Cost effectiveness of once-daily oral chelation therapy with deferasirox versus infusional deferoxamine in transfusion-dependent thalassaemia patients: US healthcare system perspective
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined two treatments, deferoxamine and deferasirox, to reduce liver iron concentrations (LIC) and serum ferritin levels in transfusion-dependent thalassaemia patients. Deferoxamine was given at a dose of 47.4 mg/kg per day for 5 days per week and deferasirox at 24.6 mg/kg per day for 7 days per week.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of transfusion-dependent thalassaemia patients aged 3 years. Patients were assumed not to have received prior chelation therapy.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The clinical data were derived from studies published between 1996 and 2006. Some data on resource use were derived from sources published in 2005 and 2006. The price year was 2006.

Source of effectiveness data
The clinical data used in the model were compliance with therapy, efficacy in maintaining or reducing LIC, and the probabilities of iron overload-related cardiac disease and death.

Modelling
A Markov model was constructed to model the clinical and economic impact of the two treatments. The time horizon of the model was 50 years. The cycle length was one year. A schematic representation of the model was provided. The model focused explicitly on cardiac complications (including mortality) that mainly depended on compliance with therapy (and age), since efficacy in maintaining or reducing LIC was similar between the two therapies.

Sources searched to identify primary studies
Efficacy in maintaining or reducing LIC was obtained from a Phase III clinical trial that compared deferoxamine and
deferasirox in 586 patients. Compliance with therapy was estimated from a large series of patients with thalassaemia major. These appear to have been derived from an observational study for deferoxamine and a prospective non-randomised study for deferasirox. The rates of cardiac complications were derived from a published Greek study, while survival was obtained from US life tables.

Methods used to judge relevance and validity, and for extracting data
To estimate compliance, the authors stated that all published studies were reviewed, although no details of a systematic search for data were reported. Some information on the patient populations included in the primary studies was given. The lowest value found in observational studies for deferoxamine was used, as the authors stated that clinicians tend to overestimate patient compliance. Estimates of compliance with deferasirox were obtained by multiplying the improvement in adherence compared with deferoxamine by the conservative baseline value for deferoxamine.

Measure of benefits used in the economic analysis
The summary benefit measure used was the expected number of quality-adjusted life-years (QALYs). These were estimated using the modelling framework in which survival was combined with QoL data. The QoL estimates were obtained from the literature. Specifically, QoL values associated with the two treatments came from a study that used time trade-off techniques in a community sample of 120 adults, giving preferences for different modes of administration of chelation therapy. QoL values for patients with cardiac disease came from a longitudinal study of health-related QoL in a random sample of 1,356 adults in a community population. The utility values were then reported as decrements from perfect health. Cardiac disease-free life-years (CDFLYs) and life-years (LYs) were also reported. The benefits were discounted at an annual rate of 3%.

Direct costs
The analysis of the costs was carried out from the perspective of the US health care system. It included the costs of the acquisition and administration of drugs and the management of iron overload-related cardiac disease. The unit costs and the resource quantities used were not presented separately. The drug costs were estimated using average wholesale prices. Drug dosages came from published studies. The administration costs for deferoxamine were mainly derived from a large health insurance claims database, while those for deferasirox were assumed to have been zero. The yearly costs of iron overload-related cardiac disease came from a sample of 35 frequently transfused thalassaemia patients in a health insurance claims database, as reported already. Since the long-term costs were evaluated, discounting was relevant and an annual rate of 3% was used. The price year was 2006.

Statistical analysis of costs
The costs appear to have been treated deterministically in the base-case analysis.

Indirect Costs
The productivity costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
A univariate sensitivity analysis was carried out with model probabilities and costs that were varied over their plausible ranges. A two-way sensitivity analysis was conducted simultaneously on the improvement in compliance with deferasirox and the disutility associated with deferoxamine. A threshold sensitivity analysis was also performed to identify the price of deferasirox at which the total costs between groups would be the same. A probabilistic sensitivity analysis was finally carried out by running a Monte Carlo simulation with 10,000 replications. Clinical and economic inputs of the model were assigned specific probabilistic distributions. The analysis generated cost-effectiveness...
acceptability curves.

**Estimated benefits used in the economic analysis**
Over the 50-year timeframe of the analysis, the expected CDFLYs were 29.3 with deferasirox and 24.0 with deferoxamine. The discounted LYs were 21.0 with deferasirox and 19.3 with deferoxamine, and the discounted QALYs 17.6 (deferasirox) and 13.2 (deferoxamine), respectively. Thus, the differences between treatments were 5.4 CDFLYs, 1.8 LYs and 4.5 QALYs in favour of deferasirox.

Interestingly, it was estimated that approximately 65% of the improvement in QALYs was due to patient preferences for oral versus infusional therapy, while approximately 35% was due to projected improvements in life expectancy.

**Cost results**
The total costs per patient were $571,156 with deferasirox and $445,139 with deferoxamine (difference $126,018).

In particular, the use of deferasirox was associated with substantially higher acquisition costs ($313,823), but also an important reduction in administration costs ($134,492) and slightly lower costs associated with cardiac disease ($8,474).

