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Deferasirox for managing iron overload in people with myelodysplastic syndrome (Review)

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[Intervention Review]

Deferasirox for managing iron overload in people with myelodysplastic syndrome

Joerg J Meerpohl[1], Lisa K Schell[1], Gerta Rücker[2], Nigel Fleeman[3], Edith Motschall[2], Charlotte M Niemeyer[4], Dirk Bassler[5]

[1]German Cochrane Centre, Medical Center - University of Freiburg, Freiburg, Germany. [2]Center for Medical Biometry and Medical Informatics, Medical Center - University of Freiburg, Freiburg, Germany. [3]Liverpool Reviews & Implementation Group, University of Liverpool, Liverpool, UK. [4]Pediatric Hematology & Oncology, Center for Pediatrics & Adolescent Medicine, University Medical Center Freiburg, Freiburg, Germany. [5]Department of Neonatology, University Hospital Zurich, Zurich, Switzerland

Contact: Joerg J Meerpohl, German Cochrane Centre, Medical Center - University of Freiburg, Berliner Allee 29, Freiburg, 79110, Germany. meerpohl@cochrane.de, joerg.meerpohl@uniklinik-freiburg.de.

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ABSTRACT

Background

The myelodysplastic syndrome (MDS) comprises a diverse group of haematopoietic stem cell disorders. Due to symptomatic anaemia, most people with MDS require supportive therapy including repeated red blood cell (RBC) transfusions. In combination with increased iron absorption, this contributes to the accumulation of iron resulting in secondary iron overload and the risk of organ dysfunction and reduced life expectancy. Since the human body has no natural means of removing excess iron, iron chelation therapy, i.e. the pharmacological treatment of iron overload, is usually recommended. However, it is unclear whether or not the newer oral chelator deferasirox leads to relevant benefit.

Objectives

To evaluate the effectiveness and safety of oral deferasirox for managing iron overload in people with myelodysplastic syndrome (MDS).

Search methods

We searched the following databases up to 03 April 2014: MEDLINE, EMBASE, *The Cochrane Library*, Biosis Previews, Web of Science, Derwent Drug File and four trial registries: Current Controlled Trials (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), ICTRP (www.who.int./ictrp/en/), and German Clinical Trial Register (www.drks.de).

Selection criteria

Randomised controlled trials (RCTs) comparing deferasirox with no therapy, placebo or with another iron-chelating treatment schedule.

Data collection and analysis

We did not identify any trials eligible for inclusion in this review.

Main results

No trials met our inclusion criteria. However, we identified three ongoing and one completed trial (published as an abstract only and in insufficient detail to permit us to decide on inclusion) comparing deferasirox with deferoxamine, placebo or no treatment.

Authors' conclusions

We planned to report evidence from RCTs that evaluated the effectiveness of deferasirox compared to either placebo, no treatment or other chelating regimens, such as deferoxamine, in people with MDS. However, we did not identify any completed RCTs addressing this question.

We found three ongoing and one completed RCT (published as an abstract only and in insufficient detail) comparing deferasirox with deferoxamine, placebo or no treatment and data will hopefully be available soon. These results will be important to inform physicians and patients on the advantages and disadvantages of this treatment option.

PLAIN LANGUAGE SUMMARY

Deferasirox for managing iron overload in people with myelodysplastic syndrome

Review question

We aimed to review the evidence about the effects of deferasirox (an oral therapeutic option) on reducing iron overload in people with myelodysplastic syndrome (MDS), which is a diverse group of haematopoietic stem cell disorders.

Background

Repeated red blood cell transfusions can lead to clinically relevant secondary (i.e. due to the transfusions) iron overload in some people with MDS, particularly of lower risk groups over the course of their disease. Since the human body has no natural means of removing excess iron, drugs to remove the excess iron (iron chelation therapy) might be indicated to prevent organ complications. Since the newer oral iron chelator deferasirox has become available, iron chelation therapy is offered more widely to people with MDS.

We wanted to assess whether administering deferasirox is beneficial in people with MDS.

Key results

We searched the available literature up to 03 April 2014. We could not include any data in this review that answered our question. However, we found three ongoing trials and one completed trial investigating deferasirox in people with MDS of lower risk groups (low and intermediate-1 risk MDS). As the completed trial has only been reported in insufficient detail (in abstract format), we were unable to definitively decide on inclusion of this study or draw any conclusions from this. Once available, these results will be important to inform physicians and patients on the comparative advantages and disadvantages of this treatment option.

BACKGROUND

Description of the condition

The myelodysplastic syndrome (MDS) comprises a diverse group of haematopoietic stem cell disorders which are usually classified according to the World Health Organization (WHO) MDS classification (Harris 1999; Vardiman 2002). They are characterised by abnormal differentiation and maturation of blood cells, bone marrow failure and a genetic instability with an enhanced risk of transformation to leukaemia. The annual incidence reported in the literature is between 2.1 to 12.6 cases per 100,000 people per year (Aul 2001). Men aged over 70 years are mainly affected, with incidence rates reaching 50 cases per 100,000 people per year (Aul 2001).

People with MDS can be subdivided in prognostic groups according to the International Prognostic Scoring System (IPSS) taking into account bone marrow blast percentage, cytogenetic profile and the number of cytopenias (Greenberg 1997). For higher risk groups, drug treatment (e.g. with azacitidine), intensive chemotherapy or even haematopoetic stem cell transplantation (depending on disease- and patient-related factors) is usually required. Recently, a new WHO classification-based prognostic scoring system (WPSS) has been proposed (Malcovati 2007), classifying patients into five risk groups according to WHO subgroups, karyotype abnormalities according to IPSS and transfusion requirements.

Mainly for the risk groups designated low and intermediate-1 (according to IPSS) only supportive therapy including red blood cell (RBC) transfusions for symptomatic anaemia might be indicated (NCCN Myelodysplastic Panel Members 2010). Regular RBC transfusions in combination with prolonged dyserythropoiesis and increased iron absorption contribute to the accumulation of iron resulting in secondary iron overload. This can ultimately lead to organ dysfunction affecting the liver, endocrine glands and the heart, resulting in reduced life expectancy (Malcovati 2005; Takatoku 2007). Since the human body has no natural means of getting rid of excess iron, iron chelation therapy, i.e. pharmacological treatment of iron overload, is usually recommended (List 2006; Valent 2008).

Description of the intervention

Deferoxamine (DFO, Desferal®), reviewed in detail in a Cochrane Review (Fisher 2013), has been the treatment of choice for iron overload for the last 40 years. Due to its long standing availability it is the only chelating agent for which profound effects on the long-term survival of a large cohort of patients with thalassaemia have been shown (Zurlo 1989; Brittenham 1994; Gabutti 1996; Borgna-Pignatti 2004). To be clinically effective DFO has to be administered as a subcutaneous infusion over eight 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). However, the arduous schedule of overnight subcutaneous infusions often leads to reduced compliance (Olivieri 1997; Cappellini 2005). Another problem concerns the toxicity of DFO, particularly at higher doses. Toxicities beside local skin reactions also 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.

