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ORIGINAL ARTICLE

Relative response of patients with myelodysplastic syndromes and other transfusion-dependent anaemias to deferasirox (ICL670): a 1-yr prospective study

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Abstract

Objectives/methods: This 1-yr prospective phase II trial evaluated the efficacy of deferasirox in regularly transfused patients aged 3–81 yrs with myelodysplastic syndromes (MDS; $n = 47$), Diamond–Blackfan anaemia (DBA; $n = 30$), other rare anaemias ($n = 22$) or β-thalassaemia ($n = 85$). Dosage was determined by baseline liver iron concentration (LIC). *Results:* In patients with baseline LIC ≥7 mg Fe/g dry weight, deferasirox initiated at 20 or 30 mg/kg/d produced statistically significant decreases in LIC ($P < 0.001$); these decreases were greatest in MDS and least in DBA. As chelation efficiency and iron excretion did not differ significantly between disease groups, the differences in LIC changes are consistent with mean transfusional iron intake (least in MDS: 0.28 ± 0.14 mg/kg/d; greatest in DBA: 0.4 ± 0.11 mg/kg/d). Overall, LIC changes were dependent on dose ($P < 0.001$) and transfusional iron intake ($P < 0.01$), but not statistically different between disease groups. Changes in serum ferritin and LIC were correlated irrespective of disease group ($r = 0.59$), supporting the potential use of serum ferritin for monitoring deferasirox therapy. Deferasirox had a safety profile compatible with long-term use. There were no disease-specific safety/tolerability effects: the most common adverse events were gastrointestinal disturbances, skin rash and non-progressive serum creatinine increases. *Conclusions:* Deferasirox is effective for reducing iron burden with a defined, clinically manageable safety profile in patients with various transfusion-dependent anaemias. There were no disease-specific adverse events. Once differences in transfusional iron intake are accounted for, dose-dependent changes in LIC or serum ferritin are similar in MDS and other disease groups.

Key words iron chelation; deferasirox; Exjade, ICL670; myelodysplastic syndromes; thalassaemia; Diamond–Blackfan anaemia

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Evidence regarding the efficacy of chelation therapy for the treatment of transfusional iron overload has largely been obtained based on experience in patients with β-thalassaemia major (1–3). In the USA, the myelodysplastic syndromes (MDS) are a frequent cause of transfusional iron overload, with an estimated 15 000 new cases each year (4). Recent data suggest that secondary iron overload is negatively associated with survival in transfusion-dependent MDS patients, with a hazard ratio of 1.3 for every 500 μg/L increase in serum ferritin level >1000 μg/L (5). Iron accumulation in the myocardium, a potential cause of death, is known to occur in MDS and related conditions in the absence of chelation therapy (6, 7). Deferoxamine (Desferal®, DFO, Novartis Pharma AG, Basel, Switzerland) induces urinary iron excretion and decreases levels of serum ferritin, liver iron (8) and heart iron (7) in MDS. However, the efficacy of iron chelation in MDS has not previously been compared directly with that of β-thalassaemia. Response to chelation therapy in MDS may not be the same as that in thalassaemia syndromes and other anaemias, as the degree of ineffective erythropoiesis and thus the magnitude of chelatable iron pools may differ. Furthermore, it is likely that transfusion requirements are more heterogeneous in MDS than in β-thalassaemia. Prospective comparisons of response to chelation therapy in MDS and thalassaemia would allow evidence-based therapeutic decisions about optimal dosing regimens.

DFO has been used clinically for more than 40 yr, although the difficulties in complying with treatment are well recognised. Subcutaneous infusions may be particularly troublesome in patients with MDS, who are typically elderly and may have decreased platelet counts or platelet dysfunction, leading to bruising at the infusion site. This has led to the need for a convenient oral chelator that can reduce or maintain body iron stores in regularly transfused patients who are iron overloaded. Deferasirox (Exjade®, ICL670, Novartis Pharma AG, Basel, Switzerland), a once-daily, oral iron chelator for the treatment of chronic iron overload, has been shown to be effective as monotherapy in maintaining or decreasing iron loading in β-thalassaemia (9–12). Evidence for the efficacy and tolerability of deferasirox in MDS and rare anaemias associated with transfusional iron overload also needs to be established. In this prospective, 1-yr multicentre study, the efficacy and safety of deferasirox have been investigated in MDS, Diamond–Blackfan anaemia (DBA) or other anaemias and in β-thalassaemia. Treatment response, according to dose and the rate of iron accumulation from blood transfusions, has been compared between the different anaemias, allowing inferences about optimal dosing schedules to be made. The relationship between change in liver iron concentration (LIC) and serum ferritin has also been compared between the different disease groups, enabling inferences to be made about the value of sequential ferritin monitoring in these conditions. This study constitutes the largest prospective trial ever undertaken on the effects of iron chelation in MDS, DBA and rare transfusion-dependent anaemias.

