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


CRD summary
This review evaluated deferasirox in the treatment of iron overload associated with regular blood transfusions in chronic anaemia. It found that, in the short term, there was no evidence available to indicate a clinical difference between any of the chelators in removal of iron from the blood and liver. These conclusions appear reliable considering the limitations of the available evidence.

Authors' objectives
To evaluate the clinical and cost effectiveness of deferasirox in the treatment of iron overload associated with regular blood transfusions in patients with chronic anaemia.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), DARE, Health Technology Assessment database, Web of Science (Proceedings and Science Citation Index Expanded) and NHS EED were searched for English-language papers published between 1950 and March 2007. Search terms were reported. Abstracts of four haematology conferences (dates ranged from 2001 to 2006) were handsearched. Publicly available licensing information from the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products was obtained to supplement published trial literature where appropriate.

Study selection
Randomised controlled trials (RCTs) of patients with chronic anaemia requiring regular blood transfusions, that compared deferasirox with placebo, deferoxamine or deferiprone, or that compared combination therapy (deferoxamine plus deferiprone) with deferoxamine or deferiprone, were eligible for inclusion. Outcomes eligible for inclusion were absolute and relative change in serum ferritin, absolute and relative change in liver iron concentration, success rate, cardiac iron, quality of life, adverse effects and quality-adjusted life-year gained.

The duration of the included trials varied between five days and two years (the majority were approximately 12 months) and outcome measures varied across trials. Most trials included patients with beta-thalassaemia major or thalassaemia and their ages ranged from two to 54 years. The proportion of men and women were balanced across trials, but there were differences in baseline liver iron concentration and serum ferritin. Deferasirox doses varied across trials.

Studies were selected independently by at least two reviewers. Disagreements were resolved by discussion and if necessary another reviewer was consulted.

Assessment of study quality
Methodological quality was assessed using criteria based on the Centre for Review and Dissemination, Report 4.

Three reviewers independently assessed study quality and disagreements were resolved through discussion.

Data extraction
Data were extracted by one reviewer and checked by another. Where meta-analysis could be performed, means and standard deviations (SDs) were calculated. Authors were contacted for additional information if necessary.

Methods of synthesis
Means and standard deviations were pooled in a fixed-effect model if there was little statistical heterogeneity (this was
only applicable to the outcome of serum ferritin). Otherwise trials were pooled using a DerSimonian and Laird random-effects model. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$. If these indicated heterogeneity, potential influences were investigated (planned a priori for age and disease). For outcomes with excessive clinical heterogeneity or poor methodological quality, trials were presented in a narrative synthesis.

**Results of the review**

Fourteen RCTs were included in the review (n=1,480 patients, range 13 to 586). One RCT was a double-blind parallel placebo controlled trial (n=65 patients). Eight RCTs were open-label parallel trials (n=1,055 patients). One RCT was a crossover trial (n=20 patients). The remaining four RCTs were parallel (n=71 patients), parallel single-blind (n=144 patients), and two were parallel three-armed (n=125 patients) trials.

Overall trial quality was described as poor. Four RCTs described the method of randomisation, three described allocation concealment, two adequately addressed blinding of assessors, four performed intention-to-treat analyses (but this may have been inappropriate in one RCT), baseline characteristics were provided in eight RCTs, and comparability achieved in six. All trials provided number of patients randomised, eligibility criteria, and reported outcomes for at least 80% of those originally randomised.

Serum ferritin was significantly improved with combination therapy compared with deferoxamine at 12 months (WMD -0.71mg/L, 95% CI: -1.01 to -0.41; three RCTs) with no associated heterogeneity. There was no significant difference in serum ferritin with combination therapy compared with deferoxamine at six months (two RCTs), although this was associated with significant heterogeneity. There was no significant difference in serum ferritin at six months (two RCTs) or 12 months (three RCTs) with deferiprone compared with deferoxamine, although these analyses were also associated with significant heterogeneity.

Two trials suggested that 20mg/kg/day deferasirox was as effective as deferoxamine in terms of reduction of liver iron concentration.

Adverse events were also reported.

**Cost information**

The economic model suggested that deferasirox may be cost-effective (cost per quality-adjusted life-year less than £30,000 per year) for beta-thalassaemia major patients or sickle cell disease patients compared with deferoxamine. However this was dependent on the age of the patient and the use of balloon infusers to administer deferoxamine. Deferasirox was unlikely to be cost-effective compared with deferiprone.

**Authors’ conclusions**

In the short term there was 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 patients with chronic anaemia.

**CRD commentary**

The research question was supported by clear inclusion criteria for participants, intervention, outcomes and study design. Only English language papers were sought, so language bias could not be ruled out. The review process was performed by at least two reviewers, reducing the possibility of reviewer error and bias.

Validity was assessed using an appropriate tool and trial quality was taken into consideration in the analysis. Meta-analysis appeared appropriate where performed and heterogeneity was investigated. Narrative synthesis appeared reasonable considering the evident clinical heterogeneity between trials. The authors discussed the limitations in terms of lack of generalisability to long-term outcomes and stated that they consider the analyses to be exploratory.

The authors’ conclusions appear to be reliable considering the limitations of the available evidence.

One of the authors disclosed financial links with the pharmaceutical company Novartis (manufacturers of deferoxamine and deferasirox evaluated in the review).
Implications of the review for practice and research

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that accurate data is needed from longer-term use of chelating agents (such as adverse events, adherence morbidity and mortality). They also stated that further research is needed to validate new diagnostic tools and to establish the link between cardiac iron and longer-term outcomes. The conduct and reporting of trials requires consistency and when trials involve a mix of age groups and disease they should be adequately powered to allow subgroup analysis. Trials are also needed for specific age and disease groups. Independent costing studies are also needed.

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