Deferasirox for the treatment of transfusional haemosiderosis in patients with chronic anaemia

Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation

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Executive summary

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Executive summary

Objectives

The review assessed the clinical effectiveness and cost-effectiveness of deferasirox for the treatment of iron overload in chronically transfused anaemic patients.

Comparisons were made between deferasirox and deferoxamine (DFO), deferiprone or placebo.

To ensure that the wider picture of iron-chelating therapy was considered, comparisons were also made between deferiprone (alone and in combination with DFO) and DFO (alone and in combination with deferiprone).

Background

Iron overload is a rare condition in which iron collects in the body. There are no natural means of removing excess iron from the body and so iron gradually accumulates (over 5–10 years) to toxic levels that affect major organs such as the heart and liver. Iron overload can be caused by a malabsorption of iron from the ingestion of food or more commonly through frequent blood transfusions. Blood transfusions represent life-saving therapy for patients with chronic anaemia, such as those suffering from thalassaemia and sickle cell disease (SCD). However, with each unit of transfused blood, 200–250 mg of iron is transferred to the patient. The risk of iron overload increases once patients have received approximately 20 transfusions.

The conventional treatment for transfusion-related iron overload is chelation therapy aimed at reducing iron stores or maintaining an iron balance. Treatment with iron chelators is primarily governed by the degree of iron overload and the transfusional requirements of patients.

Currently in the UK, patients presenting with transfusion-related iron overload are treated with DFO. Patients receive DFO via nightly infusions (5–7 times a week) from as early as 2 years of age. The regimen is not well tolerated, particularly in adolescents, and there is alleged to be a high degree of non-adherence to therapy, with resulting detrimental heath effects.

Patients over the age of 6 years who are suffering from beta-thalassaemia also have the option to try deferiprone. Deferiprone is an oral tablet given thrice daily, which limits the patient administration burden. However, it has been associated with adverse events such as neutropenia and agranulocytosis, which limits its use.

Deferasirox is a new orally active iron-chelating agent that is given once daily as a suspension (usually in water or fruit juice). Deferasirox may be of particular value in treating patients with iron overload who cannot tolerate DFO and who are not suitable for, or who are intolerant of, deferiprone.

Methods

The assessment was conducted according to accepted procedures for conducting and reporting systematic reviews and economic evaluations. Evidence on clinical effects and cost-effectiveness was identified using a comprehensive search strategy (for the period up to March 2007) of bibliographic databases (including the Cochrane Library, EMBASE, MEDLINE) as well as hand-searching activities. Unpublished evidence (such as conference abstracts) was considered for inclusion in the assessment. A number of trialists were also contacted for additional outcome data.

Inclusion criteria

Randomised controlled trials (RCTs) that compared deferasirox with DFO, deferiprone or placebo were considered for inclusion in the review. RCTs comparing deferiprone alone or in combination with DFO with DFO were also considered. The patient population was limited to patients suffering from chronic anaemia requiring regular blood transfusions. Data on the following outcome measures were considered: change in serum ferritin, change in liver iron concentration (LIC), cardiac iron (cardiac T2*), quality of life, and adverse effects of treatment.

Full economic evaluations that compared two or more chelation options and assessed both costs and consequences were considered for inclusion in the review. Only studies investigating patients with chronic anaemia requiring regular blood transfusions were considered.

Results

Clinical review

A total of 14 RCTs, making comparisons between deferasirox, deferoxamine (DFO), deferiprone and combination therapy (deferiprone and DFO) and involving a study population of 1480 (ranging from 13 to 586), met the inclusion criteria. Three RCTs comparing deferasirox with DFO were found although none contained data that could be included in the meta-analyses; there were no studies comparing deferasirox with deferiprone or combination therapy.

The majority of trials included patients with beta-thalassaemia major (beta-TM) or thalassaemia. The duration of each trial varied between 5 days and 2 years with the majority continuing for approximately 12 months. Most trials provided data on serum ferritin or liver iron concentration.

There was a high degree of heterogeneity between trials in terms of trial design and outcome reporting. As such it was only possible to meta-analyse serum ferritin data from six trials, making comparisons between deferiprone and DFO, and combination therapy and DFO.

In general it appears that there is little difference between chelation agents in terms of reducing serum ferritin. Only one of the results was statistically significant, favouring combination therapy over DFO alone for serum ferritin at 12 months. How this translates into iron loading in organs such as the heart is not clear, nor was it possible to determine the long-term benefits of chelation therapy.

Economic evaluation

Eight full economic evaluations (one full paper; seven abstracts) were included in the review. All eight studies undertook a cost–utility analysis, presenting results as cost per quality-adjusted life-year (QALY), and all compared deferasirox with DFO. Four studies considered only beta-TM patients, one study considered SCD patients, one study included only myelodysplastic syndrome (MDS) patients and two studies considered beta-TM, SCD and MDS patients all together. Two studies had a UK perspective, three studies had a US perspective and the remaining studies were Canadian, Brazilian and European. The four studies in beta-TM patients adopted a long-term time frame (lifetime/50 years); the remaining studies appeared to be limited to 1 year. All of the studies had industry author affiliations and there was a large degree of overlap, in terms of both data sources and authors, between a number of the studies.

The results of the published economic evaluations were generally consistent and appear to demonstrate the cost-effectiveness of deferasirox compared with DFO for the treatment of iron overload in a number of different patient populations and study locations. However, a number of assumptions and, in the case of the long-term studies, extrapolation from short-term RCT data were required, which render the results highly speculative.

Because of the paucity of long-term data, a simple short-term (1 year) model was developed that assessed the costs and benefits of deferasirox, deferiprone and DFO in beta-TM and SCD patients. The model used an NHS perspective and expressed outcomes in terms of cost per QALY. The only difference between chelators in the short term was assumed to be limited to quality of life. The effects of adverse events and adherence were not considered in the analysis.

Even with this relatively simple model a number of assumptions were required in order to generate results. As such all results should be interpreted as indicative rather than factual. The results of the economic model suggest that deferasirox may be a cost-effective strategy (cost per QALY below £30,000 per year) for beta-TM and SCD patients compared with DFO. However, the cost-effectiveness is highly dependent upon the age of the patient and the use of balloon infusers to administer DFO. If deferasirox is compared with deferiprone it is likely that it will be cost-effective only for young children. Furthermore, if deferiprone is proven to offer the same health benefits as deferasirox, deferasirox will not be cost-effective for any patient compared with deferiprone.

Implications for the NHS

In terms of the financial impact placed upon the NHS by the introduction of deferasirox, our analysis indicates that for both beta-TM and SCD patients the total budget impact is likely to be in the region of £8 million. However, this figure is dependent upon the usage of DFO and deferiprone in current practice. Deferasirox is most economically attractive when compared with DFO administered via a balloon infuser and least attractive when compared with deferiprone.

Conclusions

This review reveals that in the short term there is no evidence available to indicate a clinical difference between any of the three chelators in terms of removing iron from the blood and liver. In terms of cost-effectiveness, deferasirox may be cost-effective compared with DFO in beta-TM and SCD patients but it is unlikely to be cost-effective compared with deferiprone.

Recommendations for future research

Elucidating the long-term benefits of chelation therapy, including issues of adverse events and adherence, should be the primary focus for future research. As an adjunct to this, financial support for research into new strategies for measuring iron overload, such as T2*, appears justified, as do further clinical trials in other patient populations such as those with MDS. All future trials should aim to be consistent and transparent in reporting study design and results, which should aid decision-making when trying to make comparisons across trials. There is also a need for an independent costing study to be undertaken in a variety of patients and treatment centres.

Publication

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