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Title **The Clinical Effectiveness and Cost Effectiveness of Enzyme Replacement Therapy for Gaucher's Disease: A Systematic Review**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
Mailpoint 728, Boldrewood, University of Southampton, Southampton SO16 7PX, United Kingdom;
Tel: +44 2380 595586, Fax: +44 2380 595639

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Aim

To determine the clinical and cost effectiveness of enzyme replacement therapy (ERT; intravenous imiglucerase) in treating symptomatic Gaucher's disease (GD).

Conclusions and results

Sixty-three studies reporting effects of ERT were included. All studies suggested benefits from ERT, but did not clarify how these effects translate into patient well-being, survival, and need for services and resources. Quality of life (QoL) improvements with ERT were observed, but studies indicate that patients treated with ERT still have reduced health-related quality of life (HRQoL) compared to the general population. We found 31 studies on the natural history of the disease showing GD to be a progressive condition. Some suggested the disease might become more indolent in adulthood. Most disease is diagnosed in adulthood. Patients presenting in childhood have the most severe symptoms and progression. Data suggest that disease progression is likely to slow in adulthood, and genotype may be a useful predictor of clinical expression. QoL data were obtained from GD registries and 5 studies. Clinical characteristics of type I GD have little impact on subjective HRQoL. Hence, in most people with type I GD this may not be a severe condition, but some patients experience immobility and severe pain from skeletal symptoms. The mean cost per patient treated was about GBP 86 000 annually in England and Wales. Cost per patient varied considerably by dose. The 4 economic evaluations found showed a high cost per quality-adjusted life-year (QALY). In a Markov decision model, ERT was assumed to restore patients to full health in the base case. The estimated incremental cost per QALY (ICER) in the base case ranged from ~GBP 380 000 to GBP 476 000 per QALY, depending on genotype. 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 (for details see executive summary link above).

Recommendations

In treating the 'average' Gaucher's disease patient, ERT exceeds the normal upper threshold for cost effectiveness seen in NHS policy decisions by over 10-fold. Some argue that since orphan drug legislation encourages development of ERTs, and since GD can be defined as an orphan disease, the NHS should provide it, despite its expense. More information is needed to determine the generalizability of the findings. Data from the UK were used when possible, but were very thin. 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.

Methods

Bibliographic databases were searched for studies that informed on the prevalence of GD, the natural history of the disease, the effectiveness of ERT, and the costs, economic evaluation, and modeling of ERT treatment. Data were extracted independently by 2 reviewers and data synthesis achieved by quantitative and descriptive analyses. A Markov decision model was constructed based on patients moving between states defined according to a disease-specific Severity Score Index. Most parameters were derived from the published literature. ERT was assumed to restore patients to full health in the base case.

Further research/reviews required

Further research will be of clinical interest, but it is questionable whether such research in the current pricing environment would have any substantive impact on policy decisions.

Written by Dr David Moore and Dr Martin Connock, University of Birmingham, United Kingdom

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