Patients and methods

Eligibility and enrolment procedures

Eligible patients included males and females aged ≥2 yr with a diagnosis of transfusion-dependent anaemia (excluding sickle cell anaemia), who required ≥8 blood transfusions per year and had a LIC ≥2 mg Fe/g dry weight (dw). Patients were required to have a life expectancy >1 yr, although no criteria for morphological or prognostic classification were included for MDS. Patients with β-thalassaemia, who were non-compliant (having taken <50% of the prescribed DFO dose in the preceding 12 months, with LIC >14 mg Fe/g dw), intolerant of, or inadequately responsive to DFO treatment, were also included. Those patients who had previously received deferiprone (Ferriprox®, Apotex Inc., Toronto, ON, Canada) discontinued treatment at least 28 d before initiating deferasirox therapy. Patients with serum creatinine levels above the upper limit of normal (ULN) at baseline were excluded from the trial. Further exclusion criteria and enrolment procedures, including provision of informed consent, were as previously described (9).

Treatment plan

Deferasirox was administered once daily as a suspension in water, 30 min before breakfast, for 1 yr. A dosing algorithm was used as previously reported (9), such that patients with baseline LIC of 2–3, >3–7, >7–14 and >14 mg Fe/g dw were assigned to deferasirox doses of 5, 10, 20 and 30 mg/kg/d, respectively. As per the protocol, blood transfusions were regularly administered during the study period according to the patients' requirements as judged by the investigators, with the aim of maintaining haemoglobin levels ≥8 g/dL. The amount of transfusional iron received by each patient was determined using the actual haematocrit of the transfused units or on an average haematocrit for similar units prepared in the same blood bank. Therapy was only interrupted at the discretion of the investigator for intercurrent illness, adverse events, or protocol-defined laboratory test results, such as increases in serum creatinine levels.

Determination of liver iron concentration

In 65.2% of patients, LIC was determined by ultrasound-guided percutaneous liver biopsy (13) using a single central laboratory (Clinique des Maladies du Foie, Centre Hospitalier Universitaire, Rennes, France) on samples transported as paraffin-embedded blocks (14). In paediatric or other patients where biopsy was considered impractical or contraindicated (e.g. because of thrombocytopenic bleeding disorders in patients with MDS), LIC was measured by the non-invasive technique of magnetic liver susceptometry using a superconducting quantum interference device (SQUID) (15) in three centres (Turin, Italy; Hamburg, Germany; Oakland, USA). At the end of the 1-yr treatment period, it was planned that all patients had a repeat LIC determination using the same methodology as the initial determination (liver biopsy or SQUID).

Calculation of iron intake and net body iron balance

Net body iron balance (also called total body iron excretion) was calculated based on the amount of red blood cells (RBCs) transfused (iron intake in mg = K_{in}) and on the changes in total body iron stores, calculated from LIC changes (baseline to study end) (16, 17) as described previously (9). Transfusional iron intake was calculated from the total amount of transfused blood, taking into account the haematocrit of each unit. In case of missing data, either the average haematocrit of the respective blood bank centre was used or one RBC unit was calculated to contain 200 mg of iron.

Efficacy assessments

The primary endpoint of this trial was the binary success criterion defined by maintenance or reduction of LIC based on patients' baseline LIC. For patients with baseline LIC of 2 to <10 mg Fe/g dw, success was defined as an LIC after 1 yr of 1 to <7 mg Fe/g dw (failure was <1 or ≥ 7 mg Fe/g dw). For patients with baseline LIC of ≥ 10 mg Fe/g dw, success was defined as a decrease in LIC after 1 yr of ≥ 3 mg Fe/g dw (failure as decrease in LIC <3 mg Fe/g dw). If no LIC determination was available at the end of study, these patients were considered as non-responders. Secondary efficacy endpoints included evaluation of the change in LIC and serum ferritin levels over time. The key secondary criterion was to show a significant reduction in LIC in patients with baseline LIC ≥ 7 mg Fe/g dw and available values at end of study. Chelator efficiency, which can be defined as the amount of iron excretion expressed as a percentage of the theoretical iron-binding capacity of chelator dose (18), was calculated for all doses pooled.

Safety assessments

Assessments for safety were performed at monthly intervals at a central laboratory (BARC Laboratories, Gent, Belgium), and included a complete blood count and differential, electrolytes, liver function tests, trace element and urinary protein/creatinine analyses. Electrocardiograms (ECGs) and ophthalmological and auditory examinations were performed every 3 months. For patients less than 16 yr of age, additional evaluations included assessment of growth rate and sexual development.

