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Safety Profiles of Iron Chelators in Young Patients with Haemoglobinopathies

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ABSTRACT

Background

This review describes the safety of deferoxamine (DFO), deferiprone (DFP), deferasirox (DFX), and combined therapy in young patients less than 25 years of age with haemoglobinopathies.

Method

Searches in electronic literature databases were performed. Studies reporting adverse events associated with iron chelation therapy were included. Study and reporting quality was assessed using AHRQ Risk of Bias Assessment Tool and McMaster Quality Assessment Scale of Harms. Prospective clinical studies were pooled in a random-effects meta-analysis of proportions.

Results

Safety data of 2,040 patients from 34 studies were included. 92 case reports of 246 patients were identified. DFX (937 patients) and DFP (667 patients) possess the largest published safety evidence. Fewer studies on combination regimens are available. Increased transaminases were seen in all regimens (3.9-31.3%) and gastrointestinal disorders with DFP and DFX (3.7-18.4% and 5.8-18.8%, respectively). Therapy discontinuations due to adverse events were low (0-4.1%). Reporting quality was selective and poor in most of the studies.

Conclusion

Iron chelation therapy is generally safe in young patients and published data corresponds to summary of product characteristics. Each iron chelation regimen has its specific safety risks. DFO seems not to be associated with serious adverse effects in recommended doses. In DFP and DFX rare, but serious adverse reactions can occur. Data on combined therapy is scarce, but it seems equally safe compared to monotherapy.

KEY POINTS

- Both deferiprone (DFP) and deferasirox (DFX) possess the largest published safety evidence in young patients.
- However, both drugs may cause serious and severe adverse effects: agranulocytosis (DFP) and Fanconi syndrome (DFX).
- Studies in children and adolescents are scarce for combined therapy, but available data suggests that combined regimens are equally safe to their iron chelating agents in monotherapy.

KEY WORDS

Deferoxamine, deferiprone, deferasirox, haemoglobinopathies, adverse drug reactions, children

BACKGROUND

Haemoglobin disorders such as sickle cell disease and thalassaemia account for 3.4% of all deaths in children under the age of 5 years (1, 2). Long-term treatment of these conditions is an emerging issue since more and more newborns with haemoglobinopathies survive due to the reduction of childhood mortality (3).

Depending on the severity of the disease, affected patients suffer from anaemia starting in early childhood and commonly require regular blood transfusion therapy (4, 5). Over time chronic transfusion therapy leads to iron overload and, if untreated, usually results in severe organ damage.

The overall goal of iron chelation therapy is to maintain iron levels considerably safe for the patient. Currently, there are three iron chelators licensed: deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX). Since DFO needs to be administered via parenteral routes for several hours per day, oral drug alternatives DFP and DFX are preferred due to better compliance. DFX is licensed in the EU starting from the age of 6 years and from 2 years if DFO is contraindicated or inadequate. DFP is indicated if DFO is contraindicated or inadequate, but available data is limited in children below the age of 10 years and no data is available in children under 6 years of age. Newer regimens emerged in the last 10 years including the combination of DFP and DFX in order to increase iron chelation efficacy and patient acceptance (6-8).

Due to the early start of iron chelation therapy, a profound knowledge of efficacy and safety in young patients is essential. Yet only a limited amount of studies investigated the clinical properties of these drugs in children and young adults. In the past few years, several systematic reviews with meta-analyses combined data of randomised controlled trials (RCT) to better evaluate the efficacy and safety profiles of the available iron chelating drugs (9-14). However, due to the short-term nature of RCTs, neglected adverse effects reporting and inability to detect rare adverse events (AE), the value of meta-analyses of safety data derived from RCTs is limited (15). The Cochrane Adverse Effects Methods Group suggests including other study types such as non-controlled clinical trials, observational studies and case reports in safety reviews to obtain a more real-life picture (16-18).

To our knowledge, there are no published systematic reviews evaluating and quantifying the safety of iron chelating drugs strictly in the paediatric and younger adult population including studies other than RCTs. Therefore, we conducted this comprehensive systematic review to better describe and quantify the safety profiles of DFO, DFP, DFX and combination therapy in young patients less than 25 years of age suffering from haemoglobinopathies with transfusion-dependent iron overload.

METHOD

Data sources and search strategy

A systematic literature search was conducted in the following databases using the key elements ‘deferoxamine’, ‘deferiprone’, ‘deferasirox’ and ‘haemoglobinopathies’: PubMed (1948-2016 April 13), EMBASE (1947-2016 Week 15), BIOSIS Previews/Citation Index (1969-2016 April 13), Science Citation Index Expanded (1970-2016 April 13), The Cochrane Library (1898-Issue 4 of 2016 April 12). The search was conducted in April 2016. The detailed search strategies are presented in Supplementary Table S1. We screened bibliographies of Micromedex DrugDex and Lexicomp

UpToDate drug monographs, manufacturer's websites, US Food and Drug Administration and European Medicines Agency assessment reports, literature reviews and clinical trial registries Meta Register of Controlled Trials and NIH ClinicalTrials.gov.

Study selection

Only studies fulfilling the following inclusion criteria were considered: (1) population age between 0 and 25 years, (2) diagnosis of haemoglobinopathies with transfusional iron overload, (3) reporting of AEs related to iron chelation therapy, and (4) providing the number of patients affected by each AE. The exclusion criteria were (1) publication language other than English, (2) conference abstracts or proceedings (except for case reports), (3) publications not reporting original data, (4) intoxication or accidental iron chelator overdose, (5) missing or inconclusive AE reporting, (6) patient age older than 25 years, and (7) investigation of conditions other than haemoglobinopathies.

A primary selection of all citations identified was performed by screening titles and abstracts. Two investigators independently evaluated the full texts for eligibility. Disagreements were resolved by consensus involving two senior investigators.

Each study was assigned to one of the following types: RCTs, non-randomised controlled trials (NRCT), non-controlled clinical trials (NCT), retrospective observational studies (ROS), case-control studies (CC). Additionally, we identified and included eligible case reports and case series in our narrative review.

Data collection

Data was independently extracted by two investigators and included study centres, study design, interventions, study duration and follow-up, patient characteristics and reported AEs.

Quality assessment

Two investigators separately assessed the overall risk of bias (AHRQ Risk of Bias Assessment Tool (19)) and the AE reporting quality (McMaster Quality Assessment Scale of Harms (20)). Discrepancies were discussed and final assessment was assigned on agreement. If more than one publication reported data on one study, then each publication was assessed individually for reporting quality. However, the results were only considered once independent from the number of publications.

Data synthesis

Iron chelator-related AEs were assigned to system organ classes (SOC) according to the MedDRA classification (21). Incidences were the number of patients experiencing a drug-related AE divided by the number of exposed patients.

We quantitatively pooled the incidences in a random-effects meta-analysis of proportions for frequently reported AEs and AE-related permanent chelator discontinuation. Only prospective clinical trials were eligible for synthesis to avoid bias due to inappropriate data synthesis.

