

The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review

M Connock,¹ A Burls,¹ E Frew,¹ A Fry-Smith,¹
A Juarez-Garcia,¹ C McCabe,² A Wailoo,²
K Abrams,³ N Cooper,³ A Sutton,³ A O'Hagan²
and D Moore^{1*}

¹ West Midlands Health Technology Assessment Collaboration (WMHTAC),
University of Birmingham, UK

² School of Health and Related Research (SchARR),
University of Sheffield, UK

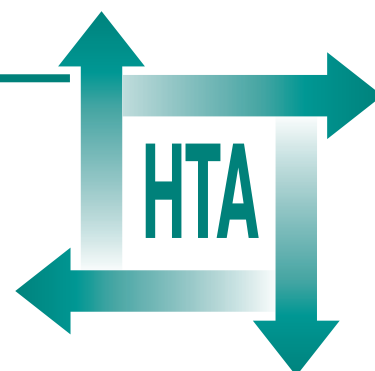
³ Department of Health Sciences, University of Leicester, UK

* Corresponding author

Executive summary

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Executive summary

Objective

Enzyme replacement therapy (ERT; intravenous imiglucerase) is used in the treatment of people with symptomatic type I and type III Gaucher's disease in order to reduce symptoms of the disease and prevent long-term damage. The aim of this review is to determine the clinical effectiveness and cost-effectiveness of ERT in the treatment of symptomatic Gaucher's disease.

Background

Gaucher's disease

Gaucher's disease is an inherited disorder caused by deficient activity of the enzyme glucocerebrosidase, found mainly in lysosomes. This results in an accumulation of glucocerebroside in the lysosomes of macrophages, predominantly in the reticuloendothelial system. Consequences of this abnormal storage include:

- visceral problems: hepatomegaly, splenomegaly, anaemia and thrombocytopenia causing fatigue, discomfort, infections, bleeding and bruising
- bone problems: pain (acute or chronic) and bone crises, and avascular necrosis
- other problems such as lung disease, impaired growth and delayed puberty.

The severity of symptoms and rate of progression vary considerably from patient to patient and range from asymptomatic to severe with early death. The variability is partly related to genotype (over 200 different mutations have been identified). Although, at a population level, different genotypes tend to be associated with certain phenotypes, making it difficult to generalise findings from one country to another, the relationship between genotype and phenotype is not rigid, as background genetics and environment also play a role. Prediction of the clinical course of an individual patient based on genotype alone is uncertain.

Gaucher's disease is classified into three subtypes by clinical features. Type I can present at any age and has predominantly visceral symptoms without neurological effects. Type II causes severe

progressive brain disease and death occurs in infancy. Type III presents in childhood and has neurological and visceral symptoms.

Imiglucerase (Cerezyme[®]) is a recombinant enzyme modified to enhance its uptake into lysosomes. It is given intravenously to replace the defective enzyme and is licensed for use in symptomatic type I disease and to treat the visceral symptoms of type III disease. Intravenous Cerezyme[®] cannot cross the blood–brain barrier and is not effective for neurological manifestations.

Prevalence

Over 90% of affected individuals have type I Gaucher's disease. It is rare, affecting between 1 in 40,000 and 1 in 60,000 individuals. There are thought to be around 250 people affected in England and Wales. Type III is even rarer, affecting less than 1 in 100,000 individuals. The focus of this report is mainly type I Gaucher's disease.

The NHS

This technology is already widely used in the NHS as patients with significant clinical symptoms have had access to the therapy following the recommendations of the National Specialist Commissioning Advisory Group. Current provision of ERT is said to cost the NHS in England and Wales around £20 million per annum. Although this currently represents a steady state, if ERT reduces disease-specific mortality, the figure will grow as the population being treated ages. Extending use to patients who are mildly symptomatic or asymptomatic individuals as a prophylactic measure would also increase the burden on the NHS.

Methods

Given the paucity of evidence from randomised controlled trials (RCTs) and controlled studies that compare ERT with alternative treatments, it was decided a priori to seek information from all study designs, including uncontrolled or poorly controlled studies, and from patient registries. The aim was to review and synthesise this information to estimate the likely clinical effectiveness and cost-effectiveness of ERT. ►

Scoping searches were performed to identify existing reviews and health technology assessments and to inform the development of the review protocol. Broad search strategies were used so that publications on effectiveness, natural history of the disease, and prevalence and incidence would be captured. References from searches of MEDLINE, Cochrane Library, EMBASE and CINAHL from their inception to August 2003 were obtained from an existing Reference Manager database that was compiled for a previous rapid review. The searches were then updated from January 2003 to July/August 2004.

