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[Intervention Review]

Deferasirox for managing transfusional iron overload in people with sickle cell disease

Joerg J Meerpohl¹, Lisa K Schell², Gerta Rücker³, Edith Motschall⁴, Nigel Fleeman⁵, Charlotte M Niemeyer⁶, Dirk Bassler⁷

¹Cochrane Germany, Medical Center – Univ. of Freiburg, Faculty of Medicine, Univ. of Freiburg, Freiburg, Germany. ²Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany. ³Institute for Medical Biometry and Statistics, Faculty of Medicine and Medical Center – University of Freiburg, Freiburg, Germany. ⁴Center for Medical Biometry and Medical Informatics, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany. ⁵Liverpool Reviews & Implementation Group, University of Liverpool, Liverpool, UK. ⁶Pediatric Hematology & Oncology, Center for Pediatrics & Adolescent Medicine, University Medical Center Freiburg, Freiburg, Germany. ⁷Department of Neonatology, University Hospital Zurich and University of Zurich, Zurich, Switzerland

Contact address: Joerg J Meerpohl, Cochrane Germany, Medical Center – Univ. of Freiburg, Faculty of Medicine, Univ. of Freiburg, Breisacher Straße 153, Freiburg, 79110, Germany. meerpohl@cochrane.de, joerg.meerpohl@uniklinik-freiburg.de.

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ABSTRACT

Background

Sickle cell disease (SCD) is a group of genetic haemoglobin disorders, that occurs in about 2.2 per 1000 births worldwide. Increasingly, some people with SCD develop secondary iron overload due to occasional red blood cell transfusions or are on long-term transfusion programmes for e.g. secondary stroke prevention. Iron chelation therapy can prevent long-term complications.

Deferoxamine and deferiprone have been found to be efficacious. However, questions exist about the effectiveness and safety of the newer oral chelator deferasirox.

Objectives

To assess the effectiveness and safety of oral deferasirox in people with SCD and secondary iron overload.

Search methods

We searched the Cystic Fibrosis & Genetic Disorders Group's Haemoglobinopathies Trials Register: date of most recent search: 13 March 2014.

We searched MEDLINE, Embase, Biosis Previews, Web of Science, Derwent Drug File, XTOXLINE, EBM and *The Cochrane Library*, respectively; date of most recent searches: 02 August 2013.

We searched four trial registries: www.controlled-trials.com; www.clinicaltrials.gov; www.who.int/ictpr/en/; www.drks.de; date of most recent searches: 03 June 2013.

Selection criteria

Randomised controlled trials comparing deferasirox with no therapy or placebo or with another iron chelating treatment schedule.

Data collection and analysis

Two authors independently assessed risk of bias and extracted data. We contacted the corresponding study authors for additional information.

Main results

Two studies (with 203 and 212 people) comparing the efficacy and safety of deferasirox and deferoxamine after 12 months and 24 weeks, respectively, were included. The overall quality, according to GRADE, for the main outcomes was moderate to low. Only limited data were available on mortality and end-organ damage, although one study did assess mortality, relative risk 1.26 (95% confidence interval 0.05 to 30.41), the 24-week follow up was too short to allow us to draw firm conclusions. One study reported a relative risk of 1.26 for the incidence of type 2 diabetes mellitus (95% confidence interval 0.05 to 30.41). Serum ferritin reduction was significantly greater with deferoxamine, mean difference of change of 440.69 µg/l (95% confidence interval 11.73 to 869.64). Liver iron concentration (reported in one study) measured by superconduction quantum interference device showed no significant difference for the overall group of patients adjusted for transfusion category, mean difference -0.20 mg Fe/g dry weight (95% confidence interval -3.15 to 2.75).

The occurrence of serious adverse events did not differ between drugs. Nausea, diarrhoea and rash occurred significantly more often in people treated with deferasirox, while adverse events of any kind were more often reported for patients treated with deferoxamine (one study). The mean increase of creatinine was also significantly higher with deferasirox, mean difference 3.24 (95% confidence interval 0.45 to 6.03). Long-term adverse events could not be measured in the included studies (follow up 52 weeks and 24 weeks). Patient satisfaction and the likelihood of continuing treatment, were significantly better with deferasirox.

Authors' conclusions

Deferasirox appears to be of similar efficacy to deferoxamine depending on the appropriate ratio of doses of deferoxamine and deferasirox being compared. However, only limited evidence is available assessing the efficacy regarding patient-important outcomes. The short-term safety of deferasirox seems to be acceptable, however, follow up in the available studies was too short to assess long-term side effects. Long-term safety and efficacy data are available from a non-controlled extension phase not included in our review; however, no valid comparative conclusions can be drawn and future studies should assess comparatively long-term outcomes both for safety and efficacy.

PLAIN LANGUAGE SUMMARY

Deferasirox for managing transfusional iron overload in people with sickle cell disease

Review question

We reviewed the evidence about the effect of deferasirox on secondary iron load in people with sickle cell disease.

Background

Sickle cell disease is a genetic disorder. An increasing number of people with this disorder show secondary iron overload (an accumulation of excess iron in the body) due to repeated red blood cell transfusions. Since the human body is not able to actively get rid of excessive iron, drug treatment (known as iron chelators) is needed. Several years ago, a new oral iron chelator, deferasirox, was introduced. However, it is not known whether deferasirox offers advantages compared to other iron chelators (deferoxamine or deferiprone) with regard to effectiveness and safety.

Study characteristics

Two randomised studies, with moderate overall quality of evidence, comparing deferasirox to deferoxamine were identified. The evidence is current to 02 August 2013. The studies with 203 and 212 participants lasted for 12 months and 24 weeks, respectively.

Key results

Only little data on patient-important outcomes such as mortality (limited by a short study follow up) and end-organ damage (incidence of diabetes mellitus) were available. Iron removal, as measured by the surrogate marker serum ferritin was significantly greater with deferoxamine. In one study, both drugs were reported to work equally well in reducing liver iron concentration.

The safety of deferasirox was acceptable; the main side effects when compared to deferoxamine were increased frequency of nausea, diarrhoea and rash as well as a mean increase of creatinine, while adverse events of any kind were observed more often in people treated with deferoxamine. Patient satisfaction and compliance with therapy was significantly greater with deferasirox.

Quality of the evidence

The overall quality of evidence rated according to the GRADE criteria was moderate due to issues with study design. For four outcomes, namely liver iron concentration, serum ferritin, creatinine increase and satisfaction with treatment, it was judged as 'moderate' quality; for one outcome (discontinuations) was judged as 'low' quality.

Summary

In summary, the evidence from the two included studies suggests that deferasirox is similarly effective as deferoxamine depending on the appropriate ratio of doses of deferoxamine and deferasirox being compared. In the short term, deferasirox appears to have an acceptable safety profile, but there are no comparative data based on randomised controlled trials available looking at long-term safety. Further data on long-term efficacy on patient-relevant outcomes and long-term adverse effects are needed to decide whether deferasirox should be used as alternative to the first-line option of deferoxamine. Currently, its use seems to be mainly warranted as a treatment option for people with sickle cell disease who cannot tolerate or comply with deferoxamine.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Deferasirox versus deferoxamine for managing transfusional iron overload in people with sickle cell disease

Deferasirox versus deferoxamine for managing transfusional iron overload in people with sickle cell disease

Patient or population: patients with sickle cell disease and transfusional iron overload

Settings:

Intervention: deferasirox

Comparison: deferoxamine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Deferoxamine	Deferasirox				
Mortality Follow up: 24 weeks	not estimable (event rate in study 0/56)	not estimable (event rate in study 1/135)	RR 1.26 (0.05 to 30.41)	191 (1 study)	⊕⊕⊕⊕ very low ^{1,2}	
End-organ damage (incidence of diabetes) Follow up: 24 weeks	not estimable (event rate in study 0/56)	not estimable (event rate in study 1/135)	RR 1.26 (0.05 to 30.41)	191 (1 study)	⊕⊕⊕⊕ very low ^{1,3}	
LIC measured by SQUID biomagnetometer (mg Fe/g dw); overall population adjusted for transfusion category Follow up: 52 weeks		The mean LIC measured by SQUID biomagnetometer (mg Fe/g dw) in the intervention group was 0.2 lower (3.15 lower to 2.75 higher)		173 (1 study)	⊕⊕⊕⊕ moderate ¹	
Serum ferritin (µg/l) Follow up: 24 to 52 weeks		The mean serum ferritin (µg/l) in the intervention groups was 440.69 higher (11.73 to 869.64 higher)		283 (2 studies)	⊕⊕⊕⊕ moderate ¹	
AE: Change in creatinine from baseline (µmol/l) Follow up: 52 weeks		The mean creatinine change from baseline in the intervention group was 3.24 higher (0.45 to 6.03 higher)		195 (1 study)	⊕⊕⊕⊕ moderate ¹	
Discontinuations	168 per 1000	89 per 1000	RR 0.53	398	⊕⊕⊕⊕	

Follow up: 24 to 52 weeks	(52 to 155)		(0.31 to 0.92)	(2 studies)	low ^{1,4}
Satisfaction Follow up: 12 months	238 per 1000	745 per 1000 (474 to 1000)	RR 3.13 (1.99 to 4.93)	195 (1 study)	⊕⊕⊕⊖ moderate ¹

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AE: adverse events; **CI:** confidence interval; **dw:** dry weight; **Fe:** iron; **LIC:** liver iron concentration; **RR:** risk ratio; **SQUID:** superconducting quantum interference device

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

¹ No ITT analysis with regard to efficacy. Unclear risk of other bias due to involvement of sponsor and possibility of selective reporting. See also risk of bias table.

² Mortality due to iron overload cannot be adequately assessed in studies with a maximum follow up of 52 weeks.

³ Wide 95% confidence interval.

⁴ Serious inconsistency with an I^2 of 77%.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is an autosomal recessive genetic disorder caused by a single nucleotide mutation of the haemoglobin β -chain. The worldwide birth rate of people who are homozygous or compound heterozygous for symptomatic SCD is about 2.2 per 1000 births (Angastiniotis 1998; Modell 2008). However, the incidence of this disease varies widely between ethnic groups (Modell 2008). Populations originating from sub-Saharan Africa, the Middle East and parts of the Mediterranean are predominantly affected, but population movement has made SCD a worldwide problem.

The inheritance of one mutated gene (substitution of valine for glutamic acid in the sixth position of the beta chain of the haemoglobin molecule) together with the normal gene for adult haemoglobin (HbA) results in a mutant protein giving rise to a defective variant of haemoglobin. People with the heterozygous state (HbAS or sickle cell trait) are called sickle cell carriers. They are asymptomatic and need neither treatment nor occupational restrictions. The heterozygous state gives some advantage to carriers against malaria infection and has therefore persisted (Weatherall 1998; Richer 2005).

The homozygous state (HbSS) results from inheriting the mutation from both parents. Sickle cell disease can also occur when people are compound heterozygous by inheriting the sickle cell gene from one parent and another variant haemoglobin gene, such as haemoglobin C, D, OArab or E, or a β -thalassaemia gene from the second parent. This gives rise to HbSC, HbSD, HbSOArab, HbSE or HbS β + or HbS β 0. All of these genotypes cause clinically significant SCD with chronic haemolytic anaemia and a predisposition to blockage of small blood vessels resulting in painful crises, acute chest syndrome, cerebral infarction and other complications due to the sickling of the red blood cells. However, the overall severity and patterns of organ damage vary widely depending upon genotype (Platt 1991; Miller 2000; Powars 2005).

Unlike people with β -thalassaemia major, who require regular blood transfusions throughout life from soon after birth, the majority of people with SCD require red cell transfusions only occasionally and intermittently. These are required for indications such as the management of acute severe anaemia in children, e.g. due to splenic sequestration or transient Parvovirus B19 induced aplastic crisis, acute chest syndrome, acute stroke or as a prophylactic measure before operations. Red cell transfusions are not usually required for the management of the chronic anaemia, or acute painful episodes (Josephson 2007). By adulthood, the majority of people with SCD have received several red blood cell transfusions for various reasons.

A small but increasing number of people with SCD are on long-term transfusions, most commonly for secondary stroke prevention, but also for primary stroke prevention, or for recurrent pulmonary complications in people who have not responded to hydroxycarbamide. Over the last decade trials have evaluated the effect of regular prophylactic transfusions for the primary prevention of stroke in children with SCD (Adams 1998; Adams 2005). Trans-cranial doppler (TCD) screening is now recommended as routine care. High-risk children are identified by high-flow velocities on TCDs and should be offered long-term transfusion therapy.

Since the body has no physiological mechanism to actively excrete excess iron, repeated blood transfusions lead to an increased body iron burden including iron deposition into the liver, heart, pancreas and other endocrine organs. This mechanism is well known for people with thalassaemia on regular transfusion programs. As studies have shown, people with SCD with repeated blood transfusions can be affected by the same long-term problems due to iron overload (Vichinsky 2005a). Even if there is no solid evidence showing that iron chelation improves clinical outcome in SCD, iron chelation therapy is generally offered to iron-overloaded people with SCD.

Description of the intervention

Deferoxamine (DFO, Desferal®), reviewed in detail in a Cochrane Review (Fisher 2013a), has been the treatment of choice for iron overload for the last 40 years. Since it has been available for a long time it is the only chelating agent for which a profound effect on the long-term survival of a large cohort of patients with thalassaemia has been shown (Zurlo 1989; Brittenham 1994; Gabutti 1996; Borgna-Pignatti 2004). To be clinically effective deferoxamine has to be administered as a subcutaneous infusion over 8 to 12 hours, five to seven days per week. This regimen has been demonstrated to reduce the body iron load, prevent the onset of iron-induced complications and even reverse some of the organ-damage due to iron (Olivieri 1994). But the arduous schedule of overnight subcutaneous infusions often leads to reduced compliance (Olivieri 1997; Modell 2000; Cappellini 2005). Another problem concerns the toxicity of deferoxamine, particularly at higher doses. Toxicities beside local skin reactions include ophthalmologic (optic neuropathy, retinal pigmentation) and hearing problems (high frequency sensorineural hearing loss). Rare adverse effects like growth retardation, renal impairment (Koren 1991), anaphylactic reactions and pulmonary fibrosis (Freedman 1990) have been reported. The high cost (about \$US 10,000 a year) of deferoxamine (Delea 2008) and the consumables required as well as its complicated mode of administration limit its use in developing countries.