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 (Kontoghiorghes 1987a; Kontoghiorghes 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), but the hypothesis of direct liver toxicity of deferiprone could not be confirmed (Wanless 2002; Wu 2006). In the meantime several studies have shown 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 remained limited due to its range of adverse effects (Hoffbrand 2003). These include gastrointestinal disturbances, arthropathy, neutropenia and agranulocytosis (Hoffbrand 1989). Recently, studies on combination therapy of deferoxamine and deferiprone have been performed (Kattamis 2003; Origa 2005; Farmaki 2006; Galanello 2006; Tanner 2007; Kolnagou 2008). A Cochrane Review on the effectiveness of deferiprone in people with thalassaemia has recently been published (Roberts 2007).

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. The US Food and Drug Administration (FDA) (Food and Drug Administration (FDA) 2010) and the European Medicines Agency (EMA) (European Medicines Agency 2010) have approved it for the treatment of secondary iron overload. It is rapidly absorbed after administration and has a bioavailability of about 70%. Safety and tolerability was shown in a randomised dose escalation trial in 24 people with β-thalassaemia (Nisbet-Brown 2003). The elimination half-life of eight 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 the phase III study in people with thalassemia by Cappellini 2006 (n= 584 patients) and 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 have been 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 (DFO), hearing loss and ocular disturbances including cataracts and retinal disorders have been reported with a lower incidence (< 1%).

Why it is important to do this review

Deferoxamine necessitates serious commitment on the user's side and deferiprone is only approved as second line therapy in some countries due to its adverse effects. Thus, much hope is being placed in the new oral chelator deferasirox, which apparently offers a promising line of treatment due to its iron chelation properties and safety and tolerability profile. Therefore, a systematic review of

the effectiveness and safety of deferasirox according to Cochrane standards is urgently needed.

OBJECTIVES

To evaluate the effectiveness and safety of oral deferasirox for managing iron overload in people with MDS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), of parallel group or cross-over design, published or unpublished. To be eligible, either 80% of trial participants should have had MDS or data should have been available for the subgroup of participants with MDS.

Types of participants

People with diagnosis of MDS regardless of age, type of MDS and setting. To be eligible people were required to receive either more than two RBC concentrates per month or to have elevated ferritin levels of > 1000 ng/mL on at least two occasions.

Types of interventions

For oral deferasirox (all schedules and doses), we considered the following comparisons:

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

These comparisons constituted two separate groups and we planned to analyse them separately.

Types of outcome measures

We did not exclude studies on the basis of reported outcomes.

Primary outcomes

1. Overall survival (measured at any point in time).

Secondary outcomes

1. Reduced end-organ damage due to iron deposition:
   a. cardiac failure (necessitating medical treatment)
   b. endocrine disease (necessitating substitution therapy of hormones 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/day).
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 / agranulocytosis (ANC less than 1000/µL)
   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.

We planned to present data for the following time points: six months, 12 months, 24 months, 36 months, etc. Otherwise, we planned to present data for the latest time points available.

We did not anticipate that there would be any additional outcome measures. However, we planned to collect data from outcomes not defined a priori but which will arise from updated versions from the review, if we considered the outcome of clinical relevance.

Search methods for identification of studies

We did not apply any language restrictions.

Electronic searches

For this update, we searched the following databases for relevant trials:

Via Wiley Interscience: *The Cochrane Library* (Issue 4, 2014 for Cochrane Database of Systematic Reviews, Issue 3, 2014 for Cochrane Central Register of Controlled Trials, Issue 1, 2014 for Other Reviews (DARE), Technology Assessments and Economic Evaluations, Issue 3, 2012 for Methods Studies); via OvidSP: MEDLINE (1946 to March Week 4 2014), MEDLINE in Process and Other Non-Indexed Citations (to April 2, 2014); via PubMed: MEDLINE subset "supplied by publisher" (to April 2, 2014); via DIMDI: EMBASE and EMBASE Alert (2010 to April 1, 2014); via Thomson Reuters: Web of Science (2010 to April 1, 2014), Biosis Previews (2010 to April 1, 2014); via DIMDI: Derwent Drug File (2010 to April 1, 2014). We performed the searches on 2nd and 3rd April 2014. We used an RCT filter MEDLINE, EMBASE, Biosis Previews, ISI Web of Science and Derwent Drug File searches; also, we limited the search to reports published between 2010 and 2014. For details of the search strategies see Appendix 1.

Since research into deferasirox treatment is ongoing, we searched the following four trial registries up to 16 April 2014 for all years available in all possible fields using the basic search function (using separately the following keyword terms: "deferasirox", "ICL670", "ICL 670" and "exjade"):

1. Current Controlled Trials: www.controlled-trials.com (all available registers were searched)
2. ClinicalTrials.gov: www.clinicaltrials.gov
3. ICTRP: www.who.int/ictrp/en/
4. German Clinical Trial Register: www.drks.de

For the previous version of this review, we searched several databases and ongoing trials registers from 24 June 2010 up to 01 July 2010. Please see Appendix 2 for full details.

Searching other resources

In addition we searched the abstract books of two major haematology conferences from 2000 to 2013: the European Haematology Association conference and the American Society of Hematology conference.

We intended to screen reference lists of all identified papers to identify other potentially relevant citations.

We contacted selected experts in the field and the manufacturer of deferasirox (Novartis) to request information on unpublished studies that involved deferasirox.

Data collection and analysis

Selection of studies

One review author (JM and LS (update search)) screened all titles and abstracts of papers identified by the trial search strategy for relevance. We only excluded citations that were clearly irrelevant at this stage. We obtained full text copies of all potentially relevant papers and two review authors (JM, DB for previous version of review; LS, JM for current update) independently screened the full papers, identified relevant studies and assessed eligibility of studies for inclusion. We resolved any disagreement on eligibility through discussion and consensus or if necessary through referral to a third party (GA or CN). We excluded all irrelevant records and recorded details of the studies and the reasons for their exclusion. We planned to categorise studies that lacked important information (including foreign language studies awaiting translation) and report them as studies pending inclusion/exclusion decision for future updates.

Data extraction and management

This was not applicable as no trials met our inclusion criteria. For details on planned methods please see section "Differences between protocol and review".

Assessment of risk of bias in included studies

This was not applicable as no trials met our inclusion criteria.

Measures of treatment effect

This was not applicable as no trials met our inclusion criteria.

Unit of analysis issues

This was not applicable as no trials met our inclusion criteria.

Dealing with missing data

We contacted the original investigators of Castellano 2011 to request more detailed data regarding patient eligibility criteria. However, we were informed that data are not to be shared prior to publication.

Assessment of heterogeneity

This was not applicable as no trials met our inclusion criteria.