Incidences were pooled using the 'metaprop' command in Stata (version 13.1, StataCorp, College Station, TX, USA) (22). A random effects model including Freeman-Tukey arcsine transformation of the incidence was used to normalise variance. For each incidence per study the 95% confidence interval (CI) was calculated and pooled incidence CIs were based on the exact-test statistics. Heterogeneity between studies and study type was assessed with Cochran's Q-test and percentage of total variation across studies due to heterogeneity was evaluated with the I^2 measure (23, 24). Sensitivity analyses were performed to identify potential sources of heterogeneity.

RESULTS

Literature search results

Figure 1 describes our literature search according to the PRISMA statement (25). In total, 34 studies comprising 2,040 young patients were included (Table 1). Reported incidences of frequently reported AEs are presented in Table 2. We identified 7 studies on DFO (198 patients), 13 studies on DFP (667 patients), 15 studies on DFX (937 patients), two studies on sequential combination of DFP and DFO (SEQ DFP+DFO, 37 patients), one study on sequential combination of DFX and DFO (SEQ DFX+DFO, 7 patients), 5 studies on simultaneous combination of DFP and DFO (SIM DFP+DFO, 131 patients), and two studies on simultaneous combination of DFP and DFX (SIM DFP+DFX, 63 patients).

Despite several identified studies on various combination regimens using DFX and DFO (26-30), only one small retrospective study in 7 patients was eligible for our purposes (31). Mean investigation time of prospective clinical trials was 13 months (range 6-36 months). Additionally, 92 appropriate case studies reporting AEs in 246 patients were identified (Table 3).

Meta-analysis of reported AE incidences

We pooled the reported incidences of 27 prospective clinical trials by iron chelator regimen and AE. The summarised results are presented in Table 4. Supplementary Figures S1-S13 show the detailed forest plots of our meta-analysis.

Quality assessment results

The general risk of bias assessment revealed that there was a high risk of selection bias (Supplementary Table S2). Reason for that was the large amount of uncontrolled single-arm clinical trials without drug blinding. Performance, attrition, detection and reporting bias were generally less present, but in most cases publications insufficiently provided enough information to assess risk of bias. Naturally, randomised studies were of superior quality compared to non-randomised studies or observational studies.

The results of the McHarm assessment generally demonstrated a poor AE reporting quality (Supplementary Table S3). Most studies did not clearly define serious or severe adverse events. Furthermore, it was often not clear who and how the AEs were assessed. Most studies did not analyse their safety data more exhaustive, in contrast to efficacy parameters. Another problem was, that several studies did not clearly state whether all observed AEs were reported or only a selection. Positively, most clinical trials measured safety parameters in an active manner, but reporting was incomplete in terms of presentation of safety assessment methods and AE presentation. Many publications on NCTs provided more extensive AE reporting than the ones on RCTs and NRCTs.

Deferoxamine (DFO) monotherapy

Four RCTs, one NRCT and two ROS investigating the safety of DFO in 198 young patients were identified (32-38). Most studies administered DFO subcutaneously with doses between 40-50 mg/kg per day for 5-6 days per week.

Only few AEs have been reported. Pooled incidence for reported neutropenia was 2.3% in 109 patients. However, there was high heterogeneity since only one study found mild neutropenia in patients with DFO (33) whereas in two other RCTs neutropenia was not seen (32, 35). Other haematological AEs reported in four studies could not be established. Elevated liver enzymes were found with a pooled incidence of 3.9% (95%-CI 0.0-26.3). Renal, gastrointestinal, visual or ocular AEs have not been observed in any clinical trial. In one long-term retrospective study hearing loss was detected in 9 (36%) patients (38). Other identified AEs were abscess at infusion site and allergic reaction after infusion in one RCT (32), however, this was not reported in the other studies.

We additionally identified 57 other publications reporting DFO-related AEs in 147 young patients. A summary of these findings is provided in Table 3. These case reports are generally in line with the information provided in the latest EU SPC (39). One notable case is the occurrence of fatal acute bone marrow aplasia in a 16-year-old Greek girl with β-TM and a high DFO dose of 80 mg/kg/day (40). The proposed mechanism is a direct damage of the megakaryocytes.

Deferiprone (DFP) monotherapy

We identified 4 RCTs, two NRCTs, 5 NCTs and two ROS reporting DFP-related AEs in 667 patients using DFP doses of 50-75 mg/kg per day (33-35, 41-52). Occurrence of mild to moderate neutropenia was reported in 425 patients with a pooled incidence of 7.1% (95%-CI 2.3-13.7). Agranulocytosis was reported in 436 patients (pooled incidence 0.002%, 95%-CI 0.0-0.7). Two observational studies reported neutropenia and agranulocytosis with incidences of 5.1-9.6% and 0-0.6%, respectively (49, 51). Arthropathy was reported in 458 patients with an incidence of 10.9% (95%-CI 2.8-22.2%) with considerable heterogeneity. Sensitivity analysis showed that without the studies by Agarwal, Choudhry, and Sanjeeva the pooled incidence dropped to 2.4% (95% CI 0.6-4.8) with low heterogeneity.

Gastrointestinal symptoms including abdominal pain, nausea, vomiting and diarrhoea were other frequently reported in 3.7% (diarrhoea) to 18.4% (nausea) of patients. Elevated liver enzymes were reported by 6 clinical trials including 321 patients. We found a pooled incidence of 6.2% (95%-CI 2.1-11.9) with moderate heterogeneity. Single cases of mild and transient serum creatinine increase, proteinuria, rash and thrombocytopenia were reported with pooled incidences of 0.5%, 0.6%, 2.4% and 4.4%, respectively. No auditory or visual toxicity has been reported.

Additionally, we identified 16 case studies (including 27 patients) on DFP-related AEs in the literature. Details are summarised in Table 3. Most case studies reported occurrences of agranulocytosis or arthropathy. We identified two rare cases of drug-induced systemic lupus erythematosus of which one was fatal (53). However, the causality to DFP was discussed controversially (54, 55). Other identified cases are in line with the latest EU and US SPCs (56, 57).

Deferasirox (DFX) monotherapy

One RCT, one NRCT, 10 NCTs and 3 ROS were identified from the literature counting 37 patients (37, 50, 52, 58-70). Investigated DFX doses ranged from 10 to 40 mg/kg per day.

No cases of thrombocytopenia or agranulocytosis were found in 80 and 316 patients, respectively. One study identified neutropenia (pooled neutropenia incidence 0.5%, 95%-CI 0.0-4.8). Elevated liver enzymes were discovered in 20.0% (95%-CI 5.8-39.4) of 516 patients with considerable heterogeneity. Observational studies reported this AE with an incidence ranging 9.9-53.2%.

Serum creatinine increase above the upper limit of normal (ULN) was investigated in almost all clinical trials (678 patients) and was seen with a pooled incidence of 2.5% (95%-CI 1.1-4.2). Heterogeneity was low. Proteinuria was not detected in 107 studied patients. Several gastrointestinal AEs have been reported with pooled incidences between 5.8% (diarrhoea) and 18.8% (vomiting). Cutaneous reactions, i.e. rash, were reported in 313 patients and occurred with a pooled incidence of 3.7% (95%-CI 1.6-6.4) and low heterogeneity. Auditory or visual toxicities were not seen in these studies.

