

The effectiveness and cost of enzyme replacement and substrate reduction therapies: a longitudinal cohort study of people with lysosomal storage disorders

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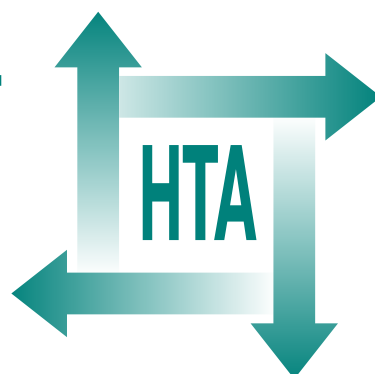


Executive summary

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Executive summary

Background

Lysosomal storage disorders (LSDs) are a group of extremely rare, inherited metabolic diseases affecting about 1 : 7000 people, each involving a deficiency of specific enzymes required for normal metabolism. The consequent accumulation of metabolic substrates results in the clinical features. Over the last two decades, treatments that provide exogenous replacement of the deficient enzyme have been developed for some disorders. Enzyme replacement therapies (ERTs) are licensed in the UK for Gaucher disease, Fabry disease, mucopolysaccharidoses type I (MPS I), type II (MPS II) and type VI (MPS VI), and Pompe disease.

The rarity and severity of these conditions has resulted in a paucity of high-quality, long-term, randomised controlled trials (RCTs) with clinical outcome measures on which to base estimates of the effectiveness and cost-effectiveness of ERTs. In a collaboration between Peninsula College of Medicine & Dentistry, the seven designated treatment centres in England and patient support groups, we conducted a longitudinal cohort study, collecting data from all consenting adults and children with these conditions at designated treatment centres, to estimate treatment effectiveness, health service costs and cost-effectiveness.

Objectives

Primary objectives

- To compare the natural history of treated and untreated LSDs for disorders where ERTs are available.
- To estimate the effectiveness of ERT.
- To estimate the cost-effectiveness of ERT for LSDs.
- To describe the natural history of LSDs where ERT is likely to become available.

Secondary objectives

- To compare the effectiveness of agalsidase alpha (Replagal[®], Shire HGT) with agalsidase beta (Fabrazyme[®], Genzyme) in people with Fabry disease.
- To estimate the lifetime health-care cost and other economic impacts on people with LSDs and their families.
- To provide the basis for future research to develop treatment-responsive measures.

Methods

The National Collaborative Study of Lysosomal Storage Disorders was a multicentre, longitudinal, observational study in which retrospective and prospective clinical data were collected from hospital records. Quality of life (QoL), service-use and cost data were collected using patient-completed questionnaires, administered locally at the hospital and/or completed by the patient at home.

The study was conducted at seven National Specialised Commissioning Group-designated centres in England for the treatment of LSDs and included patients being treated with one of the six LSDs being investigated.

Data sources

Data were collected on all consenting patients and entered into condition-specific databases. Clinical, QoL and service-use data were collected prospectively and some clinical data were collected retrospectively from patients' notes and from the Hospital Information System (HIS).

Participants

All patients with Gaucher disease, Fabry disease, MPS I, MPS II, Pompe disease or Niemann–Pick C (NPC) disease attending one of the designated treatment centres were considered for inclusion in this study. Patients were deemed ineligible for inclusion if their treating clinician felt they would be distressed in any way by being approached to participate. Owing to time constraints, and ongoing clinical trials, only conditions for which therapies are already licensed were included in this study.

Data extraction

Clinical data collected at the patient's annual review using a Case Report Form (CRF) were entered into a secure, web-based, condition-specific electronic data collection system at each site. Retrospective data were extracted from patients' medical records, and/or HIS, into a CRF and entered in the database. The database provided an audit trail of all data entries or amendments and allowed discrepancies or queries to be raised by the coordinating centre. Health-related quality of life (HRQoL), cost and service-use questionnaires were given to patients (or their carer/parent) at their annual clinical appointment and entered into the database; paper copies were kept in study folders.

Ten per cent of patients from each centre were randomly selected for source data verification against the source documents. Source data included patient medical records, letters held within these records and clinical data held on the HIS.

Data analysis

In the core analysis, linear and generalised linear mixed models were developed to study individual dynamics for selected outcomes. These models provided the basis for describing the natural history of LSDs and assessment of the effectiveness of treatments. Treated patients contributed data from the period before they were first treated as well as during treatment. Untreated patients contributed natural history data to estimate the effects of age at diagnosis and the potential time-related decline since diagnosis. The primary analyses compared the effects of time of treatment on outcomes, adjusted for effects of age, gender and, in some cases, other key covariates.

For each condition, treatment efficacy was assessed based on the estimated effects of time since first infusion from the mixed-effects models described above. Further analysis of natural history was conducted by exploring linear growth curve models in a Bayesian framework with patient-specific random effects.

