatase” AND “Mucopolysaccharidosis II”. No restriction for age, sex, country, ethnicity, language, or date of publication was applied. The search was made on September 30, 2018. Any type of publication (clinical trials, observational studies, case series, case reports or case-control studies) approaching the impact of any of the available ERT for HD were considered. Entries retrieved were initially screened by title and abstract. Final decision to include an article was based on the reading of the full text. All studies that reported on the outcomes of interest (defined below) were included. Evaluation of the methodological quality of the included studies was undertaken using the recommendations of the Cochrane Collaboration for clinical trials [7], and the recommendations of the National Library of Health for the rest of the study types [8].

A protocol was developed for the study that is available through e-mail to the corresponding author.

2.2. Data collection

Two investigators (PW and AL) performed the search independently and collected the data in a specific data collection form. Later, they were introduced in Review Manager version 5.3© (Revman 5.3, Cochrane foundation©, Denmark) [9] for further analysis. Differences were resolved by discussion.

2.3. Outcome measures

Clinical efficacy outcome measures were: Glycosaminoglycans in urine samples (mg/g of creatinine), distance covered in 6 min walking (6MWT, meters), left ventricular ejection fraction (LVEF, %), left ventricular mass index (LVMI, g/m^2), height (centimetres), cognitive status, apnoea's and hypopneas index, mortality and quality of life. The considered clinical safety measures were patients with adverse effects, patients with mild adverse effects, patients with serious adverse effects, and patients who developed anti-I2S immunoglobulins. The incidence of all the safety outcomes was expressed as the percentage of the patients with a secondary effect respect to the number of total infused patients in the sample of the study.

2.4. Statistical analysis

When, due to the different ways of communicating the results in the finally included studies (different units, analysed variables…), it was not possible to perform a formal meta-analysis of a prespecified item, a narrative synthesis was made through a critical reading of the studies. When it was possible to perform meta-analysis, the difference in means was used as the magnitude of the effect, making grouped estimates using the inverse variance method. Subgroup analyses were planned by type of HD (attenuated vs. severe defined by the presence/absence of central nervous system symptoms), age group (older or younger than 6 years, and older than 18) and by type of molecule (alpha or beta Idursulfase).

3. Results

3.1. Bibliographic search and evidence quality

The bibliographic search resulted in the finding of a total of 677 records, of which 559 remained after elimination of duplicates. After considering title and abstract, 427 publications were excluded, leaving 122 for full text reading. Forty-two 42 publications were finally included in qualitative synthesis (Fig. 1). The reasons for exclusion of articles read in full text were “no information about our items of interest”, “to be a review” and “to be an abstract of a congress”. The final list of included studies were 8 clinical trials, 21 observational studies, 12 clinical cases and 1 case-control study. Annex 1 describes the main characteristics of the included studies as well as the endpoints about efficacy and security on which they report.

The eight included clinical trials were evaluated for their risk of bias according to the Cochrane library tool for evaluating risk of bias for this kind of publication (Fig. 2). A global high risk of bias was found as the trials do not report randomization and allocation concealment clearly or they were not randomized by design. It must be noted that all the trials were industry sponsored.

A study of quality assessment was done for the finally included publications other than clinical trials, with 21% found to have a good, 68% fair and 12% poor methodological quality.

3.2. Efficacy outcomes

Consistently, in all the evaluated articles a strong reduction of urinary GAGs was found. The reduction was stabilized after approximately the first four months of treatment. A dose response gradient was seen in studies that used different doses [2,4,10]. The reduction was observed at all ages, in both attenuated and severe phenotypes, and with both IDSα and IDSβ [2,11]. In a similar way all eighteen studies that analysed the impact on liver and spleen size (Four clinical trials, five observational studies, four case series and five individual clinical cases) reported very significant decreases of both liver and spleen sizes. This effect was again observed in all age ranges, as well as in the attenuated and severe phenotype.