We found 19 case reports and case series presenting AEs in 58 young patients with DFX therapy. The results are presented in Table 3. Most reports address renal adverse reactions that are commonly associated with DFX intake. There were no reported AEs which do not correspond to the latest EU SPC (71).

Sequential deferiprone and deferoxamine combination (SEQ DFP+DFO)

We identified one RCT and one NCT investigating the safety of a sequential combined regimen of 4 days DFP plus two days DFO in 37 patients (32, 72). No haematological iron chelator-related AEs were found. Liver enzymes were elevated in 31.3% (95%-CI 16.4-48.2) of study participants. No renal AEs were identified or reported. Gastrointestinal AEs were seen in 3.3-6.7% of patients, but only reported in one study. Both studies investigated the occurrence of arthropathy resulting in a pooled incidence of 1.4% (95%-CI 0.0-10.1). Other identified AEs were dizziness and fatigue in one patient

with sequential combined therapy (32). We did not identify case reports of AEs related to sequential DFP and DFO chelation regimens.

Sequential deferasirox and deferoxamine combination (SEQ DFX+DFO)

One ROS has been identified investigating a sequential combination regimen of DFX for 4 days and DFO for the following three days in 7 paediatric patients. No haematological, renal or hepatic AEs were observed. No case reports have been identified.

Simultaneous deferiprone and deferoxamine combination (SIM DFP+DFO)

Three RCTs, one NRCT and one NCT reported safety data using a simultaneous chelation regimen of 6-7 days DFP plus 2-6 days DFO in 131 patients.

All studies investigated the occurrence of agranulocytosis but in only one trial this condition was seen in one patient (pooled incidence 0.0%, 95%-CI 0.0-1.7). Neutropenia was reported in 102 patients with a pooled incidence of 5.3% (95%-CI 1.3-11.1, low heterogeneity). Elevated liver enzymes were observed by three studies with a pooled incidence of 6.6% (95%-CI 2.0-13.3). Nausea and vomiting were seen in two studies with incidences of 31.6% and 35.3%, respectively. No auditory or visual AEs were reported. All 5 studies described arthropathy with a pooled incidence of 9.2% (95%-CI 0.6-23.7).

Three case studies describing agranulocytosis related to simultaneous DFP and DFO combination were identified (Table 3).

Simultaneous deferiprone and deferasirox combination (SIM DFP+DFX)

One RCT and one NRCT investigated the safety of the combination of daily DFP and DFX in 63 young adults. No case of agranulocytosis was identified and pooled neutropenia incidence was 6.4% (95%-CI 1.1-14.6). Elevated serum creatinine (>ULN) was seen in 3.7% (95%-CI 0.0-10.7) and liver enzyme abnormalities reported in 5.1% (95%-CI 0.5-12.7). Gastrointestinal events were only reported scarcely; one study reported non-occurrence of abdominal discomfort and one study reported any gastrointestinal event in 12.5% of patients. In 2.3% (95%-CI 0.0-8.6) of patients skin rash was observed. We did not identify any eligible case reports in our literature review.

Discontinuation rate due to adverse events

Discontinuation rates due to any iron chelator-related AE were reported by 25 prospective clinical trials and 6 observational studies. The latter reported higher rates compared to clinical trials, mostly likely due to the fact that they provided information of real-world iron chelator use.

In general, low discontinuation rates were found with pooled rates from 0.0% to 4.1%. Higher discontinuation rates were seen with DFP and SIM DFP+DFO, 2.4% (447 studied patients) and 4.1% (121 studied patients), respectively. We identified significant heterogeneity in the DFP subgroup. Taking the number of studied patients into account, DFX monotherapy had the lowest discontinuation rate of 0.2% (95%-CI 0.0-0.9) in 708 patients.

Patients on DFP therapy most commonly discontinued therapy due to moderate-to-severe neutropenia, arthropathy, gastrointestinal symptoms or liver enzyme abnormalities. Rash, gastrointestinal symptoms or liver enzyme abnormalities led to discontinuation of DFX therapy. With simultaneously combined DFP and DFO, patients experiencing severe neutropenia, arthropathy and gastrointestinal symptoms resulted in therapy discontinuation.

DISCUSSION

Strengths and limitations

Our systematic literature review is the first investigating all important iron chelation regimens in children, adolescents and young adults with haemoglobinopathies and transfusional iron overload. We used a structured and comprehensive methodology to identify and assess the safety information available in the scientific literature. We not only included RCTs in our review, but also data from cohort studies and case studies providing precious safety signals (73).

However, we are aware that some data on iron chelator safety in young patients was not considered since we excluded studies with patients of older age or other diagnoses. Furthermore, methods for the meta-analysis of rare adverse events have not been fully elaborated yet and therefore the results need to be interpreted carefully (74). Our pooling method may not be ideal for very low incidences as seen with agranulocytosis. We also did not consider therapy duration and the AE incidence rate per person-years. Lack of observation time reporting in some studies did not allow us to calculate incidence rates.

Adverse effects reporting quality

RCTs are unquestionably the gold standard for investigating drug efficacy and safety, however, study publications are commonly focused on reporting efficacy parameters. Reports on non-randomised, non-controlled studies and case studies repeatedly provided more drug safety information. We can confirm that observation.

In general, we noticed considerable selective reporting bias (75): most publications preferably reported commonly recognised AEs associated with the respective iron chelating agent. For example, all of our identified DFP studies reported agranulocytosis and arthropathy, and almost all of the DFX studies reported increased serum creatinine events, but not vice versa. Also some studies excluded patients with certain predispositions or history of AEs to an iron chelator (e.g. neutropenia in the past for DFP or renal dysfunction for DFX). Furthermore, it was not always clear whether the patients were naïve to iron chelation or switching from an existing regimen. Many publications reported only AEs exceeding a randomly defined minimum frequency (e.g. frequency at least 5%). Additionally,

some authors only reported specific AEs only if the investigated parameter met a certain threshold, e.g. liver enzymes larger than 2 times ULN, and some authors did not provide this information. Consequently, we observed considerable heterogeneity in our random effects meta-analysis.

Moreover, our McHarm assessment showed that the reporting quality is generally poor and most publications lack clear AE definitions, assessment methods and safety reporting.

General considerations

Some AEs related to iron chelators were less specific such as liver enzyme abnormalities. These occurred with all regimens and iron overload itself is also a probable cause for occurrence. Gastrointestinal toxicity was equally seen with oral iron chelators DFP or DFX. Consequent intake with food and use of newer drug formulations may improve the tolerability (45, 46, 76, 77).

Deferoxamine (DFO)

We only identified five small-to-medium scale clinical trials investigating safety of DFO in young patients. However, many case studies in the paediatric population were published in the last decades. Generally, DFO seems to have a favourable safety profile without serious AEs. AE-related DFO therapy discontinuations were only observed in one study. Despite the one case of fatal bone marrow aplasia, all identified adverse reactions were consistent with the SPC.