Assessment of reporting biases

We tried to minimise the likelihood of publication bias by using a comprehensive search strategy including the search of abstracts and contacting the manufacturer of deferasirox. However, we did not identify any trials for inclusion.

Data synthesis

This was not applicable as no trials met our inclusion criteria.

Subgroup analysis and investigation of heterogeneity

This was not applicable as no trials met our inclusion criteria.

Sensitivity analysis

This was not applicable as no trials met our inclusion criteria.

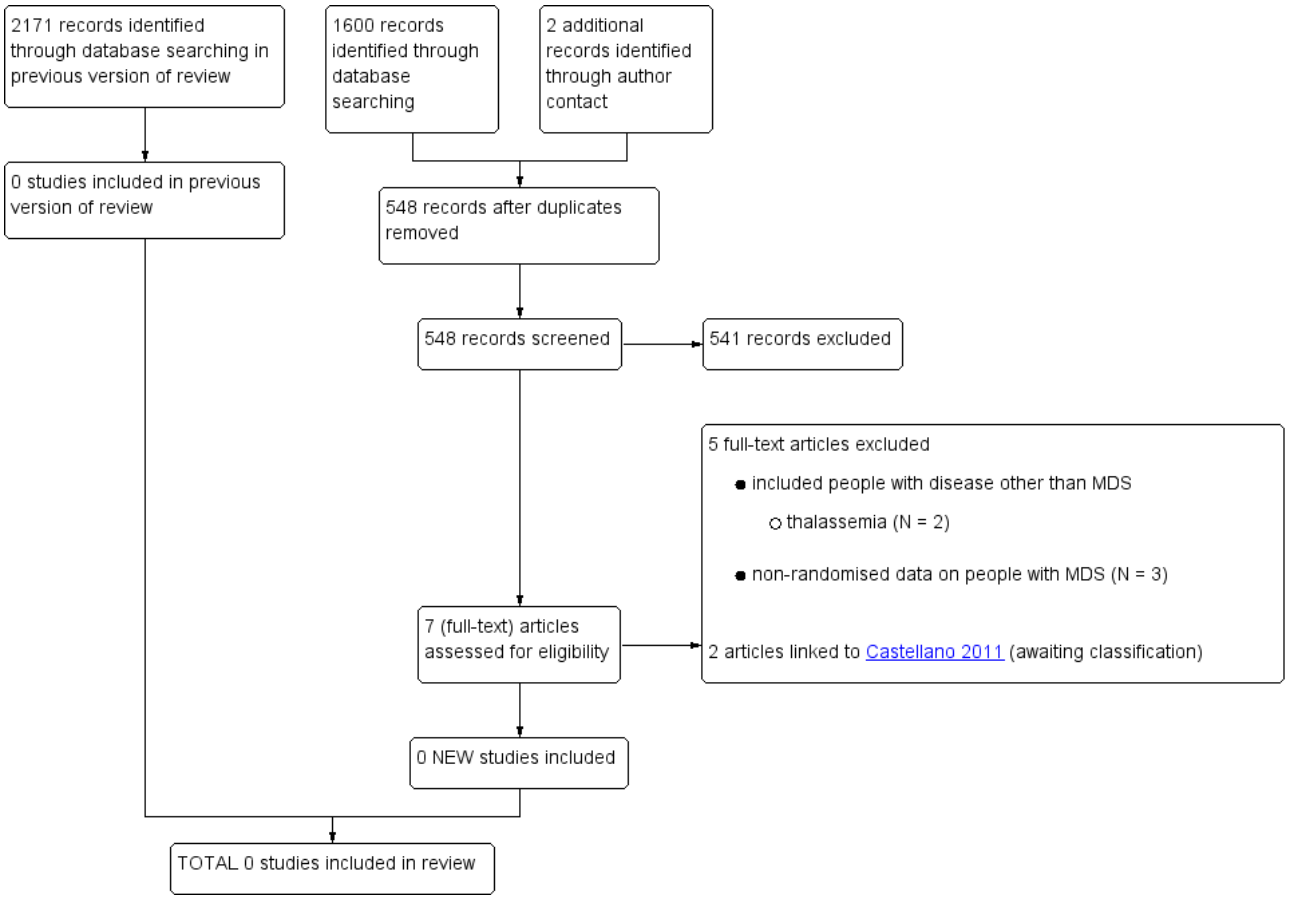
RESULTS

Description of studies

Results of the search

Based on the searches for this review update (run in April 2014), we identified 546 unique citations (Figure 1). We included two additional abstracts after we contacted the authors of Castellano 2011. After we screened titles and abstracts of these citations we identified seven as potentially eligible. We excluded five citations after full text screening for the following reasons:

Figure 1. Study flow diagram (update search performed in April 2014),



- included people with disease other than MDS
  - thalassaemia (N = 2)
- non-randomised data on people with MDS (N = 3) (see Characteristics of excluded studies).

We identified 110 unique references to trials after searching the four trial registers (run on 02/03 April 2014). We found two ongoing (Novartis 2013; NCT02038816) and one completed RCTs (published as abstract only) (Castellano 2011) by this search, in addition to the ongoing trial already identified in the previous version of this review (TELESTO 2009). We categorised the Castellano 2011 trial as awaiting classification (since the two published abstracts do not provide enough detail to decide on definitive inclusion). A fifth study, which we identified through searching the registers (Pennell 2014, CORDELIA), was planned to also include people with MDS. However, as reported in Pennell 2014, CORDELIA, none of the four screened MDS patients fulfilled the other inclusion criteria of the trial.

Previous search

For the previous version of this review, we performed the literature search in August 2008, June 2009 and lastly between 24 and 30 June 2010. Altogether, we identified 2171 citations, including 1191 duplicates. After we screened titles and abstracts of the 980 unique citations, we excluded 686 citations. In total, we screened 294 full texts but we no RCTs met our inclusion criteria. Our reasons for exclusion were as follows:

- included people with disease other than MDS
  - thalassaemia (N = 140)
  - sickle cell disease (N = 38)
  - other condition (N = 11)
- review article or editorial/comment (N = 46)
- intervention other than deferasirox (N = 1)
- cost-effectiveness analysis (N = 5)
- non-randomised data on people with MDS (N = 52) (see Characteristics of excluded studies)
- ongoing study (N = 1) (see Characteristics of ongoing studies).

After we searched the three trial registers for the previous version of this review (last run on 30 June 2010) we identified 49 unique references to trials. However, we identified only one ongoing RCT including MDS patients (TELESTO 2009).

Included studies

In this version of the review, we could not include any data from completed trials.

Excluded studies

We excluded 25 studies, most of which were non-randomised studies. For details please see Characteristics of excluded studies.

Risk of bias in included studies

We did not find any trials that were eligible for inclusion.

Effects of interventions

We did not find any eligible trials for inclusion in this review.

DISCUSSION

Summary of main results

Through our comprehensive searches, we identified three ongoing and one completed trial. However, no data from any of these RCTs are currently available for inclusion in this review.

