Enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type I

A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type I

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Executive summary

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Executive summary

Aim and objective

The aim of this review was to determine the clinical effectiveness and cost-effectiveness of the administration of intravenous enzyme replacement therapy (ERT) to symptomatic patients for the prevention of long-term damage and symptoms in Fabry's disease and in mucopolysaccharidosis type 1 (MPS1).

Epidemiology and background

Fabry's disease

Fabry's disease is an inherited X-linked disorder caused by deficient activity of the enzyme α-galactosidase A found in lysosomes. This results in an accumulation of globoside (Gb3) in the lysosomes of many tissues, including kidney, heart and blood vessels.

The classic form of the disease seen in males is characterised by early onset of pain in childhood and gradual progressive organ damage predominantly expressed in kidney, heart and brain, culminating in renal failure by about 40 years of age and increased risk of heart disease and stroke. The same constellation of manifestations is seen in female carriers but incidence is much lower, onset later and severity reduced; many carriers are essentially disease free.

More than 350 Fabry's disease mutations have been identified. At the UK population level, any given mutation is almost completely limited to a single pedigree.

Traditional therapy has comprised palliative care and interventions for specific symptoms.

Agalsidase alpha (Replagal®) and agalsidase beta (Fabrazyme®) are recombinant enzymes, produced in a genetically engineered human cell line and in genetically engineered Chinese hamster ovary cells, respectively. They are given intravenously to replace the defective enzyme and are licensed for use in symptomatic Fabry's disease.

Mucopolysaccharidosis type 1

MPS1 disease is an inherited autosomal recessive disorder caused by deficient activity of the enzyme α-L-iduronidase found in lysosomes. This results in an accumulation of glycosaminoglycans in the lysosomes of cells in many tissues, including connective tissue, brain, heart and liver. Consequences of this abnormal storage include skeletal, respiratory, neurological, cardiac and mobility problems.

MPS1 is heterogeneous and has been classified into three subtypes on clinical features that probably represent a continuum. Hurler syndrome presents in the first years of life and is severe with neurological symptoms and reduced life expectancy of only about one decade. Hurler–Scheie syndrome is an intermediate form with reduced life expectancy of only two to three decades. Scheie syndrome is a milder form with later presentation in which manifestations are greatly attenuated with longer life expectancy than the severer forms. The attenuated forms Scheie and Hurler–Scheie are associated with normal or near normal intellect and greater heterogeneity of manifestations than the Hurler phenotype.

Traditional therapy has comprised palliative care and interventions for specific symptoms.

Laronidase (Aldurazyme®) is a recombinant enzyme produced by genetically engineered Chinese hamster ovary cells. It is licensed to be administered intravenously to treat the non-neurological manifestations of the disease in patients with a confirmed diagnosis of MPS1.

Prevalence

The prevalence of Fabry's disease in the UK is of the order of 0.3 per 100,000, giving estimates of around 150 people affected with the disease in England and Wales, about 70 males and 80 females.

There are currently approximately 53, 33 and 10 live patients with Hurler, Hurler–Scheie and Scheie syndromes in England and Wales and the birth prevalences of these are estimated to be about 0.756, 0.243 and 0.070 per 100,000 live births, respectively.

Difficulties and delays in diagnosis mean that these numbers may be underestimated. ▶

NHS

ERT for Fabry's disease and MPS1 is already used within the NHS. In England, patients with significant clinical symptoms have had access to therapies through six designated treatment centres. Current provision of ERT is said to cost the NHS in England and Wales about £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.

Evidence about effectiveness

Search strategy

Broad, disease-specific search strategies were employed to capture publications on incidence, prevalence and natural history of the disease and the clinical effectiveness of treatment. These included searches of MEDLINE, EMBASE, CINAHL, Cochrane Library and Science Citation Index from their inception up to mid-2004, scrutiny of bibliographies, contact with clinical experts and identification of ongoing and unpublished studies. Primary studies of any design reporting at least 10 patients were included.

Direction of evidence

All studies are suggestive of benefit with ERT. Infusion-related adverse events, which are in general tolerable, are potentially the biggest disbenefit.