Several case studies reported systemic allergic reactions during drug administration, but mostly limited to high-dose regimens. These regimens seem also to be responsible for several reports on skeletal dysplasia and growth failure. Therefore high doses above 50 mg/kg per day should be avoided, especially before the age of 2-3 years (78-80). Regular ophthalmologic, otologic and auxologic examinations are advised in children (80). A therapeutic index (mean daily DFO dose in mg/kg divided by serum ferritin in ng/ml) above 0.025 seems to be associated with a high risk of hearing loss (81). Nevertheless, we did not observe visual or auditory toxicity in our investigated clinical trials. The chelation of enzyme co-factors iron, copper and zinc may be a potential mechanism for bone deformities and audio-visual toxicity (82, 83). There are some hints that oral supplementation of zinc and other minerals might improve tolerance (84).

Another serious event associated with high doses of DFO was acute renal failure with decreased renal perfusion due to reduced prostaglandin synthesis or inhibition of tubular reabsorption of salts (85, 86).

Some case reports identified DFO as an additional risk factor for the occurrence of Yersinia enterocolitica infections. Patients from Western countries seem to be affected more often (87). Yersinia infection is common in diseases with iron overload states and often associated with thalassaemia in children (88). Patients with higher iron burden and impaired immune system may be at greater risk as well. Experimental studies showed that DFO as a siderophore provides iron the iron-dependent bacteria and thus potentiates its growth (89-91). Patients with fever and symptoms of gastroenteritis should temporarily discontinue DFO and Yersinia infection may be considered.

Deferiprone (DFP)

All reported AEs were in agreement with the SPCs, expect for speculative cases of drug-induced systemic lupus erythematosus, cardiac failure with myocardial fibrosis and posterior subcapsular opacity.

Milder neutropenia was reported in DFP-containing regimens with pooled incidences of 5.3-7.1%. However, this has been reported in thalassaemia generally (92), occurs also with other iron chelation agents (33, 62), and is also dependent on the frequency of blood count monitoring (44, 51). Due to the publication and reporting bias, we cannot clearly elaborate a higher risk for neutropenia with DFP in young patients compared to other iron chelation regimens. Mild neutropenia does not consequently lead to agranulocytosis and not always a permanent discontinuation necessary (43, 44, 47). High heterogeneity found in all regimens and studies support this observation.

Agranulocytosis was only seen in DFP-containing chelation regimens, and seems to occur more often in non-splenectomised patients and in the first months of treatment (33, 48, 93-95). This adverse reaction is probably idiosyncratic, unpredictable and not dose-dependent (80, 96, 97). Immune origin remains unproven and antibodies against neutrophils or myeloid precursors have not been found yet (96). Other potential mechanisms are maturation arrest of granulocytic lineage or decreased production of granulocyte colony forming units (98). Specific risk factors and pharmacogenetic dispositions have also not been identified yet (44, 99). Our meta-analysis shows that the incidence of agranulocytosis in children and adolescents may be lower than the 0.5-0.9% reported previously (94, 95). However, due to the limitations of meta-analysis of very rare events, we need to consider a pooled incidence up to 0.7% (upper confidence interval). This is in agreement with previous reports and SPCs (56, 57, 100). Several case reports of non-fatal agranulocytosis in young patients have been published. From the available data we can state that dose-dependency was not obvious, most cases occurred between 2-15 months after initiation of treatment, and all patients recovered upon DFP discontinuation.

Formerly, osteoarthropathy was a frequently observed condition in haemoglobinopathies (101). DFP is also commonly associated with arthropathy. The proposed mechanism is a DFP-induced shift of iron from tissue stores to joint fluid and subsequent formation of free radicals peroxidating synovial membranes by uncomplexed iron (54). Some studies observed that arthropathy is more common in patients with high serum ferritin and DFP doses above 100 mg/kg per day (33, 42, 54, 95), but this could not be confirmed by another study (43). Suspected long term effects of DFP-related arthropathies are bony dysplasia, deformation and impaired growth of ulnar epiphyses, metaphyses and physes (102).

High heterogeneity was found in our pooled arthropathy estimate. This might be related to the subjective perception of arthralgia and associated symptoms, and different event assessment methods e.g. presence of patient questionnaires. Viprakasit et al. postulated that the quality of different DFP products influence the large differences in AE incidences (48). This should be further investigated and unfortunately most studies did not report the investigated drug brand.

Single cases of mild-to-moderate thrombocytopenia were observed in all DFP-containing regimens, but only one study reported a high incidence of 45.5%. Patients recovered upon temporary or permanent discontinuation. The impact of DFP on the platelet count needs to be further investigated in future studies. Currently, the data seems inconclusive due to the high heterogeneity found in our meta-analysis.

Worsening of hepatic fibrosis under DFP therapy was raised by Olivieri et al. but could not be confirmed in later studies (93, 103-105) and was not observed in our review. Iron accumulation and chronic hepatitis C are currently seen as the more likely cause.

Other identified events were neurological symptoms including cerebellar signs with dizziness, axial hypotonia and impaired motor coordination seen in two case reports and one clinical trial (33, 106, 107).

Deferasirox (DFX)

Although DFX is the latest oral iron chelator in the market, more trials including patients starting age 2 years were found for DFX than for the other two chelators. Serious haematological AEs such as agranulocytosis seen in DFP have not been observed. In general, the identified AEs were in line with the SPC.

Previous study showed that renal dysfunction may occur more often with DFX and also in young patients (108). Serum creatinine elevations were seen in approximately 2.5% of patients, but were also reported with DFP. Other renal abnormalities such as proteinuria were not observed. However, case studies reported life-threatening Fanconi syndrome (renal tubulopathy) which seems to be the most serious known AE to DFX. Low total iron burden might be a risk factor for its appearance (109). The mechanism is not yet well-understood and excessive rapid iron removal might modify renal haemodynamics (110, 111). Other discussed mechanisms are drug hypersensitivity reactions or direct toxic reaction with tubular necrosis (112, 113). Regular urinalyses and renal checks when using DFX are recommended to detect this condition in an early state.

Skin rash is another DFX-associated AE we identified in 8 clinical trials, three observational studies and three case reports. We found an estimated incidence of 3.7% (DFX) and 2.3% (SIM DFP+DFX). Still, in the present studies, this rash was non-serious and reversible on DFX discontinuation.

We also identified two case reports of serious ocular findings including decreased vision, retinopathy and lens opacities. Future clinical trials should assess ocular safety parameters to better understand this association and risk.

Combined iron chelation regimens

Previous literature suggested a shuttling hypothesis and an improved iron extraction from tissue when combining DFP and DFO (114, 115), and also the combination of DFX and DFO or DFX and DFP are anticipated to improve iron excretion (29, 116). Especially the latter regimen is particularly attractive because the combination of two oral iron chelating agents is expected to have an improved patient adherence.

Unfortunately, the safety evidence of any combination regimens is insufficient in young patients. However, taking this lack of publications and adequately sized studies into consideration, our review could not find a higher risk for combined regimens. Safety profiles seem to be similar to the iron chelating agents in monotherapy and no negative synergy has been identified. However, more clinical trials are necessary to support this conclusion.