Overall completeness and applicability of evidence

This was not applicable as we did not include any trials in this review.

Quality of the evidence

This was not applicable.

Potential biases in the review process

We conducted a very comprehensive search including searches of several study registers. This led to the identification of three ongoing and one completed RCTs. However, despite correspondence with trial authors, we were unable to decide on definite inclusion of the completed RCTs, nor include any data in this current review version.

Agreements and disagreements with other studies or reviews

People with MDS potentially constitute the largest group of patients at risk of iron overload. However, the impact of iron chelation therapy in people with MDS has not been investigated as extensively as in other transfusion-dependent anaemias such as thalassaemia (Roberts 2007; Cianciulli 2008; Porter 2009; Fisher 2013). In theory, the biological rationale behind treating iron overload in patients with other anaemias should also apply to people with MDS. Thus, clinical practice guidelines do suggest consideration of iron chelation therapy for certain subgroups of MDS patients (Bennett 2008; Gattermann 2008; Greenberg 2011; Malcovati 2013). With the emergence of deferasirox, which avoids the cumbersome application mode of deferoxamine, iron chelation therapy has been offered more widely to MDS patients. However, data from thalassaemia patients is not likely to be directly transferred to people with MDS considering that people with MDS are older and suffer from a different disease entity. For example, people with MDS are potentially more prone to iron-related organ dysfunction and certain adverse effects. Furthermore, reduced life-expectancy in people with MDS compared to people with other anaemias could render the beneficial effects of iron chelation therapy clinically less relevant since such patients may not survive long enough to accumulate iron to toxic levels.

The negative impacts of iron overload and the benefits of iron chelation therapy for people with MDS are nevertheless suggested by recent retrospective survey data (Takatoku 2007) and observational studies (Rose 2007; Leitch 2008), although not all studies could confirm beneficial effects of iron chelation therapy (Chee 2008). More specifically, several retrospective analyses and observational studies suggest a benefit with regard to certain outcomes in patients with MDS from deferasirox (see the Excluded studies section; also Porter 2004; List 2006, US3 study; Gattermann 2007, EPIC; List 2012; Cermak 2013). Additionally, several narrative reviews of deferasirox have been published over recent years (Shah 2012; Adams 2013; Breccia 2013). However, the impact of iron chelation therapy (either with deferasirox or any other iron chelator) on long-term outcomes or patient-relevant outcomes such as organ dysfunction or mortality has not been evaluated in rigorous RCTs (Leitch 2009b). Indeed, we found no RCTs published to date that studied the impact of iron chelation with deferasirox for patients with MDS.

Since iron chelation therapy has such a positive impact on survival in thalassaemia patients and is increasingly being offered to people with MDS, further evaluation of the effects of iron overload and chelation therapy in patients with MDS is urgently required in order for clinical practice guidelines based on high quality evidence to be formulated. In particular, the profile of adverse effects urgently needs to be established to allow adequate balancing of the benefits and potential harms of iron chelation therapy for people with MDS. Adverse events may differ compared to people with thalassaemia; an RCT conducted with acute myeloid leukaemia patients points to poor tolerability and excess gastrointestinal and infectious toxicity (Kennedy 2013). Furthermore, the generation of further data supporting the application of this intervention instead of no intervention or other iron chelating regimens seems to be even more important considering the costs implied by a continuous therapy with deferasirox (Delea 2005; Karnon 2007a; Karnon 2007b; Bozkaya 2008).

To address some of the uncertainties in the evidence base, three prospective RCTs are currently enrolling patients (TELESTO 2009; Novartis 2013; NCT02038816), while one has already completed patient recruitment and is awaiting publication (Castellano 2011). Castellano 2011 has already presented findings as an abstract at two conferences. Castellano et al. reported statistically significant decreases in serum ferritin for both groups over time, but comparative analyses between groups are not provided. Also, these abstracts did not provide sufficient information on patient eligibility criteria in order to be included in the current version of this review.

These trials should improve the evidence base and possibly lead to clearer indications being established for iron chelation therapy in MDS patients. If the effectiveness of deferasirox in MDS is confirmed in the future, further comparisons with other iron chelation regimens, such as deferiprone, will be worthwhile since the profile of adverse effects, in particular, varies between different chelating agents.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the limited evidence from retrospective analyses and observational studies, some current clinical practice guidelines do recommend consideration of iron chelation therapy for low risk MDS. However, these recommendations can not be supported by high quality data from RCTs. Therefore, data from the ongoing or completed but not fully published trial are urgently needed to inform doctors whether widespread use of deferasirox outside clinical studies is warranted. The decision to use deferasirox for individual patients with MDS, while based on personal preferences, should be informed by the potential benefits and harms and the resource use incurred.

Implications for research

RCTs investigating the effectiveness of iron chelation therapy, in general and of deferasirox in particular, in people with MDS are urgently needed. Future RCTs should include (1) patient-relevant outcomes and (2) investigate also long-term benefits and adverse effects. Furthermore, the value of iron chelation therapy should be differentially investigated (3) for the various subtypes of MDS. If the value of iron chelation therapy is unambiguously established, (4) comparative trials defining the advantages and disadvantages of the various iron chelating regimens should follow.

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Angelucci 2012	Study not randomised, not controlled. Prospective, 1-year, multi-centre, single-arm trial including 152 lower risk and transfusion dependent MDS patients.
Brosnahan 2008	Case report of MDS patient with acute interstitial nephritis.
Cermak 2013	Study not randomised. Comparative study on 48 patients receiving deferiprone (January 2006 to July 2007) and 65 patients receiving deferasirox (January 2008 to August 2010).
Di Tucci 2007	Case report of patient with primary myelofibrosis (PMF).
Fox 2009	Study not randomised. Matched-pair analysis on 186 MDS patients.
García-Delgado 2009	Study not randomised, not controlled. Single-arm study evaluating the effect of deferasirox on oxidative stress and vascular dysfunction in MDS patients with iron overload (4 people with MDS).