Oral preparations have been highly sought after for many years. In 1987 two studies showed that the orally active iron chelator deferiprone (1,2 dimethyl-3-hydroxypyrid-4-1, also known as L1, CP20, Ferriprox® or Kelfer) could achieve effective short-term iron chelation (Kontoghiorghe 1987a; Kontoghiorghe 1987b). Doubts on the efficacy to reduce liver iron and prevent liver damage arose due to individuals with progression to overt liver fibrosis (Olivieri 1998). The hypothesis of direct liver toxicity of deferiprone could not be confirmed though (Wanless 2002; Wu 2006). Several studies have shown in the meantime the efficacy of deferiprone for iron chelation (Ceci 2002; Maggio 2002) and in particular its benefit on cardiac iron and cardiac morbidity (Peng 2008). However, its use has been quite limited, mainly as second-line therapy, due to its range of adverse effects (Hoffbrand 2003). These include gastrointestinal disturbances, arthropathy, neutropenia and agranulocytosis (Hoffbrand 1989). Recently studies on combination therapy with synergistic effects of deferoxamine and deferiprone have been performed (Kattamis 2003; Origa 2005; Farmaki 2006; Galanello 2006; Tanner 2007; Kolnagou 2008). An excellent Cochrane Review on the effectiveness of deferiprone in people with thalassaemia has recently been published (Fisher 2013b).

How the intervention might work

Deferasirox (4-[3,5-bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]-benzoic acid) also known as CGP 72670, ICL670 or Exjade® is a new oral chelator available for routine use. It is approved for the treatment of secondary iron overload by the US Food and Drug Administration (FDA) (FDA 2005) and the European Medicines Agency (EMA) (EMA 2007). It is rapidly absorbed after administration and has a bioavailability of about 70%. Safety and tolerability were shown in a randomised dose escalation trial in people with β -thalassaemia in 2003 (Nisbet-Brown 2003). The elimination half-life of 8 to 16 hours allows a once-daily administration after the tablets have been added to water or juice. Being a tridentate chelator two molecules of deferasirox are needed to bind one molecule of iron. The excretion of the bound iron is mainly via faeces.

Adverse effects known from experiences in people with thalassaemia include gastrointestinal disturbances (nausea, stomach pain or diarrhoea) that are generally mild and a diffuse rash being more common at higher doses (Cappellini 2006). More rarely, fever, headache and cough are encountered. The main adverse effect with the use of deferasirox seems to be a mild to moderate elevation of the creatinine level in about a third of patients. Elevations of liver enzyme levels have also been described with a lower incidence (5.6%) (Cappellini 2006). As with standard therapy (deferrioxamine), hearing loss and ocular disturbances including cataracts and retinal disorders have been reported with a very low incidence (<1%).

Why it is important to do this review

Deferrioxamine necessitates a serious commitment from the user and due to its adverse effects deferiprone is only approved as second line therapy in some countries. Thus, much hope is being placed in the newer oral chelator deferasirox which - as studies in people with thalassaemia have shown - apparently offers a promising line of treatment due to its iron chelation properties and safety and tolerability profile (Nisbet-Brown 2003; Cappellini 2006; Piga 2006; Cappellini 2007a). Although these results are presumably generalisable to people with SCD, a thorough evaluation of deferasirox in people with SCD seems to be warranted. To adequately manage the increasing number of people with SCD being regularly transfused due to TCD screening results, a systematic review of the effectiveness and safety of deferasirox looking at people with SCD according to Cochrane standards is needed.

OBJECTIVES

To evaluate the effectiveness and safety of oral deferasirox for management of transfusional iron overload in people with SCD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were considered for this review.

Types of participants

People with SCD (irrespective of genotype, age and from any setting worldwide), who have received repeated red blood cell transfusions in the past or who are receiving regular red blood cell transfusions currently which have resulted in iron overload (defined as ferritin levels of over 1000 ng/ml on at least two occasions).

Types of interventions

For oral deferasirox (all schedules and doses), the following comparisons are conceivable:

1. deferasirox compared with no therapy or placebo;
2. deferasirox compared with another iron chelating treatment schedule (i.e. deferrioxamine or deferiprone or any combination thereof).

These comparisons constitute two separate groups and would have been analysed separately. However, the necessity of chelation therapy in iron-overloaded people is well-established and, if at all, only short-term, e.g. pharmacokinetic studies would be ethically justifiable. Longer-term studies with no therapy or placebo would not suffice the paradigm of equipoise and we did not expect to find, and in fact did not find, any studies comparing deferasirox to no therapy or placebo.

Types of outcome measures

Primary outcomes

1. Time to death (any cause)

Secondary outcomes

1. Reduced end-organ damage due to iron deposition
 - a. cardiac failure (necessitating medical treatment)
 - b. endocrine disease (necessitating substitution hormone therapy or treatment of diabetes)
 - c. histological evidence of hepatic fibrosis
 - d. pathological surrogate markers of end-organ damage (i.e. elevated liver enzymes, elevated fasting glucose or pathological oral glucose tolerance test (OGTT), pathological measures (e.g. ejection fraction) in echocardiography)
2. Measures of iron overload
 - a. serum ferritin (ng/ml)
 - b. iron levels in biopsies of liver and other tissue (mg/g liver dry weight)
 - c. tissue iron assessment by SQUID (superconducting quantum interference device) (mg/g liver wet weight)
 - d. tissue iron assessment by MRI (magnetic resonance imaging) (ms)
3. Measures of iron excretion (urine and faeces) over 24 hours (mg/kg/d)

4. Any adverse events
 - a. raised levels of creatinine or kidney failure (above upper normal limit or rise of more than 20% above baseline level)
 - b. skin rash
 - c. gastrointestinal disturbances
 - d. neutropenia or agranulocytosis (absolute neutrophil count (ANC) less than 1000/ μ l or less than 500/ μ l)
 - e. raised levels of liver enzymes (above upper normal limit or raise of more than 20% above baseline level) or progression to liver fibrosis
 - f. hearing loss
 - g. eye problems (e.g. retinal toxicity)
 - h. unanticipated adverse events as reported in the primary studies
5. Participant satisfaction (measured e.g. by questionnaire) and compliance with chelation treatment (measured by the number of people in each arm that show adequate level of adherence to treatment (intake or application of iron chelator on five or more days per week).
6. Cost of intervention per year.

For future updates, data from outcomes not defined a priori but which arise from the review will be collected, if the outcome is considered to be of clinical relevance.

Search methods for identification of studies

No language restriction was applied.

Electronic searches

We identified relevant studies from the Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: (sickle cell OR haemoglobinopathies general) AND ICL670(A).

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*) and quarterly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Haematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the [Cochrane Cystic Fibrosis and Genetic Disorders Group Module](#).

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 13 March 2014.

For this current, updated version, the following additional databases were searched in July 2012 and again in August 2013 (see [Appendix 1](#); [Appendix 2](#) for details): MEDLINE; MEDLINE In-Process; MEDLINE Daily Update; PubMed (limited to "Epub ahead of print"); Embase; Embase Alert; *The Cochrane Library* (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (Central), Other Reviews (DARE), Methods Studies, Technology Assessments, Economic Evaluations, Cochrane Groups Issue); Biosis Previews; ISI Web of Science; Derwent Drug File; XTOXLINE.

An RCT filter was used for searches in MEDLINE, Embase, Biosis Previews, ISI Web of Science, Derwent Drug File and XTOXLINE. Also, the search was limited to reports published in between 2009 and 2012 (search undertaken in July 2012) and to reports published between 2012 and 2013 (search undertaken in August 2013).

Since deferasirox treatment is an intervention where there is still ongoing research, the following four trial registries were searched on 03 June 2013 for all years available in all possible fields using the basic search function (using separately the following keyword terms; 'deferasirox', 'exjade', 'ICL670', 'ICL 760', 'CGP72670' and 'CGP 72670'):

1. Current Controlled Trials Register - via www.controlled-trials.com; (all available registers were searched);
2. ClinicalTrials.gov - via www.clinicaltrials.gov;
3. ICTRP - via www.who.int/ictcp/en/;
4. Deutsches Register klinischer Studien DRKS (German Clinical Trials Register) - via www.drks.de.

For the previous version of this review, in addition to the register search, several databases and ongoing trial registers were searched. See [Appendix 3](#) for full details.

Searching other resources

Reference lists of all identified papers were screened additionally to identify other potentially relevant citations.

Contact was made with selected experts in the field as well as the manufacturer of deferasirox (Novartis) to request information on unpublished studies that involved deferasirox.

Data collection and analysis

Selection of studies

One author (JM) screened all titles and abstracts of papers identified by the search strategies for relevance. We only excluded citations which were clearly irrelevant at this stage. We obtained full copies of all potentially relevant papers. At this stage two review authors (JM and DB) independently screened the full papers, identified relevant studies and assessed eligibility of studies for inclusion. We resolved any disagreement on the eligibility of studies through discussion and consensus, or if necessary through a third party (GA). We excluded all irrelevant records and recorded details of the studies and the reasons for exclusion.

Data extraction and management

Aside from details relating to the risk of bias of the included studies, we extracted two groups of data.

1. Study characteristics: place of publication; date of publication; population characteristics; setting; detailed nature of intervention; detailed nature of comparator; and detailed nature of outcomes. A key purpose of this data was to define unexpected clinical heterogeneity in included studies independently from the analysis of the results.
2. Results of included studies with respect to each of the main outcomes indicated in the review question. We carefully recorded reasons why an included study did not contribute data on a particular outcome and considered the possibility of selective reporting of results on particular outcomes.

Two review authors (JM, DB) independently undertook data extraction using a data extraction form developed by the authors. The review authors resolved any disagreements by consensus or through discussion with a third author (GA). Once disagreements had been resolved, we recorded the extracted data on the final data extraction form. One review author (JM) transcribed these into RevMan 5.2 ([Review Manager 2012](#)). Another review author (DB, LS) verified all data entry for discrepancies.

Assessment of risk of bias in included studies

Two review authors (JM, DB) assessed every study using a simple form and followed the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0 ([Higgins 2008a](#)).

We assessed the following domains as having either a low, unclear or high risk of bias:

1. randomisation;
2. concealment of allocation;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data;
5. selective outcome reporting;
6. other sources of bias.

We reviewed the assessments and discussed any inconsistencies between the review authors in the interpretation of inclusion criteria and their significance to the selected studies. We resolved any disagreements through discussion with a third author (GA). We did not automatically exclude any study as a result of a rating of an 'unclear' or 'high' risk of bias. We present the evaluation of the risk of bias of the included studies in tabular form in the [Results](#) section of the review.

Measures of treatment effect

We analysed extracted data using the most up-to-date version of RevMan available at the time of analysis ([Review Manager 2012](#)).

We planned to extract hazard ratios with their 95% confidence intervals (CI) for the time-to-event outcomes mortality and end-organ damage. If hazard ratios were not given, we planned to use indirect estimation methods described by Parmar ([Parmar 1998](#)) and Williamson ([Williamson 2002](#)) to calculate them.

Since we were unable to either extract these data from the study reports or receive the necessary information from the primary investigators, as an alternative we used the proportions of participants with the respective outcomes measured at certain time points (i.e. three months, six months, then six-monthly intervals) to be able to calculate risk ratios (RR).

We expressed any results for binary outcomes as RR with 95% CIs as measures of uncertainty. Continuous outcomes were expressed as mean differences (MD) with 95% CIs as measures of uncertainty.

Unit of analysis issues

We did not include any cross-over studies nor non-inferiority studies. Therefore, the following methods of analysis were not used for this current version of the review. However, for future updates, when conducting a meta-analysis combining results from cross-over studies, we plan to use the methods recommended by

Elbourne ([Elbourne 2002](#)). For combining parallel and cross-over studies, we will use the methods described by Curtin ([Curtin 2002a](#); [Curtin 2002b](#); [Curtin 2002c](#)).

For some outcomes, a possible perception of the comparison might be whether deferiasirox is not inferior to standard treatment with deferioxamine. Therefore, a per-protocol analysis would be of interest, as is often used for non-inferiority studies, for our primary outcome as well as for the groups one to five of our secondary outcomes.

Studies included in future versions of this review may report information concerning the intention-to-treat (ITT) or per protocol (PP) population or both which we would analyse according to Witte who lists several proposals for analysing these, depending on the data available ([Witte 2004](#)).

1. If all studies report only an ITT analysis (or all studies report only a PP analysis), we will perform a non-inferiority meta-analysis based on Witte's 'perfect case' proposal.
2. If some studies report only an ITT analysis and others only a PP analysis (exclusively), we will perform meta-regression with analysis type as a covariate.
3. If some studies report only an ITT analysis and others only a PP analysis, whilst others report both, we will undertake a sensitivity analysis.
4. If all studies give enough information to do both analyses, we will analyse a bivariate model.

For time-to-event data, we would state non-inferiority if the relative difference in hazard ratios is less than 10%. For RRs, we would define non-inferiority as a RR difference of less than 10% in treatment failures compared to standard therapy. For the continuous outcomes of 'measures of iron overload and iron excretion' as well as 'costs' we would also consider a relative difference of 10% as equivalent.

Dealing with missing data

We requested any missing data from the original investigators.