CONCLUSION

Safety data from studies in young patients are generally in line with the respective SPCs. DFO in doses below 50 mg/kg per day seems not to be associated with serious AEs in young patients. However, due to its burdensome application, patients often prefer oral therapies. We were able to identify at least 10 clinical trials for each oral chelator reporting safety data in young patients under the age of 25 years. However, both DFP and DFX are associated with rare but serious AEs.

Therapy discontinuation rates due to severe or serious AEs are generally low in all regimens. Each iron chelation regimen has its specific safety risks and should be considered tailoring the right treatment in young patients. Existing predispositions and comorbidities should be taken into account to avoid harmful reactions to this lifelong therapy. Combined therapy seems not to be associated with a higher risk for adverse reactions than monotherapy regimen, but combined regimens are generally less well documented. Finally, it would be desirable if publications on iron chelator studies report safety parameters more comprehensively in the future.

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AN, ICW and EWC planned, conceived and supervised this study. SB, CWS and NL conducted the literature search and collated the full-texts. SB and NL extracted the studies and assessed their quality with support of AN and EWC. SB summarised all results, conducted the meta-analysis and drafted the manuscript. All author reviewed and approved the paper.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

FIGURES & TABLES

Figure 1: Literature search flow chart according to PRISMA (25)

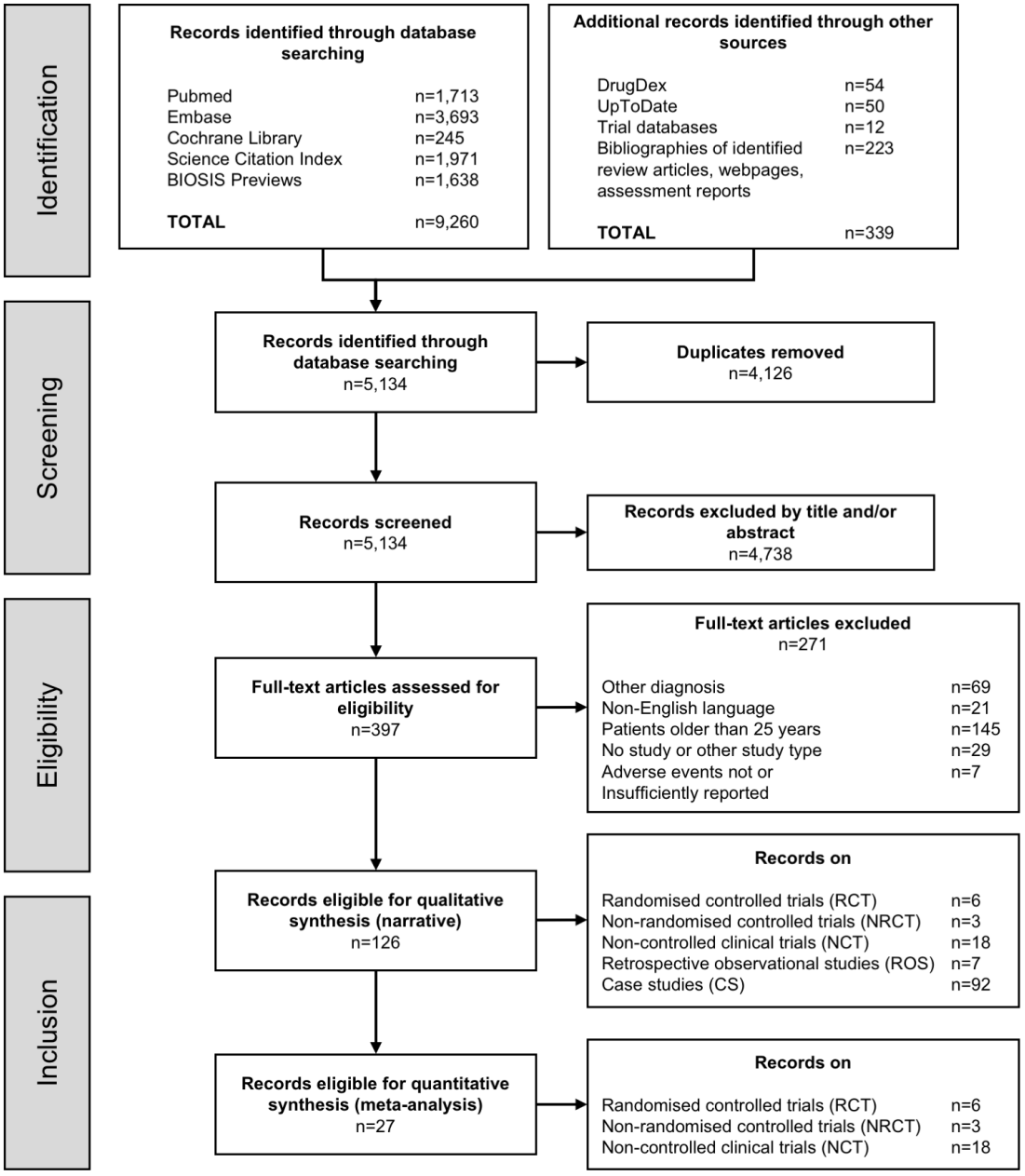

Table 1: Characteristics of all identified studies

Publication(s)	Design	Country	Chelation regimen	N	Age	Duration	Diagnosis
DEFEROXAMINE (DFO)							
Abdelrazik 2007 (32)	RCT	Egypt	DFO s.c. 40 mg/kg/d (5-6 d/wk)	30	Mean±SD 14±2.4 years	12 months	TM
Aydinok 2007 (33)	RCT	Turkey	DFO s.c. 40-50 mg/kg/d (5 d/wk)	12	Mean±SD 15.0±6.4 years (range 5-24.5)	12 months	TM
Gomber 2004 (34)	RCT	India	DFO s.c. 40 mg/kg/d (5 d/wk)	7	Children age (age not reported)	6 months	Thalassaemia
Waheed 2014 (35)	RCT	Pakistan	DFO s.c./i.v. 50 mg/kg/d (5 d/wk)	67	Mean±SD 6.0±6.4 years (range 4.5-16)	12 months	TM
Mashhadi 2011 (36)	NRCT	Iran	DFO s.c. 40 mg/kg/d (5-6 d/wk)	17	Range 10-20 years (total cohort)	12 months	TM
Aydinok 2012 (37)	ROS	Turkey	DFO s.c. 25-50 mg/kg/d (5 d/wk)	40	Median 3.1 years (range 1.3-5.9)	Median 2.75 years (range 1.0-6.1)	TM, SCD
Barratt 1987 (38)	ROS	Australia	DFO s.c. mean 57 mg/kg/d (nightly)	25	Mean 14.4 years (range 6-23)	Mean 5.5 years	TM
DEFERIPRONE (DFP)							
Aydinok 2007 (33)	RCT	Turkey	DFP oral 75 mg/kg/d (7 d/wk)	12	Mean±SD 15.9±4.2 years (range 9-23)	12 months	TM
Gomber 2004 (34)	RCT	India	DFP oral 75 mg/kg/d (7 d/wk)	11	Children age (age not reported)	6 months	Thalassaemia
Waheed 2014 (35)	RCT	Pakistan	DFP oral 75 mg/kg/d (7 d/wk)	67	Mean±SD 5.9±9.2 years (range 3-16)	12 months	TM
Sanjeeva 2016 (52)	RCT	India	DFP oral 75 mg/kg/d (7 d/wk)	22	Mean±SD 7.26±2.42 years	12 months	TM
Choudhry 2004 (43)	NRCT	India	DFP oral 50-75 mg/kg/d (7 d/wk)	51	Range 4-14 years	12 months	TM
Gomber 2016 (50)	NRCT	India	DFP oral 75 mg/kg/d (7 d/wk)	17	Mean±SD 11.6±6.21 years (total cohort)	12 months	TM