Study	Reason for exclusion
Gattermann 2007, EPIC	Study not randomised, not controlled. Prospective, 1-year, multi-centre, single-arm, open-label phase IIIB/IV trial (1744 people with various transfusion-dependent anaemias including 341 people with MDS and 116 with AA).
Gattermann 2009	Study not randomised, not controlled. Prospective, multi-centre, post-marketing, single-arm study on 123 chelation-naive (Extend) and 44 pre-chelated (Exjange) MDS patients.
Ghoti 2009	Study not randomised, not controlled. Single-arm study evaluating decrease in intra- and extra-cellular free iron species and oxidative stress parameters during treatment with deferasirox in iron-loaded patients with MDS.
Greenberg 2006, US2 study	Study not randomised, not controlled. Prospective, phase II, multi-centre, single-arm study on 30 people with MDS.
Leitch 2007	Study not randomised, not controlled. Retrospective analysis of 41 people with PMF.
Leitch 2009	Case report.
List 2006, US3 study	Study not randomised, not controlled. Prospective, phase II, open-label, single-arm study on 176 people with MDS.
Messa 2008	Retrospective case series of 7 people with MDS and 3 people with PMF.
Metzgeroth 2009	Study not randomised, not controlled. Prospective, phase II, open-label, single-arm, single-centre study of 12 people with MDS.
Min 2008	Study not randomised, not controlled. Prospective, multi-centre, open-label, single-arm study of 29 people with MDS and 50 people with AA.
Miyazawa 2006	Study not randomised, not controlled. Prospective, phase I, open-label, multi-centre, dose-escalation study on 26 people with MDS or AA.
Nolte 2013	Study not randomised, not controlled. Open label, 1-year, single-arm, multi-centre trial on 50 patients with low and intermediate-1 risk MDS and transfusional iron overload.
Peng 2013	Study on patients with thalassemia (Chinese full text not available; assessment based on English abstract and references).
Pennell 2014, CORDELIA	Study planned to include MDS patients; however, of the four screened patients with MDS, none fulfilled the inclusion criteria.
Porter 2004	Study not randomised, not controlled. Prospective, phase II, single-arm study of 184 people with transfusion-dependent anaemia including 47 people with MDS.

Study	Reason for exclusion
Rachmilewitz 2008	Study not randomised, not controlled. Prospective, single-arm study of 15 people with MDS.
Remacha 2010	Study not randomised, not controlled. Cross-sectional study on 549 MDS patients.
Rose 2007	Study not randomised, not controlled. Survey of 170 people with MDS from 18 French GFM centres.
Wimazal 2009	Case series of 14 MDS patients treated with deferasirox (500 to 1500 mg/day) for up to 24 months.

Only reports on observational studies or case series are mentioned in this table.
AA - aplastic anaemia;
GFM - Groupe Francophone des Myelodysplasies;
MDS - myelodysplastic syndrome;
PMF - primary myelofibrosis.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Castellano 2011

Methods	A single-centre, prospective, randomised, controlled phase III clinical study to evaluate the efficacy and safety of deferasirox and desferoxamine in patients with iron overload
Participants	Inclusion criteria: • Age ≥ 18 years • Diagnosis of MDS or having received a hematopoietic stem cell transplantation in the last 6 months or Gaucher's disease diagnosis • Serum ferritin concentration > 500 mcg/L • To not have received previous iron chelation therapy • No severe renal failure (creatinine clearance > 30 mL/min/1.73 m^2) • No severe liver failure (liver enzymes under twice the upper normal limit) • Life expectancy of at least 6 months Exclusion criteria: • To not accept to use reliable contraception throughout the study and during three months after cessation of treatment • Pregnancy or breast-feeding • History of cataracts or increasing risk of cataract formation • Severe renal failure (creatinine clearance < 30 mL/min/1.73 m^2) • Active chronic disease such as human immunodeficiency virus (HIV) or hepatitis B or C • To have received treatment with iron chelators in the last 6 months • Suspected or known hypersensitivity to the drug under study or any of the excipients • Dependence or current abuse of drugs or alcohol • Treatment with another investigational product in the last 6 months prior to baseline
Interventions	Group A: Deferasirox 20 mg/kg/day Group B: Desferoxamine 30 mg/kg/day
Outcomes	Primary outcome measures:

Castellano 2011 *(Continued)*

	• Treatment efficacy by measuring serum ferritin Secondary outcome measures: • Identify whether blood biomarkers of macrophage activation (chitotriosidase, CCL-18) are higher in patients with iron overload than in the population with normal serum ferritin levels stratified by age and sex and if they can be used as markers of response to chelation therapy • To study if the biomarkers concentration correlates with the serum ferritin level, liver MRI, cardiac function assessed by ultrasound and its own changes after 4-month treatment with iron chelators • To assess the quality of life of patients undergoing both these treatments
Notes	• Planned sample size: 32 • Duration of study: 4 months • Date of first enrolment: 01/03/2011 • Recruitment status: completed • EudraCT ID: EUCTR2009-017799-26-ES • ISRCTN ID: ISRCTN52984371 • Secondary ID: TRA-158 (EC09/080) • Registry entry last refreshed on 07/04/2014 **Contact information:** Pilar Giraldo Castellano Servicio de Hematología Hospital Universitario Miguel Servet Paseo Isabel La Católica 1-3 50009 Zaragoza Spain Telephone: +34 670285339 Email: giraldo.p@gmail.com

We have given the Information in tables according to entries in the ISRCTN registry and www.clinicaltrials.gov. We reviewed the registry entries on 16 April 2014.

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

NCT02038816

Trial name or title	Azacitidine Plus Deferasirox (ICL670) in Higher Risk MDS
Methods	An open-label, phase II, randomised efficacy study in patients with higher risk MDS
Participants	Inclusion criteria: • Adults > 18 years of age • WHO defined MDS with Higher risk MDS (IPSS int-2/high) • Azacitidine X at least 6 cycles with no hematologic improvement/no disease progression as per IWG 2006 criteria • Ferritin > 500 µg/L • If transfusion independent, must have Hb < 110 g/L or neutrophils < 1000/mL or platelets < 100,000/mL • ECOG ≤ 2 • CrCl > 40 mL/min Exclusion criteria: • Increased ALT (> 300 U/L) • Uncontrolled infection • HIV+

NCT02038816 *(Continued)*

	• Pregnant or breast-feeding • Previous and concurrent iron chelation • Concurrent use of hematopoietic growth factors including erythropoietin, darbepoietin and granulocyte colony stimulating factor • Concurrent use of other disease modifying agents including cytotoxic chemotherapy, histone deacetylase inhibitors, other hypomethylating agents or lenalidomide
Interventions	Experimental: Deferasirox plus azacitidine Active comparator: Azacitidine
Outcomes	Primary outcome measures: • Difference in proportion of patients with hematologic improvement as defined by the IWG criteria 30 with the addition of deferasirox to azacitidine compared with azacitidine alone in higher risk non-responding MDS patients after 6 cycles of azacitidine Secondary outcome measures: • Tolerability (defined by the percentage of patients able to remain on deferasirox for 6 cycles concurrent with azacitidine) and safety (type, using CTCAE version 4.0, frequency, severity and relationship of adverse events to study therapy • Percentage and absolute change in serum ferritin and labile plasma iron (LPI) between baseline and end of study • Percentage change in CD34 cell intracellular reactive oxygen species (ROS) from baseline to end of study • Percentage change in erythroid colony forming units (BFU-E and CFU-E) from baseline to end of study • Percentage change in markers of DNA damage (lipid peroxidation, GSH content and gH2AX expression), and activity of NFkappaB and Akt signaling pathways between baseline and end of study
Starting date	Study start date: March 2014; Estimated primary completion date: October 2016 (Final data collection date for primary measure)
Contact information	Odette Cancer Centre, Sunnybrook Health Sciences Centre Toronto, Ontario, Canada, M4N 3M5 Contact: Claudia Li (claudia.li@sunnybrook.ca)
Notes	• Planned sample size: 26 • ClinicalTrials.gov Identifier: NCT02038816 • Study ID Number: CICL670ACA02T • Registry entry last updated on 15/01/2014