Assessment of heterogeneity

For outcomes for which both studies provided data, we assessed heterogeneity using Chi² and quantified it by using the I² statistic ([Higgins 2002](#); [Higgins 2003](#)). This measure describes the percentage of total variation across studies that is caused by heterogeneity rather than by chance ([Higgins 2003](#)). The values of I² lie between 0% and 100%. We used a simplified categorization of heterogeneity with the following categories: low (I² less than 30%); moderate (I² between 30% to 60%); and high (I² more than 60%) ([Deeks 2008](#)). We considered heterogeneity to be significant when the P value of Chi² was less than 0.1.

In future updates of this review, if moderate or high heterogeneity is detected and far more than the present two studies are included (i.e. 10 or more studies), we intend to explore clinical heterogeneity by examining differences between groups as detailed below ([Subgroup analysis and investigation of heterogeneity](#)).

Assessment of reporting biases

We made a great effort to minimise the likelihood of publication bias by the use of a comprehensive search strategy including the

search of abstracts and contacting the manufacturer of deferasirox. We did not use funnel plots to assess publication bias, since asymmetry is difficult to detect with a small number of studies (i.e. less than 10) and we could only include two studies in this updated version of the review. If in future we will be able to include more than 10 studies in this review, we will use funnel plots to graphically assess the likelihood of publication bias. We took care in translating the results of the included studies into recommendations for action by involving all review authors in drawing conclusions.

Data synthesis

We conducted meta-analyses using a fixed-effect model as the primary analysis. If we found marked clinical, methodological or statistical heterogeneity (I^2 more than 30%), we performed a secondary analysis using a random-effects model and reported results from both models.

Subgroup analysis and investigation of heterogeneity

We did not perform subgroup analyses as outlined in our protocol since only two studies could be included. For the same reason investigation of clinical or methodological heterogeneity was not done. However, for future updates of this review, we plan to assess clinical heterogeneity by examining differences due to:

- age of participants (i.e., 0 to 2 years; 3 to 5 years; 6 to 11 years; 12 to 17 years; 18 years or older);
- age at commencement of the intervention (i.e., 0 to 2 years; 3 to 5 years; 6 to 11 years; 12 to 17 years; 18 years or older);
- baseline measures of iron overload (i.e. LIC (mg Fe/g dw): ≤ 3 ; > 3 to ≤ 7 ; < 7 to ≤ 14 ; < 14 or serum ferritin (ng/mL (or both)): < 1000 ; > 1000 to ≤ 2500 ; > 2500 to ≤ 4000 ; > 4000).

Subgroup analyses are planned for different:

- doses of intervention (≤ 10 mg/kg; > 10 to ≤ 20 mg/kg; > 20 to ≤ 30 mg/kg; > 30 mg/kg);
- genotypes of SCD (e.g. HbSS, HbS/ β -Thal or HbSC).

Sensitivity analysis

Sensitivity analyses based on assessment of risk of bias and publication status (unpublished and published studies) were not performed since only two studies could be included in this review. However, for future updates of this review we plan to investigate the robustness of our results through a sensitivity analysis on the basis of the risk of bias of the included studies by defining the following groups: low risk of bias (successful blinding of patients, people involved in treatment and care and outcome assessors; adequate allocation concealment; loss to follow-up of less than 20%); high risk of bias (no blinding, inadequate allocation concealment and loss to follow-up of more than 20%); unclear risk of bias (rating of unclear risk of bias in at least one of these three categories).

RESULTS

Description of studies

Results of the search

The updated searches for this current version of the review (run in July 2012 and again in August 2013) identified 715 citations, including 253 duplicates (Figure 1). The title and abstract screening of the remaining 462 citations identified 25 as potentially eligible for this review. The full text screening excluded 24 citations for the following reasons:

Figure 1. Study flow diagram combining first search & update searches (most recent search of databases: August 2013; most recent search of the Cochrane CFGD Group's Trials Register: 13 March 2014)

- review or editorial/comment or other form of published article (N = 7);
- other intervention not including deferasirox (N = 1);
- observational data on people with SCD (N = 14);
- cost-effectiveness analyses on people with SCD (N = 1);
- RCT (SWITCH trial) comparing hydroxyurea and phelobotomy to transfusions and chelation (chelation group included three patients on deferoxamine) (N = 1).

The identified abstract described a study which was labelled as ongoing in the previous version of our review (Vichinsky 2011). By ascertaining that this study had been completed by May 2011, further data listed on ClinicalTrials.gov, could be included in our analysis.

In addition, search of the Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register identified a full-text journal article to this study published after our electronic search was run (Vichinsky 2011). We added the additional data given in the published paper to our review (in addition to the data given in the ClinicalTrials.gov entry) and ascertained that no inconsistencies were to be found.

Previous searches

In August 2009, a search of eligible trials was undertaken for the previous version of the review. A total of 420 citations were identified, including 221 duplicates. The title and abstract screening of the 199 unique citations identified 62 as potentially eligible for this review. However, after full text screening no additional reports could be included. Reasons for exclusions were:

- included people with other disease than SCD (thalassaemia (N = 27), myelodysplastic syndrome (N = 14), or other conditions (N = 4))
- review or editorial/comment or other form of published article (N = 5)
- observational data on people with SCD (N = 12)

The initial search for the previous version of this review, was run on 15 August 2008 and identified 1177 citations, including 648 duplicates. The title and abstract screening of the 529 unique citations identified 153 as potentially eligible for this review. The full text screening excluded 147 citations for any of the following reasons:

- included people with other disease than SCD (thalassaemia (N = 72), myelodysplastic syndrome (N = 24) or other conditions (N = 5))
- review or editorial/comment or other form of published article (N = 31)
- other intervention not including deferasirox (N = 1)
- observational data on people with SCD (N = 12)
- cost-effectiveness analyses on people with SCD (N = 2)

For the previous version of this review, we identified six references reporting on a single study (Vichinsky 2007) (Figure 2). This RCT compared deferasirox with deferoxamine. These six reports specifically describe the RCT phase of the study (Vichinsky 2005b; Vichinsky 2005c; Vichinsky 2006a; Vichinsky 2006b; Vichinsky 2007a; Vichinsky 2008a). Of these six reports, two were published as full text articles (Vichinsky 2007a; Vichinsky 2008a) and four as abstracts (Vichinsky 2005b; Vichinsky 2005c; Vichinsky 2006a; Vichinsky 2006b). The remaining five reports listed under the Vichinsky study ID (Vichinsky 2007) report on the extension phases of four clinical trials including patients with SCD, thalassaemia, myelodysplastic syndrome (MDS) and other transfusion-dependent anemias (Cappellini 2007b; Cappellini 2007c; Piga 2007; Vichinsky 2007b; Vichinsky 2008b). The described total groups (consisting of the deferasirox groups of two observational studies and/or the primary deferasirox group(s) and the cross-over groups, i.e. patients switching to deferasirox after finishing the two primary randomised studies) only contain patients treated with deferasirox. There are no data presented of the initial control groups receiving deferoxamine. Therefore, the data presented are only observational data of a deferasirox group without a control group.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Thus, a total of two studies were included in this updated version of our review ([Vichinsky 2007](#); [Vichinsky 2011](#)).

Included studies

Two studies including 203 and 212 people, respectively, with SCD met the inclusion criteria ([Vichinsky 2007](#); [Vichinsky 2011](#)).

Vichinsky 2007

This study randomised 203 eligible people in a 2:1 ratio to receive either deferasirox or deferoxamine. The randomisation was performed using an interactive voice response system and was stratified according to the following age groups: 2 years to under 6 years; 6 years to under 12 years; 12 years to under 16 years and 16 years and older. The randomisation sequence included permuted block groups of six patients for each of the four age strata.

Only 195 of the 203 randomised patients received treatment and were included in the analysis. Patient characteristics were similar in both groups ([Table 1](#)). Drug dosing was stratified according to baseline liver iron concentration (LIC) into four groups, with baseline LIC:

1. ≤ 3 mg Fe/g dry weight (dw);
2. > 3 to 7 mg Fe/g dw;
3. > 7 to 14 mg Fe/g dw;
4. > 14 mg Fe/g dw.

For the reported LIC values a correction factor of 3.33 and for the adjusted LIC values a correction factor of 6.66 was used to convert the wet weight to dry weight values ([Brittenham 1982](#); [Olivieri 1997](#)).

Deferasirox was given once daily each morning as a dispersed solution in water, half-an-hour before breakfast. The dosing

algorithm according to baseline LIC and average daily doses administered are described in an additional table ([Table 2](#)).

Vichinsky 2011

The second study enrolled 212 patients who were randomised 2:1 to receive either deferasirox (20 mg/kg/day) or deferoxamine (175 mg/kg/week) for 24 weeks. No information regarding randomisation procedure was given in the abstract nor on ClinicalTrials.gov. After 24 weeks, the patients receiving deferoxamine were crossed over to receive deferasirox for the remaining 80 weeks; we therefore limited our analysis to the data available at 24 weeks.

Of the 212 included patients, 9 patients were excluded due to GCP violations and a further 12 patients did not receive the study drug deferoxamine. Therefore, only data on a group of 191 patients were provided in the available abstract and on clinicaltrials.gov. Patient characteristics were similar in both groups ([Table 3](#)).

Excluded studies

Our search identified one RCT comparing alternative treatment (hydroxyurea and phlebotomy) to standard treatment (transfusions and chelation) ([Ware 2011](#)). This trial did not fulfil our stated inclusion criteria and we therefore decided to exclude this study.

Risk of bias in included studies

We assessed the risk of bias of the included studies according to the six categories outlined in [Assessment of risk of bias in included studies](#). Our interpretation of the published reports of the two studies is as follows ([Vichinsky 2007](#); [Vichinsky 2011](#)).

See the risk of bias graph ([Figure 2](#)) and risk of bias summary ([Figure 3](#)).

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Vichinsky 2007	?	+	-	-	-	?
Vichinsky 2011	?	?	-	-	+	?

Allocation

Randomisation

Both studies do not describe the method of randomisation. However, the allocation is characterized as 'randomised'. Therefore, the risk of bias rating for both studies is 'unclear'.

Concealment of allocation

One study used an interactive voice response system; we therefore assumed that adequate allocation concealment was achieved and rated its risk of bias as 'low' (Vichinsky 2007). The risk of bias for the second study was concluded to be 'unclear' as this domain was not discussed (Vichinsky 2011).

Blinding

The included studies are classified as open-label trials. There is no mention of blinding. Therefore the risk of bias is high for both studies (Vichinsky 2007; Vichinsky 2011).

Incomplete outcome data

The first Vichinsky study included 203 patients, but only 195 received treatment and were included in the safety population (Vichinsky 2007). Reasons for this are not stated. Additionally, a similar percentage of patients of both groups (11.4% of the deferasirox group and 11.1% of the deferoxamine group) either discontinued treatment due to adverse events (5.3% on deferasirox

and 3.2% on deferoxamine) or were lost to follow up (two patients from the deferasirox group, one patient from the deferoxamine group), withdrew consent (six patients from the deferasirox group, one patient from the deferoxamine group) or were excluded due to protocol violations (three patients from the deferoxamine group). No intention-to-treat analysis with regard to efficacy was performed. Data are only presented as *per protocol* although the actual numbers of patients analysed is not very clearly stated. Therefore, we assessed this study as having a high risk of bias for this domain.

In the second Vichinsky study, 212 patients were originally included. Nine participants from one site were excluded due to severe 'Good Clinical Practice' (GCP) violations (Vichinsky 2011). Only 191 of the remaining 203 patients received treatment and were considered for analysis, i.e. 12 out of 68 are missing in the deferoxamine group at 24 weeks. For efficacy analysis (serum ferritin) 18 patients in deferasirox and 6 patients in deferoxamine were not considered. Therefore, we assessed this study as having a high risk of bias for this domain.

Selective reporting

According to the methods section of the first Vichinsky study, ferritin values were monitored monthly, clinical and laboratory assessments were performed for safety reasons at 12, 24 and 36 weeks; LIC was also determined by SQUID at 24 weeks (Vichinsky 2007). These data are not reported. Also, it is unclear whether other

possible outcomes were measured but not reported. We did not have any access to the original trial protocols to evaluate this. We contacted the corresponding author, but did not receive a response to our inquiry. Therefore, the risk of bias rating for this study is high risk.

The second study provided detailed outcome data on clinicaltrials.gov (Vichinsky 2011). Therefore, we assessed this study as having a low risk of bias for this domain.

Other potential sources of bias

Both studies were sponsored by Novartis. A potential influence of the manufacturer of deferasirox on the reporting of the results can not be excluded due to the cooperation between Novartis staff and the investigators. Therefore the risk of bias rating is unclear for both studies.

Effects of interventions

See: [Summary of findings for the main comparison Deferasirox versus deferoxamine for managing transfusional iron overload in people with sickle cell disease](#)

Only two studies are included in this review. Thus, sensitivity analyses, subgroup analyses or assessments of heterogeneity were not undertaken for this version of the review.

Primary outcome

1. Overall mortality

There were only limited data available on the primary outcome: the second Vichinsky trial reported one death in the deferasirox group (assessed as unrelated to the study drug) and no deaths in the deferoxamine group, resulting in a relative risk of 1.26 (95% CI 0.05 to 30.41) (Vichinsky 2011). The interpretation of this analysis is hampered by this study's short follow up. The first Vichinsky trial did not report whether any deaths had occurred (Vichinsky 2007).

Secondary outcomes

1. Reduced end-organ damage due to iron deposition

There were no data available on cardiac failure or histological evidence of hepatic fibrosis. One study reported on incidence of type 2 diabetes mellitus: one patient in the deferasirox group and no patient in the deferoxamine group contracted diabetes (Vichinsky 2011). This difference is not significant, RR 1.26 (95% CI 0.05 to 30.41) (Analysis 1.2). No other data were available on endocrine disease.