Agarwal 1991 (41), (42)	NCT	India	DFP oral 75-100 mg/kg/d (7 d/wk)	52	Mean±SD 13.05±2.6 years (range 7-22)	Mean 14.2 months (range 3-21)	TM, HbE-thal
ElAlfy 2010 (44), (45)	NCT	Indonesia, Malaysia, Egypt	DFP oral 50-100 mg/kg/d (7 d/wk)	100	Mean±SD 5.1±2.4 years (range 1-10)	6 months	TM, HbE thal, SCD
Makis 2013 (46)	NCT	Greece	DFP oral 50-100 mg/kg/d (7 d/wk)	9	Mean 6.5 years (range 2-10)	Mean 21.5 months (range 15-31)	TM, TI, SCD
Naithani 2005 (47)	NCT	India	DFP oral 75 mg/kg/d (7 d/wk)	44	Mean 3.92 years (range 2.1-6.0)	Median 13 months (range 1-46)	TM
Viprakasit 2013 (48)	NCT	Thailand	DFP oral 50-100 mg/kg/d (7 d/wk)	73	Mean±SD 11.0±3.4 years (range 3.2-19)	12 months	HbE thal, TM
Borgna-Pignatti 2006 (49)	ROS	Italy	DFP oral 75 mg/kg/d (7 d/wk)	157	Median 17.5 years (range 2.45-24.9)	Median 4.3 years (range 0.02-8.9)	TM

Belen 2016 (51)	ROS	Turkey	DFP oral (dose not reported)	52	Range 3-18 years	12 months	TM
DEFERASIROX (DFX)							
Sanjeeva 2016 (52)	RCT	India	DFX oral 20 mg/kg/d (7 d/wk)	19	Mean±SD 5.23±2.76 years	12 months	TM
Gomber 2016 (50)	NRCT	India	DFX oral 30 mg/kg/d (7 d/wk)	17	Mean±SD 11.6±6.21 years (total cohort)	12 months	TM
Chandra 2011 (60)	NCT	India	DFX oral 20-30 mg/kg/d (7 d/wk)	40	Median 13 years (range 3-18)	12 months	TM
Dhamija 2013 (61)	NCT	India	DFX oral 20-40 mg/kg/d (7 d/wk)	50	Mean 9.62 years (range 2-18)	36 months	TM
Ejaz 2015 (68)	NCT	Pakistan	DFX oral 20-40 mg/kg/d (7 d/wk)	100	Range 2-16 years	12 months	TM
Galanello 2006 (62)	NCT	Italy, France	DFX oral 10-30 mg/kg/d (7 d/wk)	40	Mean±SD 10.4±4.4 years (range 2-17)	12 months	TM
Lai 2013 (63)	NCT	China	DFX oral 10-40 mg/kg/d (7 d/wk)	117	Mean 6.8 years (range 2-19)	12 months (core study)	TM
Taher 2009 (66), (67)	NCT	Saudi Arabia, Syria, Oman, Egypt, Libanon	DFX oral 10-30 mg/kg/d (7 d/wk)	162	Mean 9.5±3.6 years (range 2-15)	12 months (core study)	TM
Alavi 2014 (58)	NCT	Iran	DFX oral 10-40 mg/kg/d (7 d/wk)	20	Mean±SD 8.02±0.70 years (range 2-13)	18 months	TM
Aycicek 2014 (59)	NCT	Turkey	DFX oral 9-40 mg/kg/d (7 d/wk)	102	Mean±SD 8.8±4.3 years (range 2-17)	36 months	TM
Naderi 2014 (64)	NCT	Iran	DFX oral 20 mg/kg/d (7 d/wk)	30	Mean±SD 4.9±3.2 years (range 2-16)	6 months	TM
Panigrahi 2012 (65)	NCT	India	DFX oral 17.2-40 mg/kg/d (7 d/wk)	30	Median 13 years (range 2-21)	24 months	TM
Aydinok 2012 (37)	ROS	Turkey	DFX oral 20-40 mg/kg/d (7 d/wk)	71	Median 2.6 years (range 1.2-5.9)	Median 2.29 years (range 1.0-7.0)	TM, SCD
Origa 2016 (69)	ROS	Italy	DFX oral 20-40 mg/kg/d (7 d/wk)	77	Children <18 years	Median 4.1 years	TM
Tsouana 2015 (70)	ROS	UK	DFX oral 10-40 mg/kg/d (7 d/wk)	62	Mean±SD 9.2 years (range 4.1-15.4)	Mean 2.5 years	SCD
SEQUENTIAL DEFERIPRONE + DEFEROXAMINE (SEQ DFP+DFO)							
Abdelrazik 2007 (32)	RCT	Egypt	DFP oral 75 mg/kg/d (4 d/wk) + DFO s.c./i.v. 40 mg/kg/d (2 d/wk)	30	Mean±SD 12±5.1 years	12 months	TM
Aydinok 1999 (72)	NCT	Turkey	DFP oral 75 mg/kg/d (4 d/wk) + DFO s.c./i.v. 40-50 mg/kg/d (2 d/wk)	7	Mean±SD 9.4±3.1 years (range 6-13)	6 months	TM
SEQUENTIAL DEFERASIROX + DEFEROXAMINE (SEQ DFX+DFO)							
Jetsrisuparb 2010 (31)	ROS	Thailand	DFX oral 20-30 mg/kg/d (4d/wk) + DFO s.c. 20-40 mg/kg/d (3 d/wk)	7	Median 12.5 years (range 8-19.9)	Median 25 months (range 8-32)	Thalassaemia
SIMULTANEOUS DEFERIPRONE + DEFEROXAMINE (SIM DFP+DFO)							