Novartis 2013

Trial name or title	Combination Study of Deferasirox and Erythropoietin in Patients With Low- and Int-1-risk Myelodysplastic Syndrome
Methods	An open-label, phase II, randomised, pilot study to assess the effect in term of erythroid improvement of deferasirox combined with erythropoietin compared to erythropoietin alone in patients with low- and int-1-risk MDS
Participants	Inclusion criteria:

Novartis 2013 *(Continued)*

- Patients with low- and Int-1-risk MDS
- 18 years and older
- Documented diagnosis of the following:
  - MDS lasting ≥ 3 months and < 2 years
  - Disease must not be secondary to treatment with radiotherapy, chemotherapy, or immunotherapy for malignant or autoimmune diseases
- A hemoglobin < 10 g/dL and > 6 g/dL (no RBC transfusions are allowed during study)
- History of transfusions < 10 RBC units
- 300 ng/mL < serum ferritin < 1000 ng/mL
- Endogenous erythropoietin levels < 500 units/L

Exclusion criteria:

- Patients with MDS with isolated del(5q)
- Patients who had received prior EPO treatment or other recombinant growth factors regardless of the outcome (patients who had received prior EPO treatment or other recombinant growth factors for less than 4 weeks and not within 3 months before screening without a documented response are allowed)
- Patients receiving steroids or immunosuppressive therapy for the improvement of hematological parameters (prophylactic hydrocortisone to prevent transfusion reaction, steroid for adrenal failure and intermittent dexamethasone as antiemetic are allowed).
- B12 and folate deficient patients (patients could be rescreened after successful therapy of B12 and folate deficiency)
- Uncontrolled seizures or uncontrolled hypertension

Other protocol-defined inclusion/exclusion criteria may apply.

Interventions	Group A: Erythropoietin alpha Group B: Deferasirox + erythropoietin alpha
Outcomes	Primary outcome measure: • Change in hemoglobin levels (time frame: within 12 weeks) Secondary outcome measures: • Change in hemoglobin, platelets and neutrophil levels (time frame: within 24 weeks) • Change in hemoglobin levels (time frame: within 24 weeks) • Time to erythroid response • Time to hematologic improvement • Duration of erythroid response • Number of adverse events (AEs) and serious adverse events (SAEs) • Iron parameters by change in serum ferritin (time frame: baseline, followed by evaluation after 1, 2, 3, 4, 5 and 6 months)
Starting date	Study start date: January 2014 Estimated primary completion date: June 2015 (Final data collection date for primary measure)
Contact information	Novartis Pharmaceuticals
Notes	• Planned sample size: 60 • ClinicalTrials.gov identifier: NCT01868477 • EUCTR identifier: EUCTR2013-000981-12-SE • Novartis Study ID Number: CICL670A2421 • Registry entry last updated on 10 April 2014

TELESTO 2009

Trial name or title	MDS event free survival with iron chelation therapy study (TELESTO)
Methods	A multi-centre, randomised, double-blind, placebo-controlled clinical trial of deferasirox in patients with MDS (low/int-1 risk) and transfusional iron overload
Participants	Inclusion criteria: • Males or females ≥ 18 years of age • MDS low and int-1 risk as determined by IPSS score and confirmed by bone marrow examination within 12 months prior to study entry • Ferritin > 1000 mcg/L at screening • History of 15 to 75 PRBC transfusions • Anticipated to be transfused at least 8 times annually during the study • Patients must weigh between 35kg to 135 kg Exclusion criteria: • More than 6 months of cumulative iron-chelation therapy (such as daily deferasirox (Exjade) or deferiprone or 5x/week deferosamine). Intermittent deferoxamine doses in association with blood transfusions are not exclusionary regardless of duration of such treatment • More than 3 years since patient began receiving regular transfusions (2 units per 8 weeks or 4 units received in a 3 month period) • Creatinine clearance < 40 mL/min • Serum creatinine > 1.5x ULN at screening • Significant proteinuria: urinary protein/creatinine ratio > 0.5 mg/mg in a non first void urine sample • ECOG performance status > 2 • Left ventricular ejection fraction < 55% by ECHO • History of hospitalization for congestive heart failure • Systemic disease that would prevent study treatment (uncontrolled hypertension, cardiovascular renal, hepatic or metabolic disease) • Hepatitis B or C (HBsAg in the absences or HBsAB or HCV Ab positive with HCV RNA positive) • History of HIV positivity (ELISA or Western blot) • Treatment with systemic investigational drug within 4 weeks or topical investigational drug within 7 days of study start • ALT or AST > 3.5 x ULN at screening • Total bilirubin > 1.5 x ULN at screening • Diagnosis of liver cirrhosis • Patient participating in another clinical trial or receiving an investigational drug • History of another malignancy within the past five years, with the exception of basal skin carcinoma or cervical carcinoma in situ or completely resected colonic polyps carcinoma in situ • History of non-compliance with medical regimen, or patients potentially unreliable or not cooperative • Presence of surgical or medical condition which might significantly alter the absorption, distribution , metabolism or excretion of study drug • Pregnant or intending to become pregnant or breast-feeding patents • History of drug or alcohol abuse within the 12 months prior to enrolment. Other protocol-defined inclusion/exclusion criteria may apply.
Interventions	Experimental: Deferasirox Placebo: Placebo

TELESTO 2009 *(Continued)*

Outcomes	Primary outcome measures: • Event-free survival (a composite primary endpoint including death and non-fatal events related to cardiac and liver function) (time frame: 1 year to 5 years) Secondary outcome measures: • Hematologic improvement in terms of erythroid responses during treatment • Overall survival • Proportion of patients with hypothyroidism • Proportion of patients with worsening of glucose metabolism • Disease progression • Time to first occurrence of serum ferritin > 2 times the baseline value • Time to at least a 10% increase from baseline in LVISD • Time to at least a 10% increase from baseline in LVISD • Infections • Proportion of patients with significant renal dysfunction • Proportion of patients with severe neutropenia or thrombocytopenia • Proportion of patients with major gastrointestinal bleeding • Time to study drug discontinuation due to an AE or laboratory abnormality
Starting date	Study start date: March 2010 Estimated primary completion date: February 2018 (final data collection date for primary measure)
Contact information	Novartis Pharmaceuticals
Notes	• Planned sample size: 210 • ClinicalTrials.gov Identifier: NCT00940602 • Study ID Number: CILC670A2302 • Registry entry last updated on 05/02/2014

Information in tables given according to www.clinicaltrials.gov. We searched ClinicalTrials.gov on 16 April 2014.