Terms for β -glucocerebrosidase were added to the updated searches to identify references that may have been missed previously. Searches were also made for ongoing and completed but unpublished studies on major research registers.

Data on type of disease, method and period of ascertainment, population and prevalence rates were extracted from included studies. A data extraction form was developed based on the range of symptoms of type I Gaucher's disease described in literature reviews and highlighted in discussions with clinical experts and Genzyme, the manufacturers of Cerezyme. Data on study characteristics, quality and results reported were extracted into tables by one reviewer and checked by another. The quality of the studies of ERT effectiveness was assessed according to study design. Disagreements were resolved by consensus. For those studies that were RCTs or probably cohort or case-control designs, the quality assessment was performed using quality recommended criteria. For other studies the following broad criteria were used, based on factors that influence the generalisability of findings reported in case-series. Where the number of patients assigned was the same as the number analysed it was assumed that withdrawals did not occur and thus were accounted for, even in the absence of an explicit statement by the authors. Where units were not equal, which can be the result of missing data or withdrawal, and the textual context did not resolve this, it was concluded that withdrawals were unaccounted for.

As most effectiveness studies were not controlled, to estimate the extent to which the outcomes observed were the results of ERT, it was important to consider what would have happened to the patients in the absence of ERT. Thus, the relevance of prevalence and natural history studies were assessed for their relevance to the UK context and the review question.

The bibliographic databases were also searched to identify existing cost studies, economic evaluations and models. To be included in the review, studies had to analyse the treatment of Gaucher's disease in terms of both the costs and effectiveness. There were no language exclusions.

Evidence about effectiveness

Number and quality of studies

Primary studies of any design, reporting at least ten patients, were included. Sixty-three studies were included. Only one RCT compared ERT with usual treatment. This was a well-designed study, but underpowered (29 patients randomised to three arms) because of poor recruitment. One other RCT compared recombinant imiglucerase with the placenta-derived predecessor alglucerase and thus only provided before and after data on the effectiveness of ERT. The rest of the studies were of moderate quality at best and none had reliable comparator data.

Direction of evidence

All studies are suggestive of benefit with ERT.

Summary of benefits

The one relevant RCT showed a potentially beneficial effect in two haematological surrogates (haemoglobin and platelet levels) and, to a lesser extent, on hepatomegaly. The other studies consistently demonstrated improvements in haematological parameters and in hepatomegaly and splenomegaly. Most measures of disease involvement on average tended to return towards normal in the majority of patients after about 1 or more years of treatment. For organomegaly and haemoglobin the rates and extent of response appeared greater the more abnormal the pre-ERT condition. Platelet levels appeared to improve more slowly and to a lesser degree the more severe the initial thrombocytopenia. Liver size in most cases approached 1.2 times that expected for body weight. Spleen enlargement appeared to reduce to between five and ten times normal in most patients.

The effect of ERT on skeletal involvement also appeared to be positive in terms of pain, bone crises and fracture rate, but the quantitative evidence for these benefits was extremely weak. There was some evidence that ERT may exacerbate the depletion in bone density; thus, caution is needed in interpretation of results and careful monitoring is required. ►

The way in which all of these effects translate into patient well-being and survival or the need for services and resources has not been reliably estimated.

Quality of life improvements with ERT have been reported. Nonetheless, studies based on the Short Form 36 (SF-36) indicate that patients treated with ERT continue to have reduced health-related quality of life (HRQoL) compared with the general population. No study attached utility values to quality of life measures for ERT-treated patients.

Natural history

Benefit from treatment probably exceeds the health gain demonstrated by before and after studies, because Gaucher's disease is a progressive condition and future deterioration may be prevented. Therefore, to be able to determine the full extent of health gain from treatment it was necessary to review the natural history of untreated Gaucher's disease to estimate the health loss prevented.

Thirty-one studies relevant to the natural history of the disease were found. Sixteen looked at multiple clinical characteristics of a cohort of patients with type I Gaucher's disease. There was considerable within-study and between-study heterogeneity, but all showed that Gaucher's disease was a progressive condition. Some suggested that the disease may become more indolent in adulthood; however, studies were discrepant on this point. Most disease is diagnosed in adulthood, although about one-quarter presented in childhood, these patients having the most severe symptoms and greatest rate of progression.