Summary of benefits

Fabry's disease

The effectiveness of ERT for treating patients with Fabry's disease has been studied in three randomised placebo-controlled trials (total $n = 70$ patients; duration: 5–6 months) and 11 uncontrolled before–after studies (total $n = 493$ patients duration up to 24 months). A total of 119 patients were treated with Fabrazyme and the remainder with Replagal or human agalsidase alfa; most patients were male. Further data come from open-label extensions to these studies and other uncontrolled studies.

In general, the studies varied widely in design, quality and end-points measured, making robust conclusions about effectiveness difficult.

The results suggested beneficial effects of ERT on measures of pain, cardiovascular function and some end-points reflecting neurosensory function. Renal function appeared to be stabilised by ERT.

MPS1

Evidence of effectiveness comes solely from two studies, a Phase I/II study enrolling 10 patients and a Phase III/randomised controlled trial (RCT) enrolling 45 patients who were further studied in an open-label extension to the trial. Duration of treatment was up to 98 weeks.

The two studies for the most part enrolled patients with moderate to mild disease (predominantly patients with Hurler–Scheie), and in the RCT the inclusion criteria appear to have selected the more physically able patients.

Outcomes measured in the two studies were a combination of those chosen as likely to reflect readily and rapidly any improvement in patient functional abilities, those related to markers of lysosomal storage, those measuring change in specific disease symptoms and those related to monitoring the safety of the intervention. On the whole, all outcomes demonstrated some degree of improvement on treatment with ERT.

At present there are no utility-related health-related quality of life data on which to assess the relative health gain of ERT in MPS1.

General considerations

Although unlikely to be undertaken, further well-designed comparative trials are required to provide clear evidence of the efficacy and effectiveness of ERT in preventing and treating clinically meaningful manifestations of both Fabry's and MPS1 disease.

How the effects of ERT treatment translate into well-being and survival or the need for services and resources has not been reliably estimated.

Furthermore, in both diseases it is likely that the benefits from treatment might exceed the health gain demonstrated in studies without a control group because such designs are unable to compensate for any deterioration after baseline measurement that would have occurred during the duration of the study in the absence of treatment. Therefore, to be able to demonstrate the full extent of health gain from treatment, it was necessary to review the natural history of untreated patients in each disease in order to try to estimate the health loss prevented. ▶

Natural history

Fabry's disease

Thirty-one studies relevant to the natural history of Fabry's disease were reviewed. A single longitudinal study of a substantial cohort of male patients indicated median survival of approximately 57 years and the development of renal insufficiency at around the third decade, rapidly followed by end-stage renal disease at a median age of about 40 years. The study also provided evidence of a rapid increase in brain lesions after about 40 years consistent with increased risk of transient ischaemic attacks and stroke. Data presented in other studies broadly confirmed these findings. The published information tallied with descriptions of a multi-system, life-threatening disorder particularly involving kidney, heart and brain with individual patients exhibiting many manifestations. No longitudinal analysis of a cohort of female carriers was found. Studies indicated that females are subject to the same constellation of symptoms as males but onset is later, severity reduced and at the individual level the spectrum of manifestations limited. Renal involvement is much less frequent in females. The incidence of disease amongst carriers is uncertain and, although some may be severely affected it is clear many remain essentially disease free.

MPS1

Published information was meagre, especially with regard to Hurler–Scheie and Scheie phenotypes. Analysis of data from the Society for Mucopolysaccharide Diseases (UK) indicated a median survival of 11.5 years for MPS1, but the large proportion of Hurler patients, with an estimated median survival of 8.6 years, drove this estimate. Median survival for the attenuated phenotypes exceeded 30 years. The fragmentary information reviewed in 16 studies relevant to the natural history of MPS1 did not generate a coherent picture of disease progression and could provide little added value to published narrative reviews.

Economic evaluation

Fabry's disease

Costs

The mean cost per patient (50 kg) treated is approximately £85,000 per annum in England and Wales. The cost per patient varies considerably by dose.