Aydinok 2007 (33)	RCT	Turkey	DFP oral 75 mg/kg/d (7 d/wk) + DFO s.c. 40-50 mg/kg/d (2 d/wk)	12	Mean±SD 16.6±4.8 years (range 9-23)	12 months	TM
Elalfy 2015 (117)	RCT	Egypt, Oman	DFP oral 75 mg/kg/d (7 d/wk) + DFP s.c. 40 mg/kg/d (6 d/wk)	48	Mean±SD 15.25±2.31 years (range 10-18)	12 months	TM
Gomber 2004 (34)	RCT	India	DFP oral 75 mg/kg/d (7 d/wk) + DFO s.c. 40 mg/kg/d (2 d/wk)	10	Children age (exact age not reported)	6 months	Thalassaemia
Mashhadi 2011 (36)	NRCT	Iran	DFP oral 70 mg/kg/d (6 d/wk) + DFO s.c. 40 mg/kg/d (2 d/wk)	19	Range 10-20 years (total cohort)	12 months	TM
Songdej 2015 (118)	NCT	Thailand	DFP oral 50-100 mg/kg/d (7 d/wk) +DFO s.c. 35-45 mg/kg/d (2 d/wk)	42	Median 10 years (range 3-18)	36 months	TM, HbE thal
SIMULTANEOUS DEFERIPRONE + DEFERASIROX (SIM DFP+DFX)							
Elalfy 2015 (117)	RCT	Egypt, Oman	DFP oral 75 mg/kg/d (7 d/wk) + DFX oral 30 mg/kd/d (7 d/wk)	48	Mean±SD 14.05±2.21 years (range 10-18)	12 months	TM
Gomber 2016 (50)	NRCT	India	DFP oral 75 mg/kg/d (7 d/wk) + DFX oral 30 mg/kg/d (7 d/wk)	15	Mean±SD 11.6±6.21 years (total cohort)	12 months	TM

RCT: randomised controlled trial; NRCT: non-randomised controlled trial; NCT: non-controlled clinical trial; ROS: retrospective observational study; TM: thalassaemia major; SCD: sickle cell disease; TI: Thalassaemia intermedia; SD: standard deviation

Table 2: Incidences of frequently reported iron chelator-related adverse events

	DFO							DFP											DFX														SEQ DFP+DFO		SEQ DFX+DFO	SIM DFP+DFO					SIM DFP+DFX	
	Abdelrazik 2007 (32)	Aydinok 2007 (33)	Gomber 2004 (34)]	Waheed 2014 (35)	Mashhadi 2011 (36)	Aydinok 2012 (37)	Barratt 1987 (38)	Aydinok 2007(33)	Gomber 2004 (34)]	Waheed 2014 (35)	Sanjeeva 2016 (52)	Choudhry 2004 (43)	Gomber 2016 (50)	Agarwal 1991 (41, 42)	ElAlfy 2010 (44, 45)	Makis 2013 (46)	Naithani 2005 (47)	Viprakasit 2013 (48)	Belen 2016 (51)	Borgna-Pignatti 2006 (49)	Sanjeeva 2016 (52)	Gomber 2016 (50)	Alavi 2014 (58)	Aycicek 2014 (59)	Chandra 201 (60)	Dhamija 2013 (61)	Ejaz 2015 (68)	Galanello 2006 (62)	Lai 2013 (63)	Naderi 2014 (64)	Taher 2009 (66, 67)	Panigrahi 2012 (65)	Aydinok 2012 (37)	Origa 2016 (69)	Tsouana 2015 (70)	Abdelrazik 2007 (32)	Aydinok 1999 (72)	Jetsrisuparb 2010 (31)	Aydinok 2007 (33)	Elalfy 2015 (117)	Gomber 2004 (34)	Mashhadi 2011 (36)	Songdej 2015 (118)	Elalfy 2015 (117)	Gomber 2016 (50)
	CT					OBS		CT											OBS		CT												OBS			CT					CT	
BLOOD AND LYMPHATIC SYSTEM DISORDERS																																										
Thrombocytopenia[a]	0		0						0				0	0			45.5	1.4				0			0									0	0	0			0		2.4		0
Neutropenia[b]	0	25		0				8.3		19.4		23.5	0	0	7	11.1	4.6	6.9	9.6	5.1		0			0			7.5	0						0	0	0	8.3	6.3			4.8	10.4	0

Agranulocytosis[c]	0	0	0	0	0			0	0	0		2	0	0	2	0	0	0	0	0.6		0		0	0			0	0							0	0	0	8.3	0	0	0	0	0	0
HEPATOBILIARY DISORDERS																																													
Elevated liver enzymes[d]	23.3	0		0		5		0		4.5			0	3.9	12			16.4		1.3		0	15	4.9	15	16	69	12.5	53			16.7	9.9	23.4	53.2	26.7	57.1	0	0	6.3			11.9	8.3	0
RENAL AND URINARY DISORDERS																																													
Elevated serum creatinine[e]						2.5							0	0	2							0	10	2	10	6	3	2.5	0.9		2.5	3.3	4.2	1.3	4.8		0	0		2.1			2.4	6.3	0
Proteinuria													0	0				2.7				0				0		0						24.7									2.4		0
GASTROINTESTINAL DISORDERS																																													
Abdominal discomfort/pain	0										4.6		0	3.9	3	11.1		11		1.3	0	11.8		12.8	15	10	41		1.7			16.7			12.9	6.7							4.8		0
Nausea		0			0			41.7			27.3			5.8			27.3	9.6	1.9		31.6			4.9	25		31	5						5.2	1.6				41.7			31.6			
Vomiting	0				0						27.3			3.9	6		27.3	9.6			31.6				20		15							5.2		3.3						31.6			
Diarrhoea	0														3	11.1		6.9							5				1.7			16.7		5.2	4.8	3.3									
Any GI toxicity						0								13.5	11	11.1	27.3	20.5														16.7	0	13	14.5		0			20.8				12.5	
OTHER																																													
Auditory toxicity	0	0		0			36	0		0				0				0							0			0								0		0	0				0		
Visual toxicity	0	0		0				0		0				0				0							0			0								0		0	0				0		
Arthropathy	0	0	0	0	0			0	9.1	1.5	40.9	41.2	0	38.5	4	11.1	9.1	2.7	3.8	6.4	5.3	0						0	0							3.3	0		8.3	18.8	10	21.1	0	16.7	6.7
Rash						0					0		0					6.9			0	0			5	8		5	3.4			6.7	2.8	3.9	8.1					0				4.2	0
Discontinuation due to drug-related AE	0	0		4.5	0	0		0		1.5	13.6	7.8	0	0	3	0	0	12.3	0	29.3	0	0	0	2	0	0	0	2.5	1.7	0	0	3.3	0	20.8	4.8	0	0	0	8.3	0		10.5	7.1	0	0

Incidence: number of patients with an AE divided by the number of investigated patients in percent; Grey box: not reported or authors did not provide sufficient information about this AE

[a] Platelet count <100-150x10^9/L; [b] Absolute neutrophil count (ANC) <1.5x10^9/L (exception: Agarwal 1991, 1992 ANC <1.8x10^9/L); [c] ANC <0.5x10^9/L; [d] Varying definitions for elevations of transaminases alanine transaminase (ALT) and/or aspartate transaminase (AST); [e] Serum creatinine > upper limit of normal (ULN) or temporary discontinuation of iron chelator therapy

CT: clinical trial; OBS: observational study

Table 3: Case studies reporting iron chelator-related adverse events in young patients with haemoglobinopathies