APPENDICES

Appendix 1. Search strategies April 2014

MEDLINE (OvidSP)	
#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.

(Continued)

#7	benzoic acid.mp.
#8	5 and 6 and 7
#9	1 or 2 or 3 or 4 or 8
#10	(2010* or 2011* or 2012* or 2013* or 2014*).ed,ep,dc. or ("2010" or "2011" or "2012" or "2013" or "2014").yr.
#11	9 and 10
#12	randomized controlled trial.pt.
#13	controlled clinical trial.pt.
#14	randomi#ed.ab.
#15	placebo.ab.
#16	drug therapy.fs.
#17	randomly.ab.
#18	trial.ab.
#19	groups.ab.
#20	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
#21	exp animals/ not humans.sh.
#22	20 not 21
#23	11 and 22

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

MEDLINE Daily Update (OvidSP)

(Continued)

#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.

MEDLINE In-Process & Other Non-Indexed Citations (OvidSP)

#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.

PubMed – subset "supplied by publisher" (www.pubmed.gov)

#1	Search deferasirox*[tw]
#2	Search ICL670*[tw] OR ICL 670*[tw]
#3	Search CGP72670*[tw] OR CGP 72670*[tw]
#4	Search exjade*[tw]

(Continued)

#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

[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

EMBASE and EMBASE Alert (DIMDI www.dimdi.de)

#1	EM05; EA08
#2	FT=DEFERASIROX*
#3	FT=ICL670* OR FT=ICL 670*
#4	FT=CGP72670* OR FT=CGP 72670*
#5	FT=EXJADE*
#6	FT=2-HYDROXYPHENYL
#7	FT=TRIAZOL-1-YL
#8	FT=BENZOIC ACID
#9	6 AND 7 AND 8
#10	2 OR 3 OR 4 OR 5 OR 9
#11	10 AND PY>=2010
#12	(FT=RANDOM* OR FT=PLACEBO*) OR FT=DOUBLE-BLIND*
#13	11 AND 12
#14	13 NOT SU=MEDLINE

Notes

EM05 = EMBASE ab 2005; EA08 = EMBASE Alert

PY = Publication year

SU = subunit

The Cochrane Library **(Wiley: www.thecochranelibrary.com)**

(Continued)

#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 Publication Date from 2010 to 2014 (Word variations have been searched)
Biosis Previews (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	#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 field
- Foreign Title field
- Abstract field
- Major Concepts field
- Concept Code(s) field
- Taxonomic Data table
- Disease Data table
- Chemical Data table

(Continued)

- Gene Name Data table
- Sequence Data table
- Geographic Data table
- Geologic Time Data table
- Methods and Equipment Data table
- Parts & Structure Data table
- Miscellaneous Descriptors field

Indexes = BIOSIS Previews

Timespan = 2010 to 2014

Web of Science via Web of Knowledge (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	#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®

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH

Timespan = 2010 to 2014

Derwent Drug file **(DIMDI** www.dimdi.de**)**	
#1	DD83
#2	DEFERASIROX*
#3	FT=ICL670* OR FT=ICL 670*
#4	FT=CGP72670* OR FT=CGP 72670*
#5	FT=EXJADE*
#6	FT=2-HYDROXYPHENYL

(Continued)

#7	FT=TRIAZOL-1-YL
#8	FT=BENZOIC ACID
#9	6 AND 7 AND 8
#10	2 OR 3 OR 4 OR 5 OR 9
#11	10 AND PY>=2010
#12	((((FT=RANDO* OR FT=PLACEBO) OR FT=TRIAL) OR (CT D "SINGLE-BLIND"* OR UT="SINGLE-BLIND"* OR IT="SINGLE-BLIND"* OR SH="SINGLE-BLIND"*)) OR FT=DOUBLE-BLIND*) OR FT=GROUPS
#13	11 AND 12

Notes

DD83 = Derwent Drug File

PY = Publication year

Appendix 2. Search strategies June 2010

MEDLINE & MEDLINE In-Process (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	and/5-7
#9	or/1-4,8
#10	remove duplicates from 9

Notes

.mp = title, original title, abstract, name of substance word, subject heading word, unique identifier

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).

EMBASE (Ovid)

(Continued)

#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	and/5-7
#9	or/1-4,8
#10	remove duplicates from 9

Notes

.mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

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).

The Cochrane Library **(Wiley Interscience)**

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

Issues searched: Issue 6, 2010 for Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Issue 2, 2010 for Other Reviews (DARE), Methods Studies, Technology Assessments, Economic Evaluations

BIOSIS Previews (Ovid)

(Continued)

#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	and/5-7
#9	or/1-4,8
#10	remove duplicates from 9

Notes

.mp = abstract, biosystematic codes, original language book title (non-english), book title (english), chemicals & biochemicals, concept codes, diseases, geopolitical locations, gene name, major concepts, miscellaneous descriptors, methods & equipment, organisms, parts, structures & systems of organisms, sequence data, super taxa, title, time, taxa 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).

Web of Science (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

Notes

ts = topic

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).

Date searched: 27 June 2010

(Continued)

Derwent Drug File and XTOXLINE (DIMDI)	
#1	deferasirox* (text field)
#2	ICL670* or ICL 670* (text field)
#3	CGP72670* or 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).

Current Controlled Trials	
#1	"deferasirox" OR "ICL670" OR "ICL 670" OR "exjade"

Notes

Date searched: 28 June 2010

ClinicalTrials.gov	
#1	"deferasirox" OR "ICL670" OR "ICL 670" OR "exjade"

Notes

Date searched: 28 June 2010

ICTRP	
#1	"deferasirox" OR "ICL670" OR "ICL 670" OR "exjade"

Notes

Date searched: 28 June 2010

WHAT'S NEW

Date	Event	Description
23 October 2014	New search has been performed	Updated

Date	Event	Description
23 October 2014	New citation required but conclusions have not changed	We performed a search update and identified two new ongoing studies and one completed study (published as an abstract in insufficient detail). In total, we included three ongoing and one completed study identified through searching trial registries. We did not include any new studies in this update.

CONTRIBUTIONS OF AUTHORS

Joerg Meerpohl: conceived, designed and coordinated the review. He performed data collection and data management, as well as analysis and interpretation of the data. He wrote the review and approved the final version.

Lisa Schell: performed data collection and data management (search update). She conducted the literature searches in 2014, was involved with writing the review update and approval of the final version.

Gerta Ruecker: provided statistical advice and methodological support. She gave general advice on the review and approved the final version.

Nigel Fleeman: was co-author of the HTA report by McLeod (McLeod 2009), gave general advice on the review and approved the final version.

Edith Motschall: gave advice on the search strategy and conducted the literature searches in 2010.

Charlotte Niemeyer: interpreted the data, provided clinical expertise and general advice on the review and approved the final version.