Twelve studies reported the effect on the walked distance during the 6MWT. Eight studies reported an improvement in both adults and children. A dose-response gradient was observed with IDSα [4,11], but not with IDSβ [2]. Likewise, the authors reflected in different studies that patients expressed an increase in subjective individual global energy and resistance [12]. It has also to be considered that in a few cases

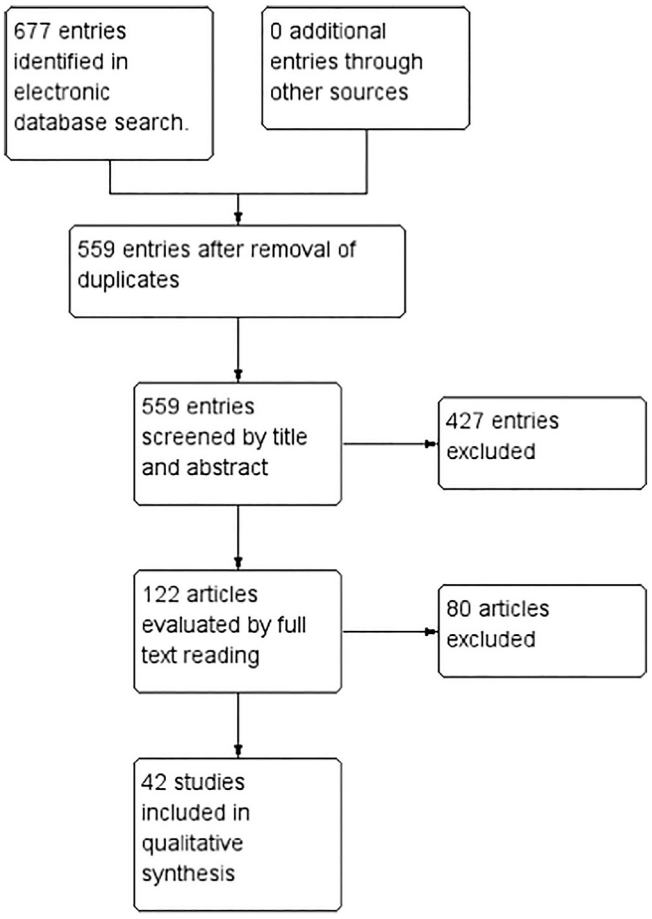

Fig. 1. Flow diagram of the systematic review.

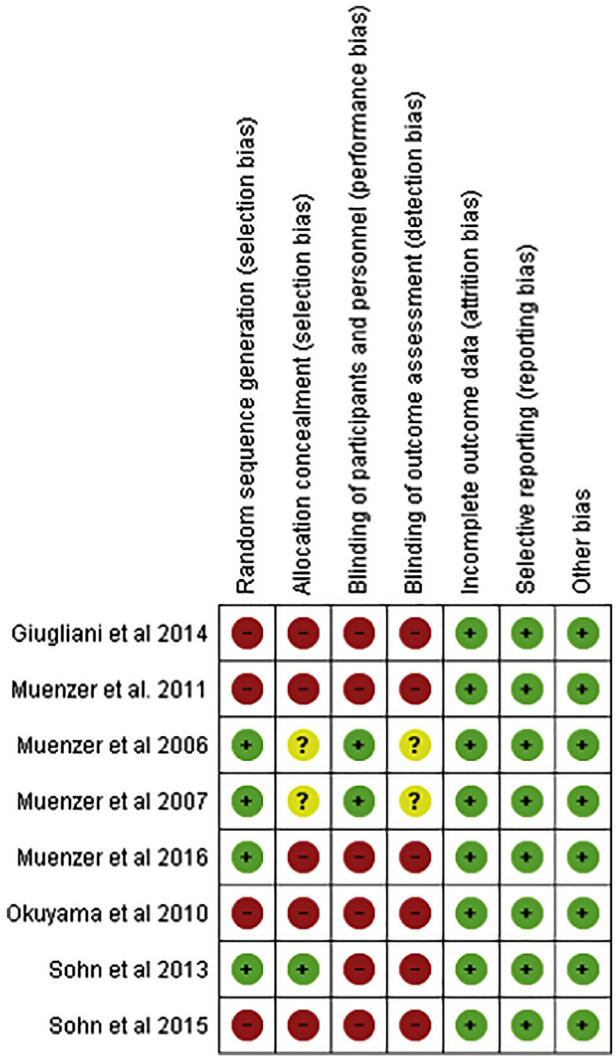

Fig. 2. Risk of bias by clinical trial.

