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Title **A Systematic Review of the Clinical Effectiveness and Cost Effectiveness of Enzyme Replacement Therapies for Fabry's Disease and Mucopolysaccharidosis Type 1**

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Aim

To determine the clinical and cost effectiveness of administering intravenous enzyme replacement therapy (ERT) to symptomatic patients to prevent long-term damage and symptoms in Fabry's disease and mucopolysaccharidosis type 1 (MPS1).

Conclusions and results

Fabry's disease is described as a multisystem, life-threatening disorder particularly involving kidney, heart, and brain with individual patients exhibiting many manifestations. Fragmentary information in 16 reviewed studies relevant to the natural history of clinical manifestations of MPS1 did not generate a coherent picture of disease progression and added little to published narrative reviews. UK MPS1 registry data indicated a birth prevalence of 1.07/100 000 births and median survival of 11.6 years (all MPS1 subtypes combined).

The results suggested beneficial effects of ERT for Fabry's disease on measures of pain, cardiovascular function, and some endpoints reflecting neurosensory function. Renal function appeared to be stabilized by ERT.

No published evidence reporting an economic evaluation of ERT for Fabry's disease was identified. A dynamic decision model was constructed based on a birth cohort of male patients followed up until death, but many assumptions had to be applied. The estimated incremental cost-effectiveness ratio (ICER) was GBP 252 000 per QALY (agalsidase beta). Univariate sensitivity analyses around the key assumptions produced ICERs ranging from GBP 602 000 to 241 000. The unit cost of ERT was taken as GBP 65.1/mg based on the cost of agalsidase beta. The unit cost would have had to be reduced to GBP 9 to obtain an ICER of GBP 30 000 per QALY.

Minimal evidence is published on the impact of ERT on the severity and rate of change of clinical manifestations of MPS. Information on the effect of ERT on mortality is also lacking owing to the relatively short time that the treatment has been available. We found no published economic evaluation of ERT for MPS1 or any study that reported the quality of life of MPS1 patients within a utility format. Given the lack of data, it was not possible to develop a cost-effectiveness model of ERT for MPS1. The mean cost of treating an MPS1 child (20 kg) with ERT (England, Wales) is approximately GBP 95 000 per annum, and the corresponding cost for an adult (70 kg) around GBP 335 000. The cost per patient varies considerably by dose.

Recommendations

The cost effectiveness of ERT treatment for an 'average' patient with Fabry's disease exceeds the normal upper threshold seen in NHS policy decisions by over 6-fold. Even large errors in assumptions made will not reduce the ICER to anywhere near the upper level usually considered cost effective. The cost effectiveness of ERT for MPS1 is likely to be similar to that for Fabry's disease. Some clinicians, and the manufacturers of ERT, argue that since these diseases have special status as orphan diseases, the NHS has little option but to provide ERT. The opportunity costs forgone under such a policy will mount as more ERTs become licensed for increasing numbers of the rare genetic storage disorders.

Methods

Relevant published studies were identified and assessed using recommended quality criteria. Data were sought via disease registries and contact with experts. Evidence was synthesized and reported in narrative review.

Further research/reviews required

- Establishment of disease-specific data registries to facilitate technology assessment and improve patient care through better knowledge of the disease progression and the effectiveness of potential treatments (should include longitudinal data on clinically relevant problems of all affected patients in the UK, interventions received, and quality of life in a utility format).

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