Modelling of natural history was undertaken using the five papers that reported the Severity Score Index (SSI) for each patient, along with patient-level data on age, age at diagnosis, splenectomy status and genotype, to address the question of whether disease stabilises in adulthood and the degree of correlation between phenotype and genotype. Analysis of the available data suggested that disease progression is likely to slow markedly in adulthood and that genotype is a useful predictor of clinical expression of the disease.

Quality of life

Five studies looked at quality of life. Data on this topic were also obtained from the registries. The evidence suggests that the vast majority of the clinical characteristics of type I Gaucher's disease have little impact on subjective HRQoL and that therefore for the majority of people with type I Gaucher's Disease this may not be a severe

condition. Bone and skeletal symptoms contribute most to the morbidity of the disease and can lead to severe pain and immobility.

Economic evaluation

Costs

The mean cost per patient treated was approximately £86,000 per annum in England and Wales. The cost per patient varied considerably by dose.

Cost per quality-adjusted life-year

Four existing economic evaluations were found, all of which calculated a very high cost per quality-adjusted life-year (QALY). The most recently published report was from 1996, therefore, a *de novo* economic model was developed. A Markov decision model was constructed based on patients moving between states defined by the modified SSI. Most of the parameters were derived from the published literature. ERT was assumed to restore patients to full health in the base case. The estimated incremental cost per QALY [incremental cost-effectiveness ratio (ICER)] in the base case ranged from £380,000 to £476,000 per QALY, depending on genotype.

Sensitivity analyses

Univariate sensitivity analyses examined ERT not restoring full health, more severe disease progression in the untreated cohort, and only treating the most severely affected patients. These produced ICERs of approximately £1.4 million, £296,000 and £275,000 per QALY, respectively. The base-case unit cost of the drug is £2.975. The unit cost would have had to be reduced ten-fold, to £0.30, to obtain an ICER of £30,000 per QALY. At a unit cost of £1 the ICER would be £120,000 per QALY.

Limitations of the calculations (assumptions made)

The evidence for effectiveness is generally based on studies that are not of a robust design. Such designs tend to exaggerate apparent treatment effects and are therefore unlikely to have contributed to the high estimate of the ICER.

Because of the weak evidence base, several substantial assumptions were required to produce an estimate of the cost-effectiveness (wherever possible assumptions that favour ERT were chosen). These assumptions are:

- that SSI categorisation identifies states that are different in relation to HRQoL from each other

- that within each of the ‘mild’, ‘moderate’ and ‘severe’ categories of SSI patients have a comparable HRQoL
- that ERT returns patients to full health
- that people on treatment have normal life expectancy
- that the natural history shows slowing of disease progression in adulthood.

Conclusion

Other important issues regarding implications

Although ERT for treating the ‘average’ Gaucher’s disease patient exceeds the normal upper threshold for cost-effectiveness seen in NHS policy decisions by over ten-fold, some argue that since orphan drug legislation encouraged the manufacture of Cerezyme, and Gaucher’s disease can be defined as an orphan disease, the NHS has little option but to provide it, despite its great expense.

Generalisability of the findings

More information is required before the generalisability of the findings can be determined. Although data from the UK have been used wherever possible, these were very thin indeed. Nonetheless, even large errors in estimates of the distribution of genotype, genotype–phenotype associations, effectiveness and numbers of patients will not reduce the ICER to anywhere near the

upper level of treatments usually considered cost-effective.

Recommendations for further research

Further research could help to clarify the many uncertainties that exist. However, although doing so will be of clinical interest, it is questionable whether, within the current pricing environment, such research would have any substantive impact on policy decisions. It is highly improbable that, whatever the findings of such research, the ICER could be brought down by the orders of magnitude required to make ERT an efficient use of health service resources. (The possible exception to this would be investigating the most efficient alternative treatment strategies for using ERT in a paediatric population only.) Moreover, if under equity considerations for orphan diseases the NHS feels it is important to provide this drug, regardless of its cost-effectiveness, then refining the precision of the ICER estimate also becomes superfluous.

Publication

Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al.* The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher’s disease: a systematic review. *Health Technol Assess* 2006;**10**(24).

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts. Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 03/64/01. The contractual start date was in June 2004. The draft report began editorial review in April 2005 and was accepted for publication in December 2005. 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.

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