Statistical methods and sample size determination

The size of the trial was determined to demonstrate, at the one-sided alpha level of 0.025, that the success rate is $>50\%$ provided that the true rate is 65%. In order to achieve 90% power, 113 patients were required to be recruited. However, the planned sample was increased to 175 patients to improve the representation of disease subgroups. The CIs for the success rates were calculated using the normal approximation. Student's *t*-test was used to test reduction of LIC in patients with LIC ≥ 7 mg Fe/g dw at baseline. To evaluate the relationship between changes in serum ferritin and LIC, an exploratory linear regression model was fitted with change in LIC as dependent variable and the following covariates: serum ferritin change, disease group and serum ferritin change by disease group interaction. Further analyses were exploratory and described in the text.

Quality control, quality assurance and monitoring

This trial was conducted in accordance with Good Clinical Practices, as outlined in the International Conference on Harmonization guidelines. Institutional Review Board or Ethics Committee approval was obtained at each participating institution and written informed consent was obtained from all patients or their legal guardians prior to participation in any study procedures.

A Study Monitoring Committee comprising four investigators supervised the trial conduct and made decisions regarding dose adjustment for individual patients. An independent Programme Safety Board monitored the study.

Patients completing 1 yr on study were eligible to receive deferasirox as part of an ongoing extension study.

Results

Patient population

Of the 184 patients enrolled in this study, 47 had MDS, 30 had DBA, 22 had 'other anaemias' (aplastic anaemia, $n = 5$; α-thalassaemia and sideroblastic anaemia, $n = 3$ for both; myelofibrosis, pure red cell aplasia, pyruvate kinase deficiency, $n = 2$ for each; autoimmune haemolytic anaemia, Fanconi's anaemia, hereditary sideroblastic anaemia, erythropenia and unspecified anaemia, $n = 1$ for all) and 85 had β-thalassaemia (Table 1). MDS patients were, on an average, older than the other disease groups. The proportion of patients with LIC determined by biopsy was 78.8% for β-thalassaemia, 46.8% for MDS and 56.7% for DBA.

In this study, LIC values obtained by SQUID were, on an average, >50% lower than those obtained by biopsy (mean baseline LIC 9.5 ± 5.4, $n = 46$ vs. 21.9 ± 10.3, $n = 101$, respectively). These observations are consistent with a cross-validation substudy that found a similar discordance in some patients whose LIC was determined using both methods (overall LIC by SQUID was half that of LIC by biopsy) (19). As a result, patients with LIC assessed by SQUID may have been assigned to a lower dose of deferasirox than if they had received a biopsy. Based on results from the cross-validation substudy, for the purposes of this analysis, LIC values obtained by SQUID have been multiplied by a factor of two to correct for the discrepancy in LIC values obtained from SQUID compared with biopsy. Based on this correction, 93% of patients had baseline LIC ≥7 mg Fe/g dw. Of these patients, 92% had been treated with 20 or 30 mg/kg/d, while the remainder had been assigned to lower doses based on their baseline SQUID value.

Patient exposure to treatment

Prior to enrolment, 135 patients (73.4%) had received iron chelation therapy with DFO and 24 patients (13.0%) had received deferiprone. Baseline LIC was comparable between disease groups.

Most of the patients (85.9%) were assigned to 20 or 30 mg/kg daily doses. Dose adjustments, mainly interruptions or decreases, were made in 89 patients (48.4%) and were primarily due to adverse events or based on defined laboratory test results. Four patients, originally assigned 5 or 10 mg/kg/d, were escalated to a higher dose after a mean of 37.4–38.0 wk.

Table 1 Baseline characteristics, exposure and disposition

	MDS ($n = 47$)	DBA ($n = 30$)	Other anaemias ($n = 22$)	β-Thalassaemia ($n = 85$)
Age, yr				
Mean	65.1	16.1	35.8	24.7
Range	20–81	3–42	4–80	4–59
Baseline LIC, mg Fe/g dw				
Mean	20.7	23.4	18.7	21.2
Range	4.8–51.3	4.6–42.7	8.6–40.4	2.3–59.0
≥7, %	89.4	96.7	100	92.9
Baseline serum ferritin, μg/L				
Mean	3343	3245	3144	4321
Range	537–9099	840–11 854	1077–7351	440–13 943
Average iron intake[1], mg/kg/d				
Mean	0.28	0.40	0.31	0.35
Range	0–0.52	0.13–0.63	0–0.61	0.11–0.8
Mean daily dose, mg/kg