this test was performed in patients with severe phenotype with inconsistent results: improvement in some patients [13] and lack of it in others [14]. Nine publications were included for meta-analysis, showing an average increase of 52.59 m (95% CI 36.42–68.76) in the 6MWT.

Only three studies were found that reported on mortality. They were all prospective observational studies, only with IDSα. The mortality ranged from 7.69–15.5% in patients treated after 2–4 years of follow-up. The most frequent causes of death were respiratory failure (34.7% in treated patients and 35.7% in non-treated patients), cardiac arrest (12.9% vs. 10.7%) and pneumonia (8.87% vs. 10.7%). The only study comparing untreated patients with those on ERT, a reduction in mortality was observed, with an odds ratio (OR) of 0.44 (0.27–0.71). Age at diagnosis of HD (OR 0, 89 (0.84–9.94)), the presence of cognitive impairment (OR 4.84 (3.13–7.47)) and being native of Latin America (OR 3.13 (1.83–5.35)) were showed as mortality predictors [15].

Consistently, in all studies (one clinical trial, two observational studies and three case series) an improvement in quality of life was observed, especially in the attenuated phenotype of HD. However, it has been measured very heterogeneously in the studies with different instruments, preventing realization of meta-analysis. Information about the impact of ERT on QOL in patients with severe HD phenotype was absent because they were not represented in the studies, but a decrease in respiratory infections and hospitalizations secondary to this problem was reported, which could lead to a better quality of life.

Eight studies reported on cardiac size expressed as left ventricular mass index (g/m^2): two clinical trials, two prospective observational studies, two clinical cases series, and two individual clinical cases. Decrease in the cardiac size was observed quite consistently with a dose-response gradient reported by Sohn et al. [2] This decrease seemed clearer in patients with ERT started at younger ages with one communication suggesting that very early onset can prevent myocardiopathy [16]. It was possible to include 3 studies in meta-analysis observing a reduction of 3.57% (1.20–5.93) of the LVMI. After considering five studies (three clinical trials, one prospective observational study, one clinical cases series, and one clinical case) the impact on LVEF was not clear with two studies reporting the absence of any effect, two others showing improvement in some patients whilst in others it gets worse. In the last study evaluated, LVEF worsened slightly. Two studies were included in meta-analysis, not detecting differences after ERT. As the third cardiac efficacy endpoint, eleven studies were found that reported about the effect of ERT on cardiac valvular system: three prospective observational studies, five case series, and three individual clinical cases. Quite consistently, ERT stabilized the valvulopathies. However, in some studies there were patients with progression of valve disease. Two papers suggest that early onset of ERT could prevent the development of heart valve disease [17,17].

When considering respiratory outcomes, eight studies reported on forced vital capacity (Five clinical trials, one prospective observational study, one retrospective observational study, and one clinical cases series). In all studies except one [18] children and young adults were predominantly included. No consistent results have been obtained for this item, with an improvement in some [19] studies and no benefit in others [20]. In fact, when meta-analysing for the first instance, a favourable tendency to IDS was observed, but it was not significant

($p = .09$). However, when performing a sensitivity analysis including only studies with a higher level of evidence, this difference was significant ($p < .0001$), with an increase of 9.59% (4.77–14.41) in forced vital capacity. Similar effect was observed in the single study with adults [19].