Questionnaire data were used to estimate lifetime health-care costs according to disorder and severity.

Outcome measures

An iterative process was used to decide which outcome measures should be collected for each condition. Clinical members of the team were first asked to define the key functions and organ systems involved for each condition and suggest which outcome measures would best reflect disease progression for each condition. Finally, they were asked to report which of these measures were routinely collected for most patients. Where possible, measures were chosen which clinicians reported would be available in hospital notes over previous years to facilitate retrospective data collection.

Results

Seven hundred and eleven patients (of an estimated 1106 eligible patients) were recruited. With the partial exception of Gaucher disease and Fabry disease, many analyses were hampered by a paucity of data. This was a consequence of both small numbers of affected patients being recruited and, in the case of a substantial proportion of patients, limited data capture for key outcomes.

Gaucher disease

One hundred and seventy-five people with Gaucher disease were recruited. Our data provided strong evidence for an association between time on ERT and a clinically significant improvement in platelet count and haemoglobin in children and adults, regardless of splenectomy status. There was also a strong, statistically significant association between time on ERT and a decrease in the likelihood of having an enlarged spleen or liver. For these analyses, the data suggest substantial improvements over the first 5–10 years of treatment followed by a plateauing of the effect. Data for liver function tests in adults suggested a strong association between time on ERT and reduced aspartate transaminase (AST) levels as well as a lower risk of having an 'abnormal' AST level. There was some evidence suggesting that a longer duration of ERT may be associated with a reduced risk of bone pain in adults and children.

There was no evidence of an association between duration of ERT and QoL or fatigue in adults [Short Form questionnaire-36 items (SF-36) and the European Quality of Life-5 Dimensions (EQ-5D)]. Although no statistically significant association was found between duration of ERT and the total Pediatric Quality of Life Inventory (PedsQL) score in children, we did find an association with a worsening in the social functioning subscale with time on ERT.

Fabry disease

Three hundred and eleven patients with Fabry disease were recruited. We found evidence of a statistically significant association between time on ERT and a small decrease in left ventricular mass index as well as a small increase in the estimated glomerular filtration rate (eGFR) in adults. This latter effect appeared to plateau after 5 or 6 years on treatment.

In gender-specific analyses, the association between time on ERT and increase in age-adjusted eGFR remained statistically significant for women but not for men. After adjusting for use of angiotensin-converting enzyme inhibitors, there was a significant reduction in the risk of proteinuria with increased time on ERT in adults. No statistically significant association between time on ERT and Pain Severity Scores was found, but there was an association between time on ERT and a decrease in the impact of pain on QoL in adults. No association between the risk of stroke or transient ischaemic attacks or the risk of needing a hearing aid and the use of ERT was found.

A statistically significant association was found between duration of ERT and decrease (i.e. worsening) in the SF-36 physical component and mental component scores but not the EQ-5D score, although a significant reduction in patient-reported health status was associated with time on ERT using the EQ-5D visual analogue scale (VAS). A statistically significant association between time on ERT and higher (i.e. worse) fatigue score was also found.

For each outcome the relative effects in those patients initially treated with agalsidase beta compared with those initially treated with agalsidase alpha were examined. No statistically significant differences in any of the outcomes for adults or children were found.

Mucopolysaccharidosis type I

Sixty-eight patients with MPS I (43 Hurler, 22 Hurler–Scheie and three Scheie) were recruited. It is important to recognise in interpreting our results that ERT is intended for use in people with the milder phenotypes; those with the more severe form are generally offered haematopoietic stem cell transplantation (HSCT) although a small number receive ERT prior to transplant. Among those recruited, all of the 43 MPS I Hurler patients had received a HSCT.

Potential associations between treatment and forced vital capacity (FVC), mobility and 6-minute walk test, stature (height and weight), hearing, prevalence of heart valve disease, presence of carpal tunnel syndrome (CTS) and QoL, were examined for MPS I patients receiving ERT or who had undergone a haematopoietic stem cell transplantation (HSCT). No statistically significant relationship between time on ERT and any of these outcomes was found with the exception of an improvement in the social functioning subscale of the PedsQL.

No statistically significant associations with time since HSCT were found with the exception of an improvement in two of the subscales of the PedsQL.

Mucopolysaccharidosis type II

Thirty-nine patients with MPS II were recruited. Potential associations between treatment and FVC, spleen or liver enlargement, mobility and 6-minute walk test, stature (height and weight), hearing, the presence/absence of heart valve disease, and the presence of CTS and QoL were examined. A statistically significant association between duration of ERT and increasing height (z-scores) but not weight (z-scores) was found. A statistically significant association between time on ERT and an increase in overall PedsQL score was found in children, but there were insufficient SF-36 data to analyse in adults.

No statistically significant relationship between use of ERT and any other outcome was found.