Reported adverse events	Comments	Reported cases	References
DEFEROXAMINE (DFO)			
Local and systemic allergic reactions including urticaria, pruritus, hypotension, oedema	Preferably in high-dose regimens above 50 mg/kg per day; desensitisation procedure successful	8	(6, 119-124)
Skeletal dysplasia, growth failure, bone lesions and bone abnormalities	Associated with early DFO start before age 2-3 years and doses above 50 mg/kg per day; partially reversible on discontinuation	54	(78, 79, 125-134)
Sensorial reactions including hearing impairment, ototoxicity, deafness, optic neuropathy, visual loss	Associated with young patient age, high doses of 50-125 mg/kg/d and low serum ferritin; partially reversible on discontinuation	46	(81-84, 135-144)
Serious pulmonary syndrome including irregular respiratory rate, tachypnea, hypoxemia	Associated with high doses above 100 mg/kg per day intravenously	7	(145-147)
Acute renal failure	Including one fatal case	4	(85, 148, 149)
Systemic Yersinia enterocolitica infection including abdominal pain, anorexia, diarrhoea, high fever, bacteraemia	Including two fatal cases, DFO potential co-factor	28	(87, 150-164)
Pelvic osteomyelitis	Potential bacterial contamination from preparation and application of the drug	1	(165)
Acute bone marrow aplasia	Fatal; high dose therapy with 80 mg/kg per day; proposed mechanism: direct damage of the megakaryocytes	1	(40)
DEFERIPRONE (DFP)			
Agranulocytosis and severe neutropenia including high fever, malaise, general weakness	No fatalities; used DFP doses 40-105 mg/kg per day; recovery after DFP discontinuation; time to event in most cases between 2-15 months	7	(96, 166-170)
Arthropathies including severe bilateral knee pain, morning stiffness, joint warmth, swelling	DFP doses 40-80 mg/kg per day; recovery after DFP discontinuation	13	(6, 54, 102, 171)
Gastric bleeding and melena	-	1	(172)
Drug-induced systemic lupus erythematosus (SLE)	One fatal case reported; highly discussed with unconfirmed causality (54, 55)	2	(53)
Cardiac failure and myocardial fibrosis	Speculative causality	1	(173)
Posterior subcapsular opacity (PSC) with blurred vision	Speculative causality	1	(174)
Neurological symptoms and cerebellar signs including dizziness, axial hypotonia, nystagmus, impaired motor coordination, vision impairment	Two cases used very high DFP doses of 230 mg/kg/d; one case with 100 mg/kg per day, no other cause evident; all resolved after DFP discontinuation	3	(106, 107)
DEFERASIROX (DFX)			
Renal dysfunction including nephrolithiasis, elevated serum creatinine levels, proteinuria and Fanconi syndrome	DFX doses of 20-30 mg/kg per day; recovery after DFX discontinuation	44	(6, 109, 175-183)
Skin rash	Resolved after DFX discontinuation; positive rechallenge in one case; desensitisation protocol successful	5	(184-186)
Gastric and duodenal ulcers including nausea, vomiting, haematemesis, abdominal pain	Resolution after DFX discontinuation	1	(187, 188)
Ocular reactions including decreased vision, retinopathy, lens opacities	Retinopathy resolved after DFX discontinuation	4	(189, 190)
Sensorineural hearing loss	Recovery after DFX discontinuation	4	(191)
SIMULTANEOUS DEFERIPRONE + DEFEROXAMINE (SIM)			
Agranulocytosis	Some cases report resolution after G-CSF and DFP discontinuation	11	(99, 192, 193)

Table 4: Pooled incidences of frequently reported iron chelator-related adverse events in prospective clinical trials

	DFO		DFP		DFX		SEQ DFP+DFO		SIM DFP+DFO		SIM DFP+DFX	
	N	PI	N	PI	N	PI	N	PI	N	PI	N	PI
BLOOD AND LYMPHATIC SYSTEM DISORDERS												
Thrombocytopenia	37	0.0 (0.0-3.8)	197	4.4 (0.0-23.7)	80	0.0 (0.0-2.4)	37	0.0 (0.0-3.8)	52	1.0 (0.0-7.2)	15[a]	0.0 (0.0-21.8)
Neutropenia	109	2.3 (0.0-16.6)	425	7.1 (2.3-13.7)	214	0.5 (0.0-4.8)	37	0.0 (0.0-3.8)	102	5.3 (1.3-11.1)	63	6.4 (1.1-14.6)
Agranulocytosis	133	0.0 (0.0-0.7)	436	0.002 (0.0-0.7)	316	0.0 (0.0-0.4)	37	0.0 (0.0-3.8)	131	0.0 (0.0-1.7)	63	0.0 (0.0-2.5)
HEPATOBILIARY DISORDERS												
Increased liver enzymes	109	3.9 (0.0-26.3)	321	6.2 (2.1-11.9)	516	20.0 (5.8-39.4)	37	31.3 (16.4-48.2)	102	6.6 (2.0-13.3)	63	5.1 (0.5-12.7)
RENAL AND URINARY DISORDERS												
Elevated serum creatinine	-	NR	169	0.5 (0.0-2.8)	678	2.5 (1.1-4.2)	7[a]	0.0 (0.0-41.0)	90	2.2 (0.0-6.8)	63	3.7 (0.0-10.7)
Proteinuria	-	NR	142	0.6 (0.0-3.3)	107	0.0 (0.0-1.7)	-	NR	42[a]	3.4 (0.1-12.6)	15[a]	0.0 (0.0-21.8)
GASTROINTESTINAL DISORDERS												
Abdominal pain/ discomfort	30[a]	0.0 (0.0-11.6)	273	4.2 (1.3-8.0)	475	11.7 (3.3-23.6)	30[a]	6.7 (0.8-22.1)	42[a]	4.8 (0.6-16.2)	15[a]	0.0 (0.0-21.8)
Nausea	29	0.0 (0.0-6.5)	203	18.4 (7.7-31.9)	301	17.1 (5.5-32.8)	-	NR	31	35.3 (18.8-53.6)	-	NR
Vomiting	47	0.0 (0.0-3.9)	291	12.2 (4.7-22.2)	159	18.8 (11.2-27.6)	30[a]	3.3 (0.1-17.2)	19[a]	31.6 (12.6-56.6)	-	NR
Diarrhoea	30[a]	0.0 (0.0-11.6)	182	3.7 (0.7-8.2)	187	5.8 (0.2-16.3)	30[a]	3.3 (0.1-17.2)	-	NR	-	NR
OTHER												
Arthropathy	133	0.0 (0.0-0.7)	458	10.9 (2.8-22.2)	193	0.0 (0.0-1.5)	37	1.4 (0.0-10.1)	131	9.2 (0.6-23.7)	63	13.7 (5.8-23.8)
Rash	-	NR	112	2.4 (0.0-8.4)	313	3.7 (1.6-6.4)	-	NR	48[a]	0.0 (0.0-7.4)	63	2.3 (0.0-8.6)
Discontinuation (drug-related AE)	126	1.1 (0.0-4.7)	447	2.4 (0.2-5.9)	727	0.1 (0.0-0.8)	37	0.0 (0.0-3.8)	121	4.1 (0.0-13.1)	63	0.0 (0.0-2.5)

N: number of studied patients; PI: pooled incidence in percent with 95% confidence interval; NR: not investigated and/or reported in any study publication; [a] only one study reported this AE; if incidence is <0.001% only one decimal place is expressed (0.0%)

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