Seven publications evaluated the effect of ERT on the rate of apnoea's and hypopneas and the development of sleep apnoea syndrome (SAS): two clinical trials, two observational studies, two case series and one individual case report. A reduction in apnoea/hypopnea index (AHI) was generally observed. However, cases have also been reported in which the patient develops SAS after the start of ERT, so the effect is not clear. In addition, the specific values of the AHI were not published in most of the articles, so meta-analysis was not possible.

When considering joint mobility, thirteen of the fourteen studies including this endpoint (Three clinical trials, three observational studies, four clinical cases series, and four individual clinical cases) reported a positive but very modest effect of ERT on this variable of efficacy. However, in most studies, patients reported a subjective feeling of improved mobility.

One clinical trial, five observational studies, two clinical case series and three individual clinical cases contained information about the impact of ERT on growth. The effect seems to be positive, but minimal, practically negligible. In the two largest studies it was observed that ERT seems to have a positive effect on the growth rate, with a decrease in the slope of regression of the height z score values with a difference since the initiation of ERT of 0.038 ($p = .004$), although the impact on the obtained final height was minimal [21,22]. In the study by Jones et al. [22], the study with the largest number of participants ($n = 133$), it was observed that cognitive impairment did not influence growth. It was found that those mutations associated with a severe phenotype and age at ERT start, influenced the rate of growth [22]. The high heterogeneity in the way of analysing the impact of ERT on growth used in the different studies precluded the use of a formal meta-analysis.

Data about the effect on cognitive impairment were present in three observational studies, two clinical case series, and three individual clinical cases. As a general summary, it can be said that patients with attenuated phenotype on ERT remain stable in their cognitive status, however, they would probably remain so regardless of the treatment. In patients with a severe phenotype, a discrete improvement in hearing and on functional status could give an increased score on cognitive tests by better interaction with the environment, but without any real impact on cognitive function [23]. Once again, the highly heterogenous way to measure and express this outcome in the studies, prevent the use of meta-analysis.

Complementary figures and tables are available in annex1.

3.3. Safety outcomes

A total of twenty-two studies were found that analysed the safety of ERT in HD: eight clinical trials, eight observational studies, four clinical case series and two individual clinical cases.

The most frequent adverse events (AE) were mostly mild-moderate and present in approximately 50% of patients. They were principally: cough, headache, feverish reaction, nausea, vomiting, pruritus and urticaria [4]. Serious adverse effects (SAE) were presented by 7–8% of patients. In four clinical trials both mild-moderate and severe adverse events occurred in the comparison group with a similar frequency.

Most adverse events were experienced during the first 3 months of treatment, beyond this point in time they were rare. It seems that the appearance of adverse effects is not related to the presence of IgG anti-IDS antibodies [24]. IgG anti-IDS antibodies do not normally affect clinical efficacy either [25], although, occasional case reports have described a lesser decline in urine GAG and lack of efficacy in patients with very high anti-IgG titer and lack of ERT efficacy [25]. Extraordinarily, the need to withdraw ERT due to serious adverse effects related to urticaria and hypotension has been described, with a communication in which switching to IDSβ relieved these symptoms [26].

The safety of home administration of ERT has been demonstrated in an observational study with 671 patient-weeks of treatment with IDSα after six or more months of hospital administration. An improved therapeutic compliance was also found in this study [27].

4. Discussion

The main findings of the present systematic review about the efficacy of ERT in HD suggest a global beneficial effect of ERT on HD at multiple levels. It seems clear that there is a reduction in the elimination of urine GAG, an improvement in the FVC, as well as the 6MWT and the LVMI. Likewise, although formal meta-analysis could not be performed because of the high methodological heterogeneity among the included publications, a normalization of hepatic and splenic volumes was observed consistently across all studies. The observed mortality decrease in the single study that compared ERT versus no treatment is especially noteworthy. It is probable that ERT also improves quality of life, although it has not been possible to perform a meta-analysis due to the different methodologies applied in the included studies. Nevertheless, the results were consistent across all of them and supports the efficacy of ERT in the treatment of HD.