Elevated liver function tests (LFTs) (alanine transaminase (ALT) $\geq$ 5x upper normal limit (UNL) on two consecutive visits), reported in two studies, were observed in five and two patients, respectively, treated with deferasirox and no patients on deferoxamine, although the difference was not significant, RR 3.66 (95% CI 0.47 to 28.65) (Analysis 1.3) (Vichinsky 2007; Vichinsky 2011). The second study reported on the number of patients in each group with abnormal liver function tests: 2 patients and 0 patients in the deferasirox group and in the deferoxamine group, respectively (no significant difference), RR 2.10 (95% CI 0.10 to 42.97) (Analysis 1.4) (Vichinsky 2011). However, since no definition of the event 'liver function test abnormal' was given, we did not pool these data with the first study.

No information was available on the surrogate markers elevated fasting glucose; pathological oral glucose tolerance test; or pathological measures in echocardiography.

2. Measures of iron overload

Ferritin reduction was greater in people treated with deferoxamine at the end of the two studies (12 months and 24 weeks, respectively). These results were statistically significant with a MD of change of 440.69 μ g/l in favour of deferoxamine (95% CI 11.73 to 869.64) (Analysis 1.5) (Vichinsky 2007; Vichinsky 2011). However, only data on 83 out of 132 (62.9%) and 117 out of 135 (86.7%) patients, respectively, treated with deferasirox and 33 out of 63 (52.4%) and 50 out of 56 (89.3%), respectively, treated with deferoxamine were available according to the study authors.

Liver tissue iron assessment by SQUID, reported in one study (Vichinsky 2007), showed no statistically significant difference for the overall group of patients, MD -0.20 mg Fe/g dw (95% CI -3.15 to 2.75) (Analysis 1.6), nor for the subgroup of patients receiving simple transfusions, MD -0.20 mg Fe/g dw (95% CI -1.97 to 1.57) (Analysis 1.7). For the subgroup of patients receiving exchange transfusions, the deferasirox-treated patients showed a higher, statistically significant reduction in LIC, MD -5.20 mg Fe/g dw (95% CI -8.56 to -1.84) (Analysis 1.7). Neither results of LIC from liver biopsies nor from MRI assessment were available.

3. Measures of iron excretion (urine and/or faeces) over 24 hours

There were no data available on iron excretion in urine or faeces.

4. Adverse events

Except for occurrence of serum creatinine values exceeding the upper limit of normal (ULN) and alanine aminotransferase levels $>$ 5x ULN, the first Vichinsky study did not report on rare adverse events (frequency of less than 10%) (Vichinsky 2007); according to the ClinicalTrials.gov entry, the second study reported only on adverse events occurring in more than 5% of participants, while no such threshold was chosen for serious adverse events (Vichinsky 2011).

Creatinine levels were reported by the first Vichinsky study and partly also by the second Vichinsky study (Vichinsky 2007; Vichinsky 2011). Mild stable increases in creatinine were observed more often (though not statistically significant) in patients treated with deferasirox, RR 1.64 (95% CI 0.98 to 2.74) (Analysis 1.8); the mean increase in creatinine over the course of the study was 3.24 μ mol/l, significantly higher in the deferasirox-treated group (95% CI 0.45 to 6.03) (Analysis 1.9). However, no statistically significant difference was seen in frequency of increases $>$ UNL of creatinine (reported by two studies), RR 0.72 (95% CI 0.12 to 4.18) (Analysis 1.8).

Adverse events of any kind were reported significantly more often in the deferoxamine group, RR 0.88 (95% CI 1.03 to 5.55) (Analysis 1.10) (Vichinsky 2011). However, no difference was observed regarding the incidence of serious adverse events. They occurred with similar frequency in both groups (Analysis 1.10). Also, the difference in serious adverse events suspected to be related to the study drug did not reach significance (Analysis 1.10).

Rash occurred significantly more often in the deferasirox group, RR 2.39 (95% CI 1.03 to 5.55) (Analysis 1.10). Gastrointestinal adverse effects such as abdominal pain, nausea, vomiting or diarrhoea were collected separately, so the overall proportion

of patients experiencing gastrointestinal side effects can not be given. Statistically significant differences in favour of deferoxamine were observed regarding the adverse events: diarrhoea, RR 3.09 (95% CI 1.53 to 6.26); and nausea, RR 2.06 (95% CI 1.11 to 3.80) (Analysis 1.10). There were no data available regarding the frequency of neutropenia or agranulocytosis, nor regarding the occurrence of hearing problems or eye problems. Further adverse events are described in another graph; no additional statistically significant differences were observed (Analysis 1.10). The mean growth velocity in cm per year, reported in one study, was about 1 cm higher in the deferasirox group; however, these differences were not statistically significant for any of the analysed age groups (Analysis 1.12).

Available data for five adverse events showed marked heterogeneity (I^2 more than 30%) and were analysed additionally with a random-effects model, in accordance with our pre-defined analysis plan as described in [Assessment of heterogeneity \(Analysis 1.11\)](#). These analyses provided similar results.

5. Participant satisfaction

Participant satisfaction was reported by the first Vichinsky study (Vichinsky 2007). Both satisfaction with treatment, RR 3.13 (95% CI 1.99 to 4.93) and convenience of this treatment, RR 3.85 (95% CI 2.28 to 6.47) were significantly better with deferasirox compared to deferoxamine (Analysis 1.13; Analysis 1.14). Also, the likelihood of continuing chelation therapy estimated by the patients themselves was significantly higher with deferasirox, RR 6.86 (95% CI 3.38 to 13.91) (Analysis 1.15). These effects were also reflected by the overall rate of discontinuations, RR 0.53 (95% CI 0.31 to 0.92), but not by the rate of discontinuations due to adverse effects, RR 1.03 (95% CI 0.29 to 3.63) (Analysis 1.16).

6. Cost of intervention per year

The included studies provided no data on the cost of either intervention (Vichinsky 2007; Vichinsky 2011).

DISCUSSION

This review is aimed at determining the effectiveness and safety of deferasirox for the management of iron overload in people with SCD.

Firstly, we planned to compare deferasirox to either no treatment or placebo. However, no study addressing this question could be identified, which is not surprising considering that the necessity of chelation therapy in iron-overloaded people is well-established and, if at all, only short-term, e.g. pharmacokinetic studies, would be ethically justifiable. Longer-term studies comparing deferasirox with no therapy or placebo would not suffice the paradigm of equipoise and would therefore be unethical.

Secondly, comparisons with other iron chelating regimens were planned. Only two studies comparing deferasirox with deferoxamine treatment could be identified (Vichinsky 2007; Vichinsky 2011).

Summary of main results

Two trials, involving 203 and 212 people, respectively, compared the efficacy and safety of deferasirox and deferoxamine after 12 months and 24 weeks, respectively. The primary outcome of the included studies was safety and tolerability; efficacy was only

addressed as a secondary endpoint. Thus, only limited data were available for most of our pre-specified patient-important long-term efficacy outcomes. One study reported on our primary outcome (mortality). However, follow up was too short to allow valid conclusions on mortality to be drawn. Also, only limited data were available for reduced end-organ damage (incidence of diabetes mellitus). In a five-year extension phase, three deaths assessed as unrelated to the study drug occurred; surrogate markers of end-organ damage were also reported. However, it has to be kept in mind that observational data are less reliable than randomised controlled trial data and thus should be interpreted with caution (Vichinsky 2007).

Two additional efficacy outcomes we were planning to analyse were addressed in the included studies, namely the surrogate marker serum ferritin (addressed in both included studies) and LIC measured by SQUID (addressed in one study). Serum ferritin reduction was greater with deferoxamine with a mean difference of change of 440.69 µg/l (95% CI 11.73 to 869.64). Deferasirox was effective in reducing LIC; however, there was no statistically significant difference in LIC reduction between deferasirox and deferoxamine for the overall group of patients adjusted for transfusion category, MD -0.20 mg Fe/g dw (95% CI -3.15 to 2.75) (Vichinsky 2007). However, based on the results from one large phase III trial including 586 people with thalassaemia, deferasirox presumably offers a similar efficacy as deferoxamine (Cappellini 2006), in particular if higher doses of deferasirox are used.

Adverse events were observed frequently in both groups. Statistically significant differences in the frequency between the deferasirox- and the deferoxamine-treated groups were encountered for rash, diarrhoea and nausea in favour of deferoxamine, and for adverse events of any kind in favour of deferasirox. The mean increase of creatinine was also significantly higher with deferasirox, although the clinical relevance is debatable. Further differences in the potential for adverse effects between deferasirox and deferoxamine could not be detected, although the data suggest differences, e.g. with regard to growth velocity in favour of deferasirox, probably due to the sample size of the reporting study. Long-term adverse events were not recorded in either of the included studies. Also, it should be stressed that the investigators of the 2007 trial reported only adverse events that occurred in at least one treatment group with a frequency of more than 10% (Vichinsky 2007). Therefore, in this particular study, no information regarding potentially rarer adverse events such as kidney failure, agranulocytosis or eye and hearing problems in people with SCD was reported (Vichinsky 2007). The later trial reported only on adverse events occurring in more than 5% of participants, while no such threshold was established for serious adverse events (Vichinsky 2011). Since both cataracts or lenticular opacities and hypoacusis or neurosensory deafness have been reported in less than 1% of patients in the phase III trial of thalassaemia patients, regular screening at 12-month intervals is advised. Also, periodic monitoring of serum creatinine and liver function test on a monthly basis is recommended.

As one would expect, satisfaction with, and convenience of, deferasirox treatment was significantly higher; the same advantage of deferasirox was observed in an ancillary study to the phase III trial with thalassaemia patients (Cappellini 2007a). These effects were reflected by the overall rate of discontinuations, which were significantly higher in the deferoxamine group.

However, it remains unclear whether compliance with deferasirox will exceed compliance achieved with deferoxamine in the long term, which is of paramount importance to prevent morbidity and mortality in people with secondary iron overload (De Sanctis 2006; Wolfe 1985).

Overall completeness and applicability of evidence

The aim of this review, namely to assess the efficacy and safety of deferasirox in the treatment of people with SCD and secondary iron overload, could only be partly accomplished. Due to limitations in data from only two studies with both a relatively short follow up and a small number of participants (12 months, 195 participants and 24 weeks, 203 participants, respectively), it is difficult to arrive at unambiguous conclusions. The available data, as well as data from studies in people with thalassaemia, show that deferasirox is effective in reducing iron overload. However, whether deferasirox is more effective than deferoxamine could not be shown; our data actually suggest that deferoxamine is more effective (as measured by serum ferritin) based on the appropriate ratio of doses of deferasirox and deferoxamine used in these two studies. It could be argued that there is no need for deferasirox to be more efficacious since equivalent effectiveness in conjunction with better compliance and a more favourable safety profile could well be a huge improvement for affected patients. For this reason, the only completed phase III trial in people with thalassaemia was designed and analysed as a non-inferiority trial (Cappellini 2006).

This review, based on the two relatively small included studies, was not able to address some patient-important outcomes such as mortality or end-organ damage in sufficient detail to allow clear conclusions to be drawn, since these events are very rare and therefore the detection of statistically significant differences in studies of this size is unlikely. Given RCTs, large enough to detect these events, are unlikely to be conducted, further large observational studies will need to provide the main evidence for decision-making. Therefore, recommendations regarding the choice of iron chelating treatment in people with SCD can only be based on limited evidence. While there is indirect evidence from studies of patients with thalassaemia, it can not necessarily be assumed that for example, the safety profile will be exactly the same in people with SCD compared to people with thalassaemia.

Quality of the evidence

There is only limited evidence on the effects of deferasirox in people with SCD. Only two studies were available for inclusion in this review. Only 195 participants of the initially 203 eligible patients and 191 of initially 212 eligible patients, respectively, were included in the safety analysis. The proportion of patients included in the *per protocol* efficacy analyses ranged from 57.1% for serum ferritin to 85.2% for LIC measured by SQUID (Vichinsky 2007). The reasons for this are not stated. The overall risk of bias of the included studies was moderate and is described in detail in the risk of bias tables (Characteristics of included studies). Participants were not blinded to treatment due to the different modes of application of deferasirox and deferoxamine. However, blinding of assessors would have been feasible and could have improved the quality of some rather subjective outcomes, e.g. some adverse events such as nausea or abdominal pain. Finally, it is noted that both studies included in this review were sponsored by Novartis, the manufacturer of deferasirox. In the past, studies conducted with pharmaceutical company involvement in other therapeutic areas

have been shown to contain a bias towards the drugs of the sponsor (Bhandari 2004).

Potential biases in the review process

A very comprehensive search strategy was applied to identify all potential studies and their reports. Despite identifying 12 reports (including 9 abstracts) of a single RCT (Vichinsky 2007) and also a full paper, an abstract, and data reported on clinicaltrials.gov for a further RCT (Vichinsky 2011), data for several relevant outcomes pre-specified in our protocol were not available. Several of these outcome measures are, however, important when making an informed and balanced decision on choice of chelator. While it is likely that some of these outcomes were not measured during the trial, others might have been collected but not reported. Unfortunately, even after contacting the primary investigators, we have not been able to obtain any additional data to date.

To minimize bias in the process of doing this review, we followed the rigid methodology for systematic reviews as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008b).

Agreements and disagreements with other studies or reviews

A review based on a systematic literature search focusing on deferasirox was published in 2006 (VanOrden 2006). In addition to data from a phase III trial, the 2006 review included evidence from phase I and phase II studies, as well as from pharmacokinetic studies, in both humans and non-humans. However, since the studies on patients with SCD included in this review was not yet published, their review did not include any data from a RCT of patients with SCD. Most of the patients included in the 2006 review had thalassaemia and approximately three-quarters of these patients are from a single phase III RCT. The authors made no attempt to pool the data; so findings are presented narratively (including observational data). The authors concluded that their findings suggest that deferasirox is as safe and effective as deferoxamine. However, further studies would be needed to assess its efficacy in other transfusion-requiring diseases such as SCD.