Cost per quality-adjusted life-year (QALY)

No published evidence reporting an economic evaluation of ERT for Fabry's disease was identified by this review. A dynamic decision model was constructed based on a birth cohort of male patients who are followed up until death. Owing to lack of information reported in the literature, many assumptions had to be applied. The key assumptions were that ERT returns patients to full health and a normal life expectancy. As far as possible, all assumptions favoured rather than detracted from the value of ERT. ERT was assumed to restore patients to full health in the base case. The estimated incremental cost-effectiveness ratio (ICER) in the base case was £252,000 per QALY (Fabrazyme).

Sensitivity analyses

Univariate sensitivity analysis around the key assumptions produced ICERs ranging from £602,000 to £241,000. The base case unit cost of ERT was taken as £65.1/mg based on the cost of Fabrazyme. The unit cost would have had to be reduced to £9 to obtain an ICER of £30,000 per QALY.

MPS1

Costs

The mean cost per child patient (20 kg) treated is approximately £95,000 and an adult (70 kg) approximately £335,000 per annum in England and Wales. The cost per patient varies considerably by dose.

Cost per QALY

There is no published evidence reporting an economic evaluation of ERT for MPS1 and no study was identified that reported the quality of life of MPS1 patients within a utility format. Furthermore, no or minimal information of the severity and rate of change of clinical manifestations of disease or the impact of ERT on these factors was identified. Information on the effect of ERT on mortality is also lacking owing to the relatively short time that the treatment has been available.

Given this lack of data, it was not possible to develop a cost-effectiveness model of ERT treatment for MPS1 as the model would consist almost completely of assumptions based on no published evidence, leading to an incremental cost per QALY result that would be meaningless.

Other important issues regarding implications

Although ERT for treating the 'average' patient with Fabry's disease exceeds the normal upper threshold for cost-effectiveness seen in ▶

NHS policy decisions by over sixfold, and the value for MPS1 is likely to be of a similar order of magnitude, clinicians and the manufacturers argue that, as the disease is classified as an orphan disease under European Union legislation, it has special status, and the NHS has no option but to provide ERT.

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, this was very thin indeed. Nonetheless, even large errors in assumptions made will not reduce the ICER to anywhere near the upper level of treatments usually considered cost-effective.

Recommendations and the need for further research

Further research could help clarify the many uncertainties that exist. However, although doing so may be of clinical interest and refine patient care, 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 by current standards. A possible exception to this would be to investigate the most efficient alternative treatment strategies for using ERT in a paediatric population only. Moreover, if under European orphan drug legislation or for equity considerations the NHS feels that it is important to provide these drugs, regardless of its cost-effectiveness, then refining the precision of the ICER estimate becomes superfluous.

At least two ERTs for other lysosomal storage diseases are in Phase III development. It is likely that if these and subsequent ERTs and non-ERT interventions are granted marketing approval, then evaluation of their clinical and cost-effectiveness will also be hampered by limited evidence on the natural history of the disease and the clinical effectiveness of the intervention. To overcome these limitations, the authors of this report recommend the establishment of disease-specific data registries which attempt to include all affected patients in the UK, and collect longitudinal patient level data on clinically relevant problems, interventions received and quality of life in a utility format. Although there are international industry-supported registries for those ERTs already licensed and undoubtedly similar registries will be established for emerging ERTs, these registries are usually only established as a result of gaining regulatory approval for the ERT, and therefore tend to include data only on treated patients. Furthermore, it is the authors' experience that obtaining data from these registries, in a timely manner to undertake a health technology assessment, is not necessarily easy. Disease-specific registries should be established well before marketing approval is granted for an ERT in order to capture sufficient longitudinal evidence on the natural history of the disease in the absence of ERT. The point at which an application is made for orphan drug status might be the latest appropriate time to begin such data collection. Data from registries should be readily accessible (in anonymised form) to facilitate the process of technology assessment and improving patient care. A requirement of such a process should be that the results of any analysis are subject to peer review and placed in the public domain. It is clearly evident to the authors of this report that there is a willingness by clinicians, patients and patient advocacy organisations collectively to support such registries.

Publication

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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 03/64/02. The contractual start date was in June 2004. The draft report began editorial review in July 2005 and was accepted for publication in November 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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