At other levels, the efficacy seems to be less clear or absent. The two largest studies, both indicate that the growth of patients with Hunter disease is within normal range until 8 years of age, then the growth rate decreases with a final height 2 standard deviations below the general population average. On this endpoint the effect of the ERT seems positive but limited to a reduction in the growth slowdown. The effect on LVEF, valvular disease, joint mobility and SAHS seemed to be minimal or even lacking. On other variables the effect was even less clear. In the CNS a very doubtful benefits for patients with mild cognitive impairment was seen, and no significant improvement in those patients with severe cognitive deterioration [24]. This was an expected result as the IDS molecule does not cross the blood-brain barrier. The intrathecal administration of IDS has been tried and a marked reduction of GAGs in CSF has been observed [28]. However, it is still to be seen if it has an impact on cognitive decline.

Intravenous administration of IDS was generally safe. One third to half of the treated patients developed mild adverse effects, that did not require the suspension of ERT. Although the information is scarce, it seems that the appearance of adverse events is not related to the presence of IgG anti-IDS antibodies [25]. It also seems that the presence of IgG anti-IDS antibodies does not affect clinical efficacy either, unless titer is very high [25,26]. The review of the available literature confirms that for the few patients that develop reactions to the ERT infusions, it is easy to treat by decreasing the speed of infusion and premedicating patients with antihistaminics, antipyretics and corticosteroids. It has even been observed that the administration of ERT at home is safe and produces an increase in the QOL of both patients and their families [29].

Because most of the studies on ERT in HD published in the literature and among the included studies in the present review (37 of 42) evaluated IDSα, the reported benefits should be interpreted as mainly representing this molecule. Nevertheless, it can be established that IDSβ has also demonstrated a reduction in urine GAG, reduction in liver and spleen size, increase in the 6MWT and a similar safety profile as IDSα. On the other hand, IDSα has shown a correlation between the dose and the efficacy in some endpoints as the walked distance on 6MWT. A significant decrease in the mortality rate compared with untreated patients has also been communicated.

The main strength of the present work is that it is the largest and most complete review of ERT in HD to date. It provides clarity on the improvement in some clinically relevant parameters such as the FVC that in previous reviews did not show significance, as well as the LVMI [30]. The present study also provides an analysis of the existing

evidence on the impact of ERT on quality of life and mortality, which were absent in previous reviews [31]. The main limitation is that the existing evidence is rather scarce, with few well-designed clinical trials and fundamentally supported by observational studies and case series. It seems clear that ERT has a beneficial effect on GAG metabolism, since it reduces accumulation in the body and mitigates the consequences that derive from this deposit, mainly organomegaly and respiratory distress. However, studies to date have not sufficiently evaluated relevant results for the patient, such as reduction in respiratory infections, hospital admissions, improvement in quality of life or reduction in mortality. Nonetheless, as illustrated in the present study, ERT seems to have a beneficial effect on these two last variables. It is also clear that IDSα and IDSβ are safe for the treatment of HD with the possibility of home based administration. Future investigations should evaluate and clarify these gaps being recommendable to achieve a methodological consensus to unify ways to measure and define efficacy and safety endpoints.

5. Conclusions

ERT in HD was found effective reducing GAG in urine, improving 6MWT, and FVC. It also seems clear that it reduces the liver and spleen volume as the LVMI and mortality. The effect on growth is not clear, since long-term comparative studies with enough numbers are necessary to draw adequate conclusions, but it seems that it could have a positive effect, albeit very modest. Regarding cognitive deterioration, no clear effect was observed. It seems that ERT could improve the quality of life in these patients and, although the quality of the evidence is poor, the effect seems quite consistent in the studies where it has been evaluated. Further studies are necessary to evaluate the efficacy of ERT in HD, patient centred outcomes and a detailed evaluation of the impact on quality of life seems especially relevant and necessary. A methodological consensus on the definition and measurement of endpoints could improve the quality of the results and conclusions.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2020.07.005.

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