**Synthesis of costs and benefits**
An incremental cost-utility ratio was calculated in order to combine the costs and benefits of the two treatments.

The incremental cost per QALY gained with deferasirox in comparison with deferoxamine was $28,255.

The determinisic sensitivity analysis showed that the cost-utility ratio was quite sensitive to the equivalent daily dose of deferasirox, the unit cost of both drugs, the cost of deferoxamine administration, and the disutility associated with deferoxamine versus deferasirox. The cost-effectiveness of deferasirox was more favourable in younger patients. The incremental cost per QALY did not change substantially except when compliance with deferasirox was varied.

The two-way sensitivity analysis showed that the cost-effectiveness of deferasirox remained below a value of $50,000 per QALY under reasonable assumptions.

The threshold analysis suggested that the break-even price of deferasirox was $69 per gram ($89 per gram was used in the base-case). It was also estimated that using the generic price for deferoxamine ($28 instead of the $35.77 used in the base-case), the incremental cost per QALY for deferasirox increased to $39,110.

The probabilistic sensitivity analysis indicated that deferasirox was more costly and more effective than deferoxamine in 55% of the simulations, while it was dominant (both more effective and less expensive) in 34% of the simulations. Deferasirox was the preferred option in 62% of the simulations at a threshold of $50,000 per QALY, in 76% of the simulations at a threshold of $100,000 per QALY, and in 81% of the simulations at a threshold of $150,000 per QALY.

**Authors' conclusions**
Deferasirox was a cost-effective treatment to reduce liver iron concentrations (LIC) and serum ferritin levels in transfusion-dependent thalassaemia patients. Its advantages in terms of increased quality-adjusted life-years (QALYs) arose mainly from patient preferences for oral versus infusional administration and its associated higher compliance.

**CRD COMMENTARY - Selection of comparators**
The authors provided a clear justification for their choice of the comparators. Deferoxamine represented the current standard for iron chelation therapy, while deferasirox was a member of a new class of tridentate iron chelators. The authors stated that another available treatment, deferiprone, was not included in the comparison because of its restricted availability in the USA. Similarly, the strategy of bone marrow transplantation was not considered as it is not feasible for many patients. You should decide whether these are valid comparators in your own setting.
Validity of estimate of measure of effectiveness
The effectiveness data were derived from published studies. The authors stated that all relevant studies were reviewed but no systematic search for clinical data was reported. It is therefore possible that some primary studies might have been identified selectively. The authors reported some information about the design and the number of patients involved in each study. Conservatives estimates were used for compliance with both therapies. An extensive sensitivity analysis was performed on this parameter, which was the key model driver. Equal efficacy in maintaining or reducing LIC for the two therapies was assumed on the basis of a published trial, but this assumption was not varied in a sensitivity analysis.

Validity of estimate of measure of benefit
The benefits (QALYs) were appropriately modelled. Extensive information on the source of utility values used to calculate the QALYs was provided. The impact of using alternative QoL estimates was investigated in the sensitivity analysis. Discounting was applied, as recommended by US guidelines. Other benefits, including disease-specific outputs, were reported.

Validity of estimate of costs
The cost analysis was restricted to the medical costs associated with disease management, in accordance with the perspective of the study. The unit costs and the quantities of resources used were presented separately only for drug costs. The annual cost of treating complications was presented as a macro-category. Data on resource consumption were derived from published sources. Most of the costs came from a large health insurance database, which is likely to have been representative of US costs. The price year was reported, which will aid reflation exercises in other time periods. The impact of changes in cost assumptions was extensively addressed in the sensitivity analysis.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. The issue of the generalisability of the study results to other settings was not explicitly addressed. However, the extensive use of both deterministic and probabilistic sensitivity analyses enhances the external validity of the study. The results of the base-case analysis and the sensitivity analyses were presented clearly. The authors noted some limitations to their evaluation. For example, some cost estimates (e.g. administration costs) were based on data derived from a small sample of patients, although these estimates are likely to reflect the US setting. The rate of compliance came from an Italian study, but a conservative assumption was made in order to use a less favourable value. Finally, the potential adverse effects of deferasirox were not included in the analysis given their transient and mild nature.

Implications of the study
The study results suggest that deferasirox should be considered in patients with beta-thalassaemia major who are appropriate candidates for such a therapy.

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Other publications of related interest
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**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Administration, Oral; Benzoates /administration & dosage /economics /therapeutic use; Blood Transfusion /economics /methods; Cost-Benefit Analysis; Delivery of Health Care /economics /methods; Drug Administration Schedule; Drug Utilization Review /statistics & numerical data; Economics, Pharmaceutical /statistics & numerical data /trends; Humans; Infusions, Intravenous; Insurance Claim Review /statistics & numerical data; Iron Chelating Agents /administration & dosage /economics /therapeutic use; Iron Overload /drug therapy; Markov Chains; Treatment Outcome; Triazoles /administration & dosage /economics /therapeutic use; United States; beta-Thalassemia /drug therapy

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