Dirk Bassler: performed data collection and data management. He analysed and interpreted the data, was involved with writing the review and approved 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 over five years ago. The other review authors have no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- German Cochrane Centre, Freiburg, Germany.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no deviations from the protocol first published in *The Cochrane Library* (Meerpohl 2008).

Methods not implemented

Since we did not find any trials that met our inclusion criteria, we did not implement the following aspects of the protocol.

Data extraction and management

Aside from details relating to the quality of the included studies, we planned to extract 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 these data is to define unexpected clinical heterogeneity in included studies independently from analysis of results.
2. Results of included studies with respect to each of the main outcomes indicated in the review question. We intended to carefully record reasons why an included study does not contribute data on a particular outcome and to consider the possibility of selective reporting of results on particular outcomes.

We planned to undertake data extraction by authors independently (JM, LS), using a data extraction form developed by the review authors. We planned to resolve disagreements by consensus. Missing data was requested from the original investigators. Either JM or LS were to transcribe data from the data extraction form into Review Manager 2014 and DB would verify all data entry for discrepancies.

Assessment of risk of bias in included studies

We did not perform an assessment of risk of bias because of insufficient data. We planned that JM and LS would assess every trial independently using a simple form following the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

We would have assessed the following domains as either 'Yes' (i.e. low risk of bias), 'Unclear' (i.e. uncertain risk of bias) or 'No' (i.e. high risk of bias):

1. Sequence generation
2. Allocation concealment
3. Blinding (of participants, personnel and outcome assessors)
4. Incomplete outcome data
5. Selective outcome reporting
6. Other sources of bias

We planned to discuss any inconsistencies between the review authors in the interpretation of risk of bias and their significance to the selected trials and to resolve any differences with a third author (DB). No study was to be automatically excluded as a result of a rating of 'Unclear' or 'No'. We intended that we would present the evaluation of the risk of bias in included studies in tabular form in the 'Results' section of the review.

Measures of treatment effect

We planned to analyse extracted data using the most up-to-date version of RevMan available at the time of analysis (Review Manager 2014).

We planned to extract hazard ratios with their 95% confidence intervals (CIs) for the time-to-event data mortality and end-organ damage (see below). If hazard ratios were not given, we would have used indirect estimation methods described by Parmar 1998 and Williamson 2002 to calculate them.

If we were neither able to extract these data from the study reports nor able to receive the necessary information from the primary investigators, we would, as an alternative, have used the proportions of participants with the respective outcomes measured at three months, six months and then at six-monthly intervals (i.e. 12 months, 18 months and so on) to be able to calculate relative risks. If outcome data were recorded at other time periods, then we would have given consideration to examining these as well.

We planned to express results for binary outcomes as relative risk (RR) with 95% CIs as measure of uncertainty. We planned to express continuous outcomes as mean difference (MD) with 95% CIs as measure of uncertainty.

Unit of analysis issues

When conducting a meta-analysis combining results from cross-over studies we planned to use the methods recommended by Elbourne 2002. For combining parallel and cross-over trials, we would use methods described by Curtin (Curtin 2002a; Curtin 2002b; Curtin 2002c).

For some outcomes, a possible perception of the comparison might be whether deferasirox is equivalent to standard treatment with deferoxamine. Therefore, as secondary analysis, we planned to consider per-protocol analysis, as is often used for equivalence studies, for our primary outcome as well as for the groups one to five of our secondary outcomes.

For time-to-event data, we would have considered a relative difference in hazard ratios of less than 10% equivalent. For relative risks, we would have defined non-inferiority as a relative risk 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 have considered a relative difference of 10% as equivalent. Resulting CIs would have been discussed with respect to methods suggested by Witte 2004.

In principle it is conceivable that the evidence found might be suitable for indirect comparisons or multiple-treatment meta-analysis. If so, we planned to apply these concepts according to methods discussed by Glenny 2005 and Salanti 2008, respectively, as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), once they are supported by Review Manager 2014.

Dealing with missing data

We planned to follow the general recommendations for dealing with missing data in Cochrane Reviews (Higgins 2011b):

- Whenever possible we planned to contact the original investigators to request missing data.

- We would have clearly stated the assumptions of any methods used to cope with missing data (e.g. imputation of missing data and accounting for the fact that these were imputed with uncertainty).
- We would have performed sensitivity analyses to assess how sensitive results are to reasonable changes in the assumptions that are made.
- We would have addressed the potential impact of missing data on the findings of the review in the Discussion section.

Assessment of heterogeneity

We planned to assess statistical heterogeneity using the I^2 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 I^2 lie between 0% and 100%. We planned to use a simplified categorisation of heterogeneity with the following categories: low (I^2 less than 30%), moderate (I^2 between 30% and 60%) and high (I^2 more than 60%) (Deeks 2011).

In future review updates, if we detect moderate or high heterogeneity we intend to explore clinical heterogeneity by examining differences between groups as detailed below.

Assessment of reporting biases

If we include more than 10 trials, we will use funnel plots to graphically assess the likelihood of publication bias. We will take care in translating the results of included studies into recommendations for action by involving all review authors in drawing conclusions.

Data synthesis

We planned to conduct meta-analyses of pooled data from all contributing trials using a fixed-effect model for the primary analysis. Since no trials met our inclusion criteria, we did not perform meta-analyses.

For future updates of the review we will use both a fixed-effect and a random-effects model and report results from both models.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses for the different prognostic subtypes of MDS according to the IPSS (Greenberg 1997), as well as to the morphological MDS subtypes according to the WHO classification (Harris 1999; Vardiman 2002). We planned to assess clinical heterogeneity by examining differences due to baseline measures of iron overload, dose of intervention, concomitant use of growth factors (erythropoietin, G-CSF) and age. In addition, we planned to assess heterogeneity regarding study characteristics as described in the paragraph on Data collection and analysis and Assessment of risk of bias in included studies.

Sensitivity analysis

We did not perform sensitivity analyses based on assessment of risk of bias and publication status (unpublished and published studies) as we could not include any trials in this review. However, for future updates we plan to investigate the robustness of our results through a sensitivity analysis on the basis of the methodological quality of the included trials by defining the following groups: low risk of bias (successful blinding of all patients, people involved in treatment and care and outcome assessors; adequate allocation concealment; and 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).

'Summary of findings' table

We will develop a 'Summary of findings' table according to the GRADE methodology (Balshem 2011; Guyatt 2011). We plan to present information on the following outcomes: mortality; cardiac failure; endocrine disease; iron status (assessed by magnetic resonance imaging (MRI) or superconducting quantum interference device (SQUID)), if not available, ferritin; two most relevant or severe AEs; discontinuations.

INDEX TERMS

Medical Subject Headings (MeSH)

Benzoates [*therapeutic use]; Chelation Therapy [*methods]; Deferasirox; Iron Chelating Agents [*therapeutic use]; Iron Overload [*drug therapy]; Myelodysplastic Syndromes [*complications]; Triazoles [*therapeutic use]

MeSH check words

Humans