A further systematic review published in 2007 summarized the available data from five phase I and II and one phase III study (Lindsey 2007). All six studies are critically discussed, but no data were pooled and only synthesized qualitatively. Based on the only trial looking at efficacy as a primary endpoint (Cappellini 2006), the authors came to the conclusion that the two agents had similar efficacy although, overall the non-inferiority of deferasirox could not be shown by the primary phase III study investigators. Tolerability was assessed as good, even though deferasirox was associated with a higher incidence of adverse effects. The authors concluded that long-term efficacy and safety remained to be established.

In 2009 a comprehensive health technology assessment on deferasirox for secondary iron overload in patients with chronic anaemia, such as thalassemia and SCD was published (McLeod 2009). It identified 14 RCTs looking at various iron chelation regimens with a high degree of heterogeneity between trials in terms of trial design and outcome reporting. Only three of these compared deferasirox to deferoxamine, none of them contained data that could be included in a meta-analysis. Furthermore,

eight economic evaluations were included in their report. The authors concluded that there appeared to be little difference between agents in terms of reducing serum ferritin. The economic evaluations appeared to demonstrate the cost-effectiveness of deferasirox compared to deferoxamine. However, the authors stated that both their clinical and economic analyses were restricted by the available evidence and should only be considered as exploratory.

Additionally, several narrative reviews on deferasirox have been published over recent years ([Brittenham 2011](#); [Cappellini 2008](#); [Cappellini 2009](#); [Galanello 2012](#); [Walter 2009](#)).

A review published in 2011 evaluated different chelation treatments in sickle cell anaemia, including deferasirox, regarding their effectiveness, safety and costs ([Lucania 2011](#)). Based on one RCT ([Vichinsky 2007](#)), two prospective cohort studies ([Cappellini 2010](#); [Raphael 2009](#)) and one case report ([Yusuf 2008](#)) in people treated with deferasirox, the authors concluded that deferasirox was effective and seemed to be as safe as deferoxamine. However, the authors stated that follow up was too short to judge treatment with deferasirox as completely safe; and concerns about patients with possible pre-existing renal impairment should be emphasized. The overall conclusion by the authors was that chelation treatment in SCD, even though widely recommended and practised, had been based on little efficacy and safety evidence. According to this review, the cost-benefit ratio had also not been fully explored.

An economic evaluation in 2009 reported that deferasirox resulted in US\$3197 savings compared to deferoxamine with a gain of 2.63 quality-adjusted life-years per patient ([Kim 2009](#)). We were unable to assess the costs of treatment with deferasirox since no data were reported in the included studies.

Finally, several reports have recently raised concerns about the safety of deferasirox and possible toxic side effects. Kontoghiorghe summarized several reports on mortality caused by deferasirox, with one study giving a 11.7% mortality rate (1935 of 16514 patients) ([Kontoghiorghe 2013](#)). An observational study reported that nine out of 10 observed patients presented at least one sign of proximal tubular dysfunction at a mean (SD) of 17.2 (8.9) months after initiation of deferasirox therapy ([Dubourg 2012](#)). Therefore, a systematic safety review including observational data seemed to be warranted.

AUTHORS' CONCLUSIONS

Implications for practice

Deferasirox offers a new interesting option to the treatments available for secondary iron overload in people with sickle cell disease. It appears to be of similar efficacy as deferoxamine depending on the appropriate ratio of doses of deferoxamine and deferasirox being compared as chosen in the two randomised

studies, or even higher, with regard to surrogate endpoints after 12 months and 24 weeks, respectively. Accordingly, it is now widely used due to its easier mode of application. The short-term safety of deferasirox seems to be acceptable; however, follow up in the included studies was too short to evaluate comparative efficacy and long-term side effects. Currently, only limited evidence on long-term efficacy and safety is available from the extension phase of one trial following patients treated with deferasirox only.

Even though there are no randomised trials looking at long-term patient-important outcomes in people with sickle cell disease on deferoxamine, there is long-standing experience with this drug. Thus, for people faced with initiating iron chelating therapy, both treatment options should be discussed in detail. Advantages and disadvantages should be pointed out, taking account of the limited evidence on deferasirox, this should be followed by fully informed shared decision-making. For people being well-managed with deferoxamine, it does not seem to be necessary to change the regimen to deferasirox. For people experiencing intolerance to deferoxamine or with low compliance due to the laborious mode of application, deferasirox should be offered as an alternative. However, effort should be made to enrol these patients in clinical trials to further gain insight into the effects of deferasirox; if no randomised controlled trials enrolling patients are being conducted, observational data should be collected in surveillance studies to better monitor adverse events.

Implications for research

Further studies on the effects of deferasirox in people with sickle cell disease are needed for several reasons. Firstly, they need to overcome the limitations of the available two randomised controlled trials, namely short duration and limited data on patient-relevant outcomes. Also, focusing on efficacy measures is of high importance. Furthermore, the producer of deferasirox sponsored not only the included studies in sickle cell disease, but also the aforementioned studies in other conditions, such as thalassaemia. In our opinion, investigator-initiated studies designed and conducted independently from Novartis are desirable. Finally, further studies should be undertaken looking at, e.g. different dosing schemes or a combination of deferasirox with other iron chelators (or both) to establish the optimal treatment algorithm for individual patients based on their iron overload status.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Vichinsky 2007

Methods	Open label, randomised, parallel, multinational, multicentre trial
Participants	<p>People with SCD:</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> ≥ 2 years of age iron overload from repeated blood transfusions serum ferritin level for entry ≥ 1000 µg/l receiving simple transfusions: LIC of ≥ 2 mg Fe/g dw receiving exchange transfusions: LIC of ≥ 5 mg Fe/g dw <p>Exclusion criteria</p> <ul style="list-style-type: none"> serum creatinine above the ULN significant proteinuria (as indicated by a urinary protein:creatinine ratio of ≥ 0.5 confirmed at two visits) active hepatitis B or C second and third atrioventricular block, QT interval prolongation therapy with digoxin or similar medications chelation therapy-associated ocular toxicity <p>Further exclusion criteria as given in ClinicalTrials.gov</p> <ul style="list-style-type: none"> elevated liver enzymes in the year preceding enrolment HIV seropositivity history of nephrotic syndrome

Vichinsky 2007 (Continued)

- uncontrolled systemic hypertension
- fever and other signs/symptoms of infection within 10 days prior to the start of the study
- diseases (cardiovascular, renal, hepatic, etc.) that would prevent the patient from undergoing any of the treatment options
- psychiatric or addictive disorders that would prevent the patient from giving informed consent
- history of drug or alcohol abuse within the 12 months prior to the study
- pregnant or breast feeding patients
- patients treated with systemic investigational drugs within 4 weeks or topical investigational drugs within 7 days before the start of the study
- patients who require concomitant therapy with hydroxyurea
- any surgical or medical condition that might significantly alter the absorption, distribution, metabolism or excretion of any drug, such as gastrointestinal disease or major surgery, renal disease, difficulty voiding or urinary obstruction, or impaired pancreatic function

Interventions	Daily oral DFX (10 - 30 mg/kg according to baseline LIC; n = 132) versus subcutaneous DFO over 8 - 12 hours on 5 - 7 days/week (20 - 62 mg/kg according to baseline LIC; dose normalised to administration for 5 days/week; n = 63).
Outcomes	<p>Safety assessment</p> <ul style="list-style-type: none"> • physical examination • laboratory testing: FBC, electrolytes, glucose, LFT, γ-GT, LDH, cholesterol, triglycerides, uric acid, total protein, CRP, copper and zinc levels • urinary testing: creatinine, total protein and albumin • ECG, audiometry, and ophthalmological tests <p>Efficacy assessment</p> <ul style="list-style-type: none"> • liver iron concentration measured by SQUID • serum ferritin <p>Compliance was measured by number of tablets/vials returned</p>
Notes	<p>The sample-size calculation was based on the number of DFX-treated patients required to detect adverse effects with an underlying event rate of at least 4% with a 95% CI, according to the method of Hanley and Lippman-Hand (Hanley 1983).</p> <p>ClinicalTrials.gov identifier: NCT00067080</p> <p>Study ID number: C1CL670A0109</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>"Patients were randomised to receive deferasirox or deferoxamine in a 2:1 manner. The randomisation was performed using an interactive voice response system and was stratified according to the following age groups: 2 to < 6 years, 6 to < 12 years, 12 to < 16 years and 16 years and older. The randomisation sequence included permuted block groups of six patients for each of the three age strata."</p> <p>Method of randomisation is not described, e.g. computer-generated random numbers.</p>
Allocation concealment (selection bias)	Low risk	"The randomisation was performed using an interactive voice response system."

Vichinsky 2007 (Continued)

		The included study did not report explicitly on concealment of allocation. However, since an interactive voice response system was used, we assumed that adequate allocation concealment was achieved.
Blinding (performance bias and detection bias) All outcomes	High risk	It is classified as an open-label trial. There is no mentioning of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>203 eligible patients were randomised, but only 195 received treatment and are included in the safety population. Reasons for this are not stated.</p> <p>A similar percentage of patients of both groups (11.4% of the DFX group and 11.1% of the DFO group) either discontinued treatment due to adverse events (5.3% on DFX and 3.2% on DFO) or were lost to follow up (2 patients from the DFX group, 1 patient from the DFO group), withdrew consent (6 patients from the DFX group, 1 patient from the DFO group) or were excluded due to protocol violations (3 patients from the DFO group).</p> <p>No intention-to-treat analysis with regard to efficacy was performed. Data are only presented as '<i>per protocol</i>' although the actual numbers of patients analysed is not very clearly stated.</p>
Selective reporting (reporting bias)	High risk	Ferritin values were monitored monthly, clinical and laboratory assessment was performed for safety reasons also at 12, 24 and 36 weeks. LIC was also determined by SQUID at 24 weeks. These data are not reported.
Other bias	Unclear risk	<p>A potential influence of the producer of deferasirox on the reporting of the results can not be excluded due to the cooperation between Novartis staff and the investigators.</p> <p>Citation from Vichinsky 2007: "Novartis Pharmaceuticals Corporation (East Hanover, NJ, USA) coordinated the design and execution of this trial and contributed to the analysis and interpretation of the trial data. Novartis Pharmaceuticals Corporation also collaborated with the external authors to assist in the development and approval of the manuscript for publication."</p>

Vichinsky 2011

Methods	Randomized, open-label, active-control, safety/efficacy study.
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • age ≥ 2 years • male or female patients with SCD (SS, SC, SD, Sβo or Sβ+ thalassaemia) • iron overload from repeated blood transfusion, as defined below <ol style="list-style-type: none"> a. for patients > 16 years old receiving simple transfusions: lifetime history of receipt of at least 120 ml/kg or 30 adult units of packed red blood cells, or b. for patients ≤ 16 years old receiving simple transfusions: lifetime history of receipt of at least 120 ml/kg of packed red blood cells, or c. for all patients receiving exchange transfusions in the absence of a previous attempt to achieve negative iron balance: lifetime performance of at least 20 procedures, or d. for all patients: liver iron content ≥ 7 mg Fe/g • for entry into the screening period: serum ferritin of ≥ 1000 μg/mL on at least 2 occasions during the prior year obtained in the absence of concomitant infection • body weight > 10 kg • no known allergy or contraindication to the administration of DFO • ability to comply with all study-related procedures, medications, and evaluations

Deferasirox for managing transfusional iron overload in people with sickle cell disease (Review)

Vichinsky 2011 (Continued)

- sexually active pre-menopausal female patients must use double-barrier contraception, oral contraceptive plus barrier contraceptive, or must have undergone clinically documented total hysterectomy or oophorectomy (or both), tubal ligation or be postmenopausal defined by amenorrhoea for at least 12 months.
- written informed consent by the patient or for paediatric patient's consent of the patient's legal guardian

The definition of the term 'paediatric' for enrolment and study conduct will be in accordance with the local legislation.

Exclusion criteria

- serum creatinine above the ULN
- significant proteinuria
- history of nephrotic syndrome
- ALT $\geq$ 250 U/L at screening
- clinical evidence of active hepatitis B or hepatitis C
- history of HIV
- fever or other signs/symptoms of infection within 10 days prior to the screening visit
- uncontrolled systemic hypertension
- history of MI, CHF or unstable cardiac disease not controlled by standard medical therapy
- clinically relevant cataract or a previous history of clinically relevant ocular toxicity related to iron chelation
- presence of a surgical or medical condition that might significantly alter the absorption, distribution, metabolism or excretion of any study drug
- history of drug or alcohol abuse within the 12 months prior to enrolment
- pregnant or breastfeeding patients
- patients treated with systemic investigational drug within 4 weeks prior or with topical investigational drug 7 days prior to the screening visit
- randomisation in a previous clinical trial involving ICL670

Other protocol-related inclusion/exclusion criteria may apply.