Pompe disease

Seventy-seven patients with Pompe disease were recruited. Only 12 patients with infantile-onset Pompe disease were included and all started treatment at diagnosis providing insufficient data to reliably estimate associations with ERT.

For patients with adult-onset Pompe disease, there was evidence for an association between time on ERT and increased distance walked in the 6-minute walk test, as well as increased muscle strength scores. Improvements in these measures are seen over the first 2 years of treatment.

No statistically significant association between time on ERT and the risk of developing restricted mobility, on body mass index or on respiratory function as assessed by either FVC or the risk of becoming ventilator dependent was found.

No statistically significant associations between fatigue scores or either the physical or mental component scale scores of the SF-36, or the EQ-5D and duration of treatment with ERT were found.

Niemann–Pick disease type C

Thirty-seven patients with NPC disease were recruited. Potential associations between treatment [substrate reduction therapy (SRT) as no ERT is licensed for NPC] and stature (height and weight) and several central nervous system (CNS) measures as well as QoL and the carer burden were examined. No statistically significant association was found between SRT and height or weight. There were no statistically significant relationships between any of the CNS measures and SRT, apart from an apparent increase in the number of cataplexic episodes.

A small improvement in the mental component scale score of the SF-36 was found with time on SRT. However, we found no statistically significant association between SRT and any other QoL measure or with the Carer Strain Index.

Cost data

Based on self-reported health- and social-care service use, and excluding the cost of ERT or SRT, the annual cost of caring for people with LSDs varies from just over £3000 to nearly £12,000 for adults and from £1300 to £18,600 for children (2010 prices). While the care for Gaucher, Fabry and NPC patients costs ≤£4000 per year, care costs are >£10,000 for adults with MPS II and children with Pompe, and >£18,000 for children with MPS I. For all LSDs, on average, hospital care accounted for a higher proportion of care costs for children than for adults. The annual per patient cost of ERT for adults varied from £108,000 (for Fabry patients on agalsidase beta) to £538,000 (for MPS II patients on idursulfase), and for children from £79,000 (for Fabry child patients on agalsidase beta) to £314,000 (for MPS II child patients on idursulfase) (2011 prices). No cost-effectiveness analyses were undertaken owing to the paucity of clear evidence of effectiveness based on clinical or HRQoL outcomes.

Conclusions

These data provide further evidence on the effectiveness of ERT in people with LSDs. The confidence with which conclusions can be drawn inevitably hinges primarily on the numbers of patients with a particular condition.

For both Gaucher disease and Fabry disease these data provide some evidence for a beneficial effect of treatment with ERT across a number of domains. We did not find an association with improvements in QoL measures for either condition, and indeed in people with Fabry disease there was a statistically significant association between duration of ERT use and decline in QoL scores and worsening of fatigue scores. These data on fatigue and QoL should be interpreted with some caution as, unlike with the clinical data, we have scores only from prospective data points and, because almost all participants are currently taking ERT, the comparisons are primarily based across different durations of ERT.

In Fabry disease we found no statistically significant differences in estimates of treatment effectiveness between the two different preparations licensed for this condition.

In patients with Pompe disease these data provide some evidence of a beneficial effect on muscle strength and on mobility as measured by the 6-minute walk test.

In MPS I we found no statistically significant associations between ERT and any outcome measure.

In MPS II the data suggest a beneficial effect of ERT on growth in children. No other statistically significant associations were found in these data.

There were insufficient data for patients with NPC to draw any conclusions regarding the effectiveness of SRT.

In interpreting all of these conclusions it is important to take account both of the inevitable limitations of longitudinal observational data and of the relative lack of power owing to small numbers, particularly for conditions other than Gaucher and Fabry diseases.

The cost data make clear that, in addition to the high costs to the NHS, burden on patients with these conditions and their carers is substantial.

We have shown that it is feasible to use longitudinal data from records to estimate effectiveness but the analyses have been hampered by problems with recruitment and poor collection and recording of key outcome measures.

Recommendations for research

If future research is to more effectively address the unanswered question regarding effectiveness and cost-effectiveness the following steps will be required:

1. Agreement regarding appropriate outcome measures that can be used to assess disease progression for each condition.
2. Agreement between designated UK treatment centres to collect these measures in a common data set for all patients with these conditions receiving ERT or SRT.
3. For the less common conditions, to attempt to extend this approach to include centres in other countries.

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Publication

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 05/04/01. The contractual start date was in May 2007. The draft report began editorial review in April 2012 and was accepted for publication in July 2012. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

Disclaimer: At various points, representatives of the Association for Glycogen Storage Disease, The Gauchers Association, the Society for Mucopolysaccharide Diseases (the MPS Society) and the Niemann-Pick Disease Group (UK) advised on the development and conduct of this collaborative study. However, the views expressed in this publication are those of the authors and do not necessarily reflect those of these support groups.

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