Interventions	DFX (20 mg/kg; n = 135) once daily versus DFO subcutaneously 175 mg/kg/week (n = 68). Dose adjustments were implemented for changes in patient weight, serum ferritin, serum creatinine, liver function tests and rash.
Outcomes	Primary outcome measures <ul style="list-style-type: none"> to assess the safety of ICL670 compared to DFO during 24 weeks in patients with SCD and iron overload Secondary outcome measures <ul style="list-style-type: none"> to assess the long-term safety of ICL670 for up to 104 weeks in patients with SCD and iron overload to assess the safety in ICL670 in a subgroup of the patients receiving concomitant hydroxyurea to evaluate the efficacy of ICL670 versus DFO after 24 weeks in patients with SCD and iron overload to evaluate the efficacy of ICL670 up to 104 weeks in patients with SCD and iron overload
Notes	ClinicalTrials.gov identifier: NCT00110617 Study ID number: C1CL670A2201
Risk of bias	
Bias	Authors' judgement Support for judgement

Vichinsky 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No information provided with regard to random sequence generation (neither in clinicaltrials.gov nor in ASH abstract). However, the allocation is characterized as "randomized".
Allocation concealment (selection bias)	Unclear risk	No information provided with regard to allocation concealment (neither in clinicaltrials.gov nor in ASH abstract).
Blinding (performance bias and detection bias) All outcomes	High risk	It is classified as an open-label trial. There is no mentioning of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	9 participants from one site were excluded due to severe GCP violations. For analysis, only patients who received study drug were considered (n = 191), i.e. 12 out of 68 are missing in the DFO group at 24 weeks. For efficacy analysis (ferritin) 18 patients in DFX and 6 patients in DFO were not considered.
Selective reporting (reporting bias)	Low risk	Detailed outcome data provided in clinicaltrials.gov.
Other bias	Unclear risk	A potential influence of the producer of DFX on the reporting of the results can not be excluded due to sponsoring by Novartis and cooperation between Novartis staff and the investigators.

ALT: alanine aminotransferase
 ASH: American Society of Hematology
 CI: confidence interval
 CRP: C-reactive protein
 DFO: deferoxamine
 DFX: deferasirox
 dw: dry weight
 ECG: electrocardiogram
 FBC: full blood count
 Fe: iron
 GCP: good clinical practice
 LDH: lactate dehydrogenase
 LFT: liver function test
 LIC: liver iron concentration
 SCD: sickle cell disease
 SQUID: superconduction quantum interference device
 ULN; upper limit of normal
 γ-GT: gamma-glutamyl transferase

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ware 2011	SWITCH trial: randomised non-inferiority trial comparing alternative treatment (hydroxyurea and phlebotomy) to standard treatment (transfusions and chelation) for reduction of secondary stroke and improved management of iron overload. This trial did not fulfil our stated inclusion criteria. Also, although chelation was mainly deferasirox based, deferoxamine was used in some patients.

DATA AND ANALYSES

Comparison 1. Deferasirox versus deferoxamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Diabetes mellitus	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Elevated ALT levels (> 5 UNL) on two consecutive visits	2	386	Risk Ratio (M-H, Fixed, 95% CI)	3.66 [0.47, 28.65]
4 Abnormal liver function tests	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Serum ferritin (µg/l)	2	283	Mean Difference (IV, Fixed, 95% CI)	440.69 [11.73, 869.64]
6 LIC measured by SQUID Biomagnetometer (mg Fe/g dw); Overall population adjusted for transfusion category	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 LIC measured by SQUID Biomagnetometer (mg Fe/g dw); Per transfusion category subgroup	1	129	Mean Difference (IV, Fixed, 95% CI)	-1.29 [-2.85, 0.28]
7.1 receiving simple transfusions	1	97	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.97, 1.57]
7.2 receiving exchange transfusions	1	32	Mean Difference (IV, Fixed, 95% CI)	-5.20 [-8.56, -1.84]
8 Creatinine increase	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Mild stable increases in serum creatinine	1	195	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.98, 2.74]
8.2 Creatinine exceeding UNL	2	386	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.12, 4.18]
9 Change in creatinine from baseline (µmol/l)	1	195	Mean Difference (IV, Fixed, 95% CI)	3.24 [0.45, 6.03]
10 Other adverse events (fixed-effect model)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Serious adverse events	2	386	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.74, 1.27]
10.2 Serious adverse events suspected to be related to study drug	1	191	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.19, 14.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Any adverse event	1	191	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.79, 0.98]
10.4 Adverse events suspected to be related to study drug	1	191	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.57, 1.54]
10.5 Sickle cell anaemia with crisis	2	386	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.82, 1.74]
10.6 Headache	2	386	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.58, 1.12]
10.7 Abdominal pain	2	386	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.95, 2.46]
10.8 Nausea	2	386	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [1.11, 3.80]
10.9 Pyrexia	2	386	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.66, 1.70]
10.10 Vomiting	2	386	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.71, 1.88]
10.11 Diarrhoea	2	386	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [1.53, 6.26]
10.12 Back pain	2	386	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.87, 3.82]
10.13 Upper respiratory tract infection	2	386	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.45, 1.21]
10.14 Arthralgia	2	386	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.63, 2.48]
10.15 Pain in extremity	2	386	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.62, 2.32]
10.16 Pharyngeal pain	2	386	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.55, 2.10]
10.17 Cough	2	386	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.08]
10.18 Nasopharyngitis	2	386	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.35, 1.16]
10.19 Nasal congestion	1	191	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.18, 2.12]
10.20 Rash	2	386	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [1.03, 5.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.21 Pruritus	1	191	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.19, 1.75]
10.22 Constipation	2	386	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.50, 1.96]
10.23 Chest pain	2	386	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.34, 1.29]
10.24 Viral infection	1	195	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.14, 1.17]
10.25 Urinary tract infection	1	191	Risk Ratio (M-H, Fixed, 95% CI)	7.96 [0.47, 134.53]
10.26 Insomnia	1	191	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.09, 1.99]
10.27 Dizziness	1	191	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.05, 1.61]
10.28 Injection site pain	1	191	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 1.14]
10.29 Cardio-respiratory arrest	1	191	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.05, 30.41]
11 Other adverse events (random-effects model)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Back pain	2	386	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.47, 5.42]
11.2 Constipation	2	386	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.34, 3.36]
11.3 Abdominal pain	2	386	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.85, 2.61]
11.4 Upper respiratory tract infection	2	386	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.35, 1.42]
11.5 Pharyngeal pain	2	386	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.39, 2.53]
12 Growth velocity (cm/year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 < 6 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 6 to < 12 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.3 12 - 16 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Satisfaction	1	195	Risk Ratio (M-H, Fixed, 95% CI)	3.13 [1.99, 4.93]
13.1 Patients previously on DFO	1	121	Risk Ratio (M-H, Fixed, 95% CI)	3.56 [2.00, 6.35]
13.2 Patients not on chelation therapy prior to study start	1	74	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [1.18, 5.14]
14 Convenience	1	195	Risk Ratio (M-H, Fixed, 95% CI)	3.85 [2.28, 6.47]
14.1 Patients previously on DFO	1	121	Risk Ratio (M-H, Fixed, 95% CI)	4.32 [2.19, 8.50]
14.2 Patients not on chelation therapy prior to study start	1	74	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [1.40, 7.13]
15 Likelihood of continuing treatment	1	195	Risk Ratio (M-H, Fixed, 95% CI)	6.86 [3.38, 13.91]
15.1 Patients previously on DFO	1	121	Risk Ratio (M-H, Fixed, 95% CI)	8.01 [3.16, 20.34]
15.2 Patients not on chelation therapy prior to study start	1	74	Risk Ratio (M-H, Fixed, 95% CI)	5.27 [1.79, 15.57]
16 Discontinuations	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Discontinuations due to AEs	2	398	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.29, 3.63]
16.2 Overall Discontinuations	2	398	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.31, 0.92]

Analysis 1.1. Comparison 1 Deferasirox versus deferoxamine, Outcome 1 Mortality.

Study or subgroup	Deferasirox n/N	Deferoxamine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Vichinsky 2011	1/135	0/56		0%	1.26[0.05,30.41]

Analysis 1.2. Comparison 1 Deferasirox versus deferoxamine, Outcome 2 Diabetes mellitus.

Analysis 1.3. Comparison 1 Deferasirox versus deferoxamine, Outcome 3 Elevated ALT levels (> 5 UNL) on two consecutive visits.

Analysis 1.4. Comparison 1 Deferasirox versus deferoxamine, Outcome 4 Abnormal liver function tests.

Analysis 1.5. Comparison 1 Deferasirox versus deferoxamine, Outcome 5 Serum ferritin (µg/l).

Analysis 1.6. Comparison 1 Deferasirox versus deferoxamine, Outcome 6 LIC measured by SQUID Biomagnetometer (mg Fe/g dw); Overall population adjusted for transfusion category.

Study or subgroup	Deferasirox		Deferoxamin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Vichinsky 2007	117	-3 (6.2)	56	-2.8 (10.4)		-0.2[-3.15,2.75]
Favours Deferasirox -5 -2.5 0 2.5 5 Favours Deferoxamine						

Analysis 1.7. Comparison 1 Deferasirox versus deferoxamine, Outcome 7 LIC measured by SQUID Biomagnetometer (mg Fe/g dw); Per transfusion category subgroup.

Study or subgroup	Deferasirox		Deferoxamine		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
1.7.1 receiving simple transfusions							
Vichinsky 2007	62	-1.6 (5.8)	35	-1.4 (3.1)		78.29%	-0.2[-1.97,1.57]
Subtotal ***	62		35			78.29%	-0.2[-1.97,1.57]
Heterogeneity: Not applicable Test for overall effect: Z=0.22(P=0.82)							
1.7.2 receiving exchange transfusions							
Vichinsky 2007	22	-6.6 (5.6)	10	-1.4 (3.9)		21.71%	-5.2[-8.56,-1.84]
Subtotal ***	22		10			21.71%	-5.2[-8.56,-1.84]
Heterogeneity: Not applicable Test for overall effect: Z=3.03(P=0)							
Total ***	84		45			100%	-1.29[-2.85,0.28]
Heterogeneity: Tau ² =0; Chi ² =6.64, df=1(P=0.01); I ² =84.95% Test for overall effect: Z=1.61(P=0.11) Test for subgroup differences: Chi ² =6.64, df=1 (P=0.01), I ² =84.95%							
Favours Deferasirox -10 -5 0 5 10 Favours Deferoxamine							

Analysis 1.8. Comparison 1 Deferasirox versus deferoxamine, Outcome 8 Creatinine increase.

Study or subgroup	Deferasirox n/N	Deferoxamine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Mild stable increases in serum creatinine					
Vichinsky 2007	48/132	14/63		100%	1.64[0.98,2.74]
Subtotal (95% CI)	132	63		100%	1.64[0.98,2.74]
Total events: 48 (Deferasirox), 14 (Deferoxamine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.88(P=0.06)					
1.8.2 Creatinine exceeding UNL					
Vichinsky 2007	3/132	2/63		100%	0.72[0.12,4.18]
Vichinsky 2011	0/135	0/56			Not estimable
Subtotal (95% CI)	267	119		100%	0.72[0.12,4.18]
Total events: 3 (Deferasirox), 2 (Deferoxamine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					
<div>Favours Deferasirox0.020.111050Favours Deferoxamine</div>

Analysis 1.9. Comparison 1 Deferasirox versus deferoxamine, Outcome 9 Change in creatinine from baseline ($\mu\text{mol/l}$).

Analysis 1.10. Comparison 1 Deferasirox versus deferoxamine, Outcome 10 Other adverse events (fixed-effect model).

Analysis 1.11. Comparison 1 Deferasirox versus deferoxamine, Outcome 11 Other adverse events (random-effects model).

Analysis 1.12. Comparison 1 Deferasirox versus deferoxamine, Outcome 12 Growth velocity (cm/year).

Analysis 1.13. Comparison 1 Deferasirox versus deferoxamine, Outcome 13 Satisfaction.

Analysis 1.14. Comparison 1 Deferasirox versus deferoxamine, Outcome 14 Convenience.

Analysis 1.15. Comparison 1 Deferasirox versus deferoxamine, Outcome 15 Likelihood of continuing treatment.

Analysis 1.16. Comparison 1 Deferasirox versus deferoxamine, Outcome 16 Discontinuations.

ADDITIONAL TABLES

Table 1. Characteristics of included patients (Vichinsky 2007)

	Deferasirox (n = 132)	Deferoxamine (n = 63)	All patients (n = 195)
Age, years			
Median	15	16	15
Range	3 - 54	3 - 51	3 - 54
Age group, # of patients (%)			
< 6 years	4 (3.0)	3 (4.8)	7 (3.6)
6 to < 12 years	30 (22.7)	15 (23.8)	45 (23.1)
12 to < 16 years	33 (25.0)	13 (20.6)	46 (23.6)
16 to < 50 years	63 (47.7)	31 (49.2)	94 (48.2)
50 to < 65 years	2 (1.5)	1 (1.6)	3 (1.5)
Sex, # of patients (%)			
Female	80 (60.6)	35 (55.6)	115 (59.0)
Male	52 (39.4)	28 (44.4)	80 (41.0)
Race, # of patients (%)			
Caucasian	8 (6.1)	3 (4.8)	11 (5.6)
Black	118 (89.4)	59 (93.7)	177 (90.8)
Others	6 (4.5)	1 (1.6)	7 (3.6)
Ferritin, µg/l			
Median	3'460	2'834	3'298
Range	1'082 - 12'901	1'015 - 15'578	1'015 - 15'578
Baseline ALT, # of patients (%)			
≤ 2.5 ULN	110 (83.3)	58 (92.1)	168 (86.2)
> 2.5 ULN	21 (15.9)	5 (7.9)	26 (13.3)
Missing	1 (0.8)	-	1 (0.5)
History of HAV and/or HBV, # of patients (%)			
Present	10 (7.6)	4 (6.3)	14 (7.2)
Absent	122 (92.4)	59 (93.7)	181 (92.8)

Table 1. Characteristics of included patients (Vichinsky 2007) *(Continued)*

Prior chelation therapy, # of patients (%)			
Deferoxamine or deferiprone	83 (62.9)	38 (60.3)	121 (62.1)
No prior chelation therapy	49 (37.1)	25 (39.7)	74 (37.9)
Blood transfusions during study (units of packed RBCs)			
Median	12	12	12
Range	0 - 24	1 - 22	0 - 24

ALT: alanine aminotransferase

HAV: hepatitis A virus

HBV: hepatitis B virus

RBCs: red blood cells

ULN: upper limit of normal

Table 2. Dosing algorithm according to LIC groups and average daily doses administered (Vichinsky 2007)

Baseline LIC group	Baseline LIC (mg Fe / g dw)			
	≤ 3	> 3 - ≤ 7	> 7 - ≤ 14	> 14
Deferasirox (n = 132)	(n = 4)	(n = 64)	(n = 46)	(n = 18)
Protocol assigned dose	5 mg/kg	10 mg/kg	20 mg/kg	30 mg/kg
Reported mean LIC ± SD	2.5 ± 0.4	7.9 ± 5.5	9.8 ± 1.9	17.5 ± 3.0
Adjusted mean LIC ± SD	5.0 ± 0.8	15.8 ± 11.0	19.6 ± 3.8	35.0 ± 6.0
Deferasirox dose (mg/kg)	9.5 ± 3.2	13.0 ± 3.1	19.7 ± 2.1	28.0 ± 2.8
Min - Max deferasirox dose	5.0 - 12.3	8.4 - 23.9	10.0 - 24.5	22.8 - 30.0
Deferoxamine (n = 63)	(n = 6)	(n = 21)	(n = 20)	(n = 16)
Protocol assigned dose	20 - 30 mg/kg	25 - 35 mg/kg	35 - 50 mg/kg	≥ 50 mg/kg
Reported mean LIC ± SD	3.9 ± 3.5	5.2 ± 2.1	8.6 ± 3.0	14.3 ± 5.4
Adjusted mean LIC ± SD	7.8 ± 7.0	10.4 ± 4.2	17.2 ± 6.0	28.6 ± 10.8
Deferoxamine dose (mg/kg)	22.9 ± 3.9	28.7 ± 3.2	36.6 ± 9.5	50.0 ± 7.3
Min - Max deferoxamine dose	20.0 - 29.5	21.6 - 34.4	7.0 - 52.6	32.4 - 62.0
Deferasirox / Deferoxamine dose ratio	1 : 2.4	1 : 2.2	1 : 1.85	1 : 1.8

dw: dry weight

FE: iron

LIC: liver iron concentration

SD: standard deviation

Table 3. Characteristics of included patients (Vichinsky 2011)

	Deferasirox (n = 135)	Deferoxamine (n = 68)	All Patients (n = 203)
Age, years			
Mean ± Standard deviation	16.4 ± 10.31	16.2 ± 10.15	16.3 ± 10.23
Age group, # patients (%)			
2 to < 6 years	6 (4.4)	4 (5.9)	10 (4.9)
6 to < 12 years	42 (31.1)	21 (30.9)	63 (31.0)
12 to < 16 years	35 (25.9)	18 (26.5)	53 (26.1)
16 to < 50 years	50 (37.0)	24 (35.3)	74 (36.5)
50 to < 65 years	2 (1.5)	1 (1.5)	3 (1.5)
≥ 65 years	0	0	0
Gender, # patients (%)			
Female	56 (41.5)	33 (48.5)	89 (43.8)
Male	79 (58.5)	35 (51.5)	114 (56.2)
Race, # patients (5)			
Caucasian	2 (1.5)	0	2 (1.0)
Black	130 (96.3)	65 (95.6)	195 (96.1)
Oriental	0	0	0
Other	3 (2.2)	3 (4.4)	6 (3.0)
Weight group, # patients (%)			
< 15 kg	0	0	0
15 to < 35 kg	39 (28.9)	23 (33.8)	62 (30.5)
35 to < 55 kg	43 (31.9)	18 (26.5)	61 (30.0)
55 to < 75 kg	42 (31.1)	22 (32.4)	64 (31.5)
≥ 75 kg	10 (7.4)	3 (4.4)	13 (6.4)
Missing	1 (0.7)	2 (2.9)	3 (1.5)
History of splenectomy, #patients (%)			
Yes	22 (16.3)	10 (14.7)	32 (15.8)

Table 3. Characteristics of included patients (Vichinsky 2011) *(Continued)*

No	113 (83.7)	58 (85.3)	171 (84.2)
Serum ferritin, ng/mL			
Median	3406	3300	n.a.
Range	920 - 12535	1178 - 16535	n.a.
Serum ferritin category, # of patients (%)			
≤ 1000 ng/mL	4 (3.0)	0	4 (2.0)
> 1000 - ≤ 2500 ng/mL	34 (25.2)	28 (41.2)	62 (30.5)
> 2500 - ≤ 4000 ng/mL	45 (33.3)	16 (23.5)	61 (30.0)
> 4000 ng/mL	52 (38.5)	24 (35.3)	76 (37.4)
Transfusional iron intake, mL RBC/kg/day			
Median	0.3	0.3	n.a.
Range	0.1 - 2.4	-0.1 - 0.8	n.a.
Dose of iron chelating drug, mean (SD)			
Planned dose (mg/kg/day)	19.8 (2.0)	41.1 (4.6) *	n.a.
Received dose (mg/kg/day)	19.6 (2.2)	34.1 (4.7) *	n.a.

* based on dose per day over 5 days/week

RBC: red blood cells

APPENDICES

Appendix 1. Search strategies August 2013

MEDLINE (via Ovid)	
#1	deferasirox*.mp.
#2	(ICL670* or ICL 670*).mp.
#3	(CGP72670* or CGP 72670*).mp.
#4	exjade*.mp.
#5	2-hydroxyphenyl.mp.
#6	triazol-1-yl.mp.
#7	benzoic acid.mp.

(Continued)

#8	5 and 6 and 7
#9	1 or 2 or 3 or 4 or 8
#10	remove duplicates from 9
#11	(2012* or 2013*).ed,ep,dc. or ("2012" or "2013").yr.
#12	10 and 11
#13	randomized controlled trial.pt.
#14	controlled clinical trial.pt.
#15	randomi#ed.ab.
#16	placebo.ab.
#17	drug therapy.fs.
#18	randomly.ab.
#19	trial.ab.
#20	groups.ab.
#21	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
#22	exp animals/ not humans.sh.
#23	21 not 22
#24	12 and 23

Notes

.mp. = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier.

.sh. or / = Medical Subject Heading

exp = explode

.ti. title

.ab. = abstract

.pt. = publication type

.yr. = year

.ed. = entry date

.ep. = electronic date of publication

.dc. = date created

searched 01 January 2012 to week 4, July 2013

date searched: 02 August 2013

(Continued)

MEDLINE Daily Update / In-Process & Other Non-Indexed Citations (via Ovid)

#1	deferasirox*.mp.
#2	(ICL670* or ICL 670*).mp.
#3	(CGP72670* or CGP 72670*).mp.
#4	exjade*.mp.
#5	2-hydroxyphenyl.mp.
#6	triazol-1-yl.mp.
#7	benzoic acid.mp.
#8	5 and 6 and 7
#9	1 or 2 or 3 or 4 or 8

Notes

.mp. = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier.

searched to 01 August 2013

date searched: 02 August 2013

PubMed Epub ahead of print

#1	Search deferasirox*[tw]
#2	Search ICL670*[tw] OR ICL 670*[tw]
#3	Search CGP72670*[tw] OR CGP 72670*[tw]
#4	Search exjade*[tw]
#5	Search 2-hydroxyphenyl[tw]
#6	Search triazol-1-yl[tw]
#7	Search benzoic acid[tw]
#8	Search #5 AND #6 AND #7
#9	Search #1 OR #2 OR #3 OR #4 OR #8
#10	Search #9 AND publisher[sb]

Notes

(Continued)

[tw] = textword: title, abstract, other abstract, MeSH terms, MeSH Subheadings, Publication Types, Substance Names, Personal Name as Subject, Corporate Author, Secondary Source, and Other Terms.

[sb] = subset

Date searched: 02 August 2013

Embase & Embase Alert (via DIMDI)

#1	EM05; EA08
#2	DEFERASIROX*
#3	(ICL670* OR ICL 670*)
#4	(CGP72670* OR CGP 72670*)
#5	EXJADE*
#6	2-HYDROXYPHENYL
#7	TRIAZOL-1-YL
#8	BENZOIC ACID
#9	6 AND 7 AND 8
#10	2 OR 3 OR 4 OR 5 OR 9
#11	10 AND PY>=2012
#12	RANDOM* OR PLACEBO* OR DOUBLE-BLIND*
#13	11 AND 12
#14	13 NOT SU=MEDLINE

Notes

EM05 = Embase since 2005; EA08 = Embase Alert

PY = Publication year

SU = subunit

Embase: update status 01 January 2005 to 02 August 2013

Embase Alert: update status 05 June 2013 - 02 August 2013

Date searched: 02 August 2013

Cochrane Library (via Wiley)

#1	(deferasirox*)
----	----------------

(Continued)

#2	ICL670* OR (ICL next 670*)
#3	CGP72670* OR (CGP next 72670*)
#4	exjade*
#5	2 next hydroxyphenyl
#6	triazol next 1 next yl
#7	benzoic next acid
#8	(#5 AND #6 AND #7)
#9	(#1 OR #2 OR #3 OR #4 OR #8)
#10	(#9), from 2012 to 2013

Notes

Issues searched:

Issue 7, 2013 of Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Groups Issue

Issue 3, 2013 of Other Reviews (DARE), Methods Studies, Technology Assessments, Economic Evaluations

Date searched: 02 August 2013

Biosis Previews (via Thomson Reuters)

#1	ts=deferisirox*
#2	ts=(ICL670* or "ICL 670*")
#3	ts=(CGP72670* or "CGP 72670*")
#4	ts=exjade*
#5	ts="2-hydroxyphenyl"
#6	ts="triazol-1-yl"
#7	ts="benzoic acid"
#8	#5 AND #6 AND #7
#9	#1 OR #2 OR #3 OR #4 OR #8
#10	ts=(rando* or placebo or trial or "single-blind*" or "double-blind*" or groups)
#11	#10 AND #9

Notes

(Continued)

Ts = topic

Time-span=2012-2013

Updated 2013-08-01

Date searched: 02 August 2013

Web of Science (via Thomson Reuters)

#1	ts=deferasirox*
#2	ts=(ICL670* or "ICL 670*")
#3	ts=(CGP72670* or "CGP 72670*")
#4	ts=exjade*
#5	ts="2-hydroxyphenyl"
#6	ts="triazol-1-yl"
#7	ts="benzoic acid"
#8	#5 AND #6 AND #7
#9	#1 OR #2 OR #3 OR #4 OR #8
#10	ts=(rando* or placebo or trial or "single-blind*" or "double-blind*" or groups)
#11	#10 AND #9

Notes

TS = topic: Title, Abstract, Author Keywords, Keywords Plus®

Time-span: 2012 - 2013

Update status: 01 August 2013

Date searched: 02 August 2013

Derwent Drug File (via DIMDI)

#1	DD83
#2	DEFERASIROX*
#3	(ICL670* OR ICL 670*)
#4	(CGP72670* OR CGP 72670*)
#5	EXJADE*
#6	2-HYDROXYPHENYL

(Continued)

#7	TRIAZOL-1-YL
#8	BENZOIC ACID
#9	6 AND 7 AND 8
#10	2 OR 3 OR 4 OR 5 OR 9
#11	10 AND PY>=2012
#12	RANDO* OR PLACEBO OR TRIAL OR SINGLE-BLIND* OR DOUBLE-BLIND* OR GROUPS
#13	11 AND 12
Notes	
DD83 = Derwent Drug File	
PY = Publication year	
Update status: 01 January 1983 - 01 August 2013	
Date searched: 02 August July 2013	

Xtoutline (via DIMDI)

#1	<u>T165</u>
#2	DEFERASIROX*
#3	ICL670* OR ICL 670*
#4	CGP72670* OR CGP 72670*
#5	EXJADE*
#6	2-HYDROXYPHENYL
#7	TRIAZOL-1-YL
#8	BENZOIC ACID
#9	6 AND 7 AND 8
#10	2 OR 3 OR 4 OR 5 OR 9
#11	10 and py>=2012
#12	RANDO* OR PLACEBO OR TRIAL OR SINGLE-BLIND* OR DOUBLE-BLIND* OR GROUPS
#13	11 AND 12
Notes	
T165 = Xtoutline	
PY = Publication year	

(Continued)

Update status: 01 January 1965 - 02 August 2013

Date searched: 02 August 2013

Appendix 2. Search strategies July 2012

MEDLINE (via Ovid)	
#1	deferasirox*.mp.
#2	(ICL670* or ICL 670*).mp.
#3	(CGP72670* or CGP 72670*).mp.
#4	exjade*.mp.
#5	2-hydroxyphenyl.mp.
#6	triazol-1-yl.mp.
#7	benzoic acid.mp.
#8	5 and 6 and 7
#9	1 or 2 or 3 or 4 or 8
#10	remove duplicates from 9
#11	(2009* or 2010* or 2011* or 2012*).ed,ep,dc. or ("2009" or "2010" or "2011" or "2012").yr.
#12	10 and 11
#13	randomized controlled trial.pt.
#14	controlled clinical trial.pt.
#15	randomi#ed.ab.
#16	placebo.ab.
#17	clinical trials as topic.sh.
#18	randomly.ab.
#19	trial.ti.
#20	or/13-19
#21	exp animals/ not humans.sh.
#22	20 not 21
#23	12 and 22

(Continued)

Notes

.mp. = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier.

.sh. or / = Medical Subject Heading

exp = explode

.ti. title

.ab. = abstract

.ed. = entry date

.ep. = electronic date of publication

.dc. = date created

.yr. = year

The chemical substance name "4-(3,5-bis(2-hydroxyphenyl)-(1,2,4)-triazol-1-yl) benzoic acid" was searched by splitting it up in searchable terms (2-hydroxyphenyl, triazol-1-yl, benzoic acid) and combining those by AND.

Searched 1 January 2009 to week 1, July 2012

Date searched: 17 July 2012

MEDLINE Daily Update / In-Process & Other Non-Indexed Citations (via Ovid)

#1	deferasirox*.mp.
#2	(ICL670* or ICL 670*).mp.
#3	(CGP72670* or CGP 72670*).mp.
#4	exjade*.mp.
#5	2-hydroxyphenyl.mp.
#6	triazol-1-yl.mp.
#7	benzoic acid.mp.
#8	5 and 6 and 7
#9	1 or 2 or 3 or 4 or 8
#10	remove duplicates from 9
#11	(2009* or 2010* or 2011* or 2012*).ed,ep,dc. or ("2009" or "2010" or "2011" or "2012").yr.
#12	10 and 11

Notes

.mp. = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier.

(Continued)

.yr. = year
.ed. = entry date
.ep. = electronic date of publication
.dc. = date created
Searched to 16 July 2012
Date searched: 17 July 2012

PubMed Epub ahead of print

#1	Search deferasirox*[tw]
#2	Search ICL670*[tw] OR ICL 670*[tw]
#3	Search CGP72670*[tw] OR CGP 72670*[tw]
#4	Search exjade*[tw]
#5	Search 2-hydroxyphenyl[tw]
#6	Search triazol-1-yl[tw]
#7	Search benzoic acid[tw]
#8	Search #5 AND #6 AND #7
#9	Search #1 OR #2 OR #3 OR #4 OR #8
#10	Search pubstatusaheadofprint AND #9

Notes

[tw] = textword: title, abstract, other abstract, MeSH terms, MeSH Subheadings, Publication Types, Substance Names, Personal Name as Subject, Corporate Author, Secondary Source, and Other Terms

Date searched: 17 July 2012

Embase & Embase Alert (via DIMDI)

#1	EM05; EA08
#2	DEFERASIROX*
#3	(ICL670* OR ICL 670*)
#4	(CGP72670* OR CGP 72670*)
#5	EXJADE*

(Continued)

#6	2-HYDROXYPHENYL
#7	TRIAZOL-1-YL
#8	BENZOIC ACID
#9	6 AND 7 AND 8
#10	2 OR 3 OR 4 OR 5 OR 9
#11	PY>=2009
#12	10 AND 11
#13	RANDOM* OR PLACEBO* OR DOUBLE-BLIND*
#14	12 AND 13
#15	14 NOT SU=MEDLINE

Notes

EM05 = Embase since 2005; EA08 = Embase Alert

PY = Publication year

SU = subunit

Embase: update status 01 January 2005 - 25 July 2012

Embase Alert: update status 28 May 2012 - 25 July 2012

Date searched: 25 July 2012

Cochrane Library (via Wiley)

#1	(deferasirox*)
#2	ICL670* OR (ICL next 670*)
#3	CGP72670* OR (CGP next 72670*)
#4	exjade*
#5	2 next hydroxyphenyl
#6	triazol next 1 next yl
#7	benzoic next acid
#8	(#5 AND #6 AND #7)
#9	(#1 OR #2 OR #3 OR #4 OR #8)
#10	(#9), from 2009 to 2012

Notes

Deferasirox for managing transfusional iron overload in people with sickle cell disease (Review)

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(Continued)

Issues searched:

Issue 7, 2012 of Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Groups Issue

Issue 3, 2012 of Other Reviews (DARE), Methods Studies, Technology Assessments, Economic Evaluations

Date searched: 17 July 2012

Biosis Previews (via Thomson Reuters)

#1	ts=deferasirox*
#2	ts=(ICL670* or "ICL 670*")
#3	ts=(CGP72670* or "CGP 72670*")
#4	ts=exjade*
#5	ts="2-hydroxyphenyl"
#6	ts="triazol-1-yl"
#7	ts="benzoic acid"
#8	#5 AND #6 AND #7
#9	#1 OR #2 OR #3 OR #4 OR #8
#10	ts=(rando* or placebo or trial or "single-blind*" or "double-blind*" or groups)
#11	#10 AND #9

Notes

Ts = topic

Time-span: 2009 - 2012

Updated 20 July 2012

Date searched: 25 July 2012

Web of Science (via Thomson Reuters)

#1	ts=deferasirox*
#2	ts=(ICL670* or "ICL 670*")
#3	ts=(CGP72670* or "CGP 72670*")
#4	ts=exjade*
#5	ts="2-hydroxyphenyl"

(Continued)

#6	ts="triazol-1-yl"
#7	ts="benzoic acid"
#8	#7 AND #6 AND #5
#9	#8 OR #4 OR #3 OR #2 OR #1
#10	ts=(rando* or placebo or trial or "single-blind*" or "double-blind*" or groups)
#11	#10 AND #9

Notes

TS = topic: Title, Abstract, Author Keywords, Keywords Plus®

Lemmatization=On

Time-span: 2009 - 2012

Update status: 20 July 2012

Date searched: 25 July 2012

Derwent Drug File (via DIMDI)

#1	DD83
#2	DEFERASIROX*
#3	(ICL670* OR ICL 670*)
#4	(CGP72670* OR CGP 72670*)
#5	EXJADE*
#6	2-HYDROXYPHENYL
#7	TRIAZOL-1-YL
#8	BENZOIC ACID
#9	6 AND 7 AND 8
#10	2 OR 3 OR 4 OR 5 OR 9
#11	PY>=2009
#12	10 AND 11
#13	(RANDO* OR PLACEBO OR TRIAL OR SINGLE-BLIND* OR DOUBLE-BLIND* OR GROUPS)
#14	12 AND 13

(Continued)

Notes

DD83 = Derwent Drug File

PY = Publication year

Update status: 01 January 1983 - 24 July 2012

Date searched: 25 July 2012

Xtotoxline (via DIMDI)

No	Search Expression
#1	T165
#2	DEFERASIROX*
#3	(ICL670* OR ICL 670*)
#4	(CGP72670* OR CGP 72670*)
#5	EXJADE*
#6	2-HYDROXYPHENYL
#7	TRIAZOL-1-YL
#8	BENZOIC ACID
#9	6 AND 7 AND 8
#10	2 OR 3 OR 4 OR 5 OR 9
#11	PY>=2009
#12	10 AND 11
#13	(RANDO* OR PLACEBO OR TRIAL OR SINGLE-BLIND* OR DOUBLE-BLIND* OR GROUPS)
#14	12 AND 13

Notes

T165 = Xtotoxline

PY = Publication year

Update status: 01 January 1965 - 20 July 2012

Date searched: 25 July 2012

Appendix 3. Search strategies June 2009

MEDLINE (via Ovid)

#1	deferasirox*.mp
#2	(ICL670* or ICL 670*).mp
#3	(CGP72670* or CGP 72670*).mp
#4	exjade*.mp
#5	2-hydroxyphenyl.mp
#6	triazol-1-yl.mp
#7	benzoic acid.mp
#8	#5 and #6 and #7
#9	#1 or #2 or #3 or #4 or #8

Notes

.mp = Abstract (AB), Subject Heading Word (HW), Name of Substance Word (NM), Original Title (OT), Title (TI)

The chemical substance name "4-(3,5-bis(2-hydroxyphenyl)-(1,2,4)-triazol-1-yl) benzoic acid" was searched by splitting it up in searchable terms (2-hydroxyphenyl, triazol-1-yl, benzoic acid) and combining those by AND (lines #5 - #8).

Searched from 1950 to week 3, June 2009

Date searched: 22 June 2009

Embase (via Ovid)

#1	deferasirox*.mp
#2	(ICL670* or ICL 670*).mp
#3	(CGP72670* or CGP 72670*).mp
#4	exjade*.mp
#5	2-hydroxyphenyl.mp
#6	triazol-1-yl.mp
#7	benzoic acid.mp
#8	#5 and #6 and #7
#9	#1 or #2 or #3 or #4 or #8

Notes

(Continued)

.mp = Abstract (AB), Device Manufacturer (DM), Drug Manufacturer Name (MF), Drug Trade Name (TN), Heading Word (HW), Original Title (OT), Subject Headings (SH, DE, CT, SW), Title (TI)

The chemical substance name "4-(3,5-bis(2-hydroxyphenyl)-(1,2,4)-triazol-1-yl) benzoic acid" was searched by splitting it up in searchable terms (2-hydroxyphenyl, triazol-1-yl, benzoic acid) and combining those by AND (lines #5 - #8).

Searched from 1980 to week 3, June 2009

Date searched: 22 June 2009

Evidence Based Medicine Reviews (via Ovid)

#1	deferasirox*.mp
#2	(ICL670* or ICL 670*).mp
#3	(CGP72670* or CGP 72670*).mp
#4	exjade*.mp
#5	2-hydroxyphenyl.mp
#6	triazol-1-yl.mp
#7	benzoic acid.mp
#8	#5 and #6 and #7
#9	#1 or #2 or #3 or #4 or #8

Notes

.mp = Abstract (AB), Accession Number (AN), Author (AU), Drug Trade Name (TN), Institution (IN), Source (SO), Subject Heading (SH), Title (TI)

The chemical substance name "4-(3,5-bis(2-hydroxyphenyl)-(1,2,4)-triazol-1-yl) benzoic acid" was searched by splitting it up in searchable terms (2-hydroxyphenyl, triazol-1-yl, benzoic acid) and combining those by AND (lines #5 - #8)

searched from 1991 to week 3, June 2009

Date searched: 22 June 2009

Web of Science and BIOSIS Previews (ISI Web of Knowledge) (via Thomson Reuters)

#1	deferasirox* (Topic)
#2	(ICL670* or "ICL 670*") (Topic)
#3	(CGP72670* or "CGP 72670*") (Topic)
#4	exjade* (Topic)
#5	2-hydroxyphenyl (Topic)

(Continued)

#6	triazol-1-yl (Topic)
#7	"benzoic acid" (Topic)
#8	#5 and #6 and #7
#9	#1 or #2 or #3 or #4 or #8
Notes The chemical substance name "4-(3,5-bis(2-hydroxyphenyl)-(1,2,4)-triazol-1-yl) benzoic acid" was searched by splitting it up in searchable terms (2-hydroxyphenyl, triazol-1-yl, benzoic acid) and combining those by AND (lines #5 - #8). searched from 1945/1969 to week 3, June 2009 Date searched: 22 June 2009	

Derwent Drug File and Xtozline (via DIMDI)

#1	deferasirox* (text field)
#2	ICL*670* (text field)
#3	CGP*72670* (text field)
#4	exjade* (text field)
#5	2-hydroxyphenyl (text field)
#6	triazol-1-yl (text field)
#7	"benzoic acid" (text field)
#8	#5 and #6 and #7
#9	#1 or #2 or #3 or #4 or #8
Notes The chemical substance name "4-(3,5-bis(2-hydroxyphenyl)-(1,2,4)-triazol-1-yl) benzoic acid" was searched by splitting it up in searchable terms (2-hydroxyphenyl, triazol-1-yl, benzoic acid) and combining those by AND (lines #5 - #8). searched from 1983/1965 to week 3, June 2009 Date searched: 22 June 2009	

Current Controlled Trials Register (www.controlled-trials.com)

#1	deferasirox OR ICL670 OR ICL 670 OR exjade
Notes	

(Continued)

Date searched: 06 August 2009

ClinicalTrials.gov (www.clinicaltrials.gov)

#1 deferasirox OR ICL670 OR ICL 670 OR exjade

Notes

Date searched: 06 August 2009

ICTRP (www.who.int/ict rp/en/)

#1 deferasirox OR ICL670 OR ICL 670 OR exjade

Notes

Date searched: 06 August 2009

WHAT'S NEW

Date	Event	Description
29 June 2017	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 8, 2010

Date	Event	Description
6 May 2014	New citation required but conclusions have not changed	Data from one new trial have been included in the review (Vichinsky 2011). However, the conclusions of the review have not changed.
6 May 2014	New search has been performed	Additional literature searches were updated. One additional new study was included (Vichinsky 2011).
22 May 2012	Amended	Contact details updated.
20 September 2010	Amended	Contact details updated.
13 July 2007	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Joerg Meerpohl: Conception, design and coordination of the review. Data collection and data management as well as analysis and interpretation of the data. Writing of the review and approval of the final version.

Lisa Schell: Data collection and data management. Involvement in writing the review. Verification of data entries for discrepancies.

Gerta Ruecker: Statistical advice and methodological support. General advice on the review and approval of the final version.

Edith Motschall: Advice on the initial search strategy and literature searches for the current version of this review .

Nigel Fleeman: Co-author of the HTA report by McLeod ([McLeod 2009](#)). General advice on the review and approval of the final version.

Charlotte Niemeyer: Interpretation of the data, clinical expertise, providing general advice on the review and approval of the final version.

Dirk Bassler: Data collection and data management. Analysis and interpretation of data. Involvement in writing the review and approval of the final version.

DECLARATIONS OF INTEREST

Joerg Meerpohl enrolled two adolescents with thalassaemia and one with Diamond-Blackfan anaemia in a post marketing surveillance study on deferasirox and participated once in a Novartis advisory board meeting on paediatric iron overload. None declared for other authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia, Sickle Cell [blood] [*therapy]; Benzoates [adverse effects] [*therapeutic use]; Chelation Therapy [adverse effects] [*methods]; Deferasirox; Deferoxamine [adverse effects] [therapeutic use]; Erythrocyte Transfusion [adverse effects]; Ferritins [blood]; Iron Chelating Agents [adverse effects] [*therapeutic use]; Iron Overload [*drug therapy] [etiology]; Randomized Controlled Trials as Topic; Triazoles [adverse effects] [*therapeutic use]

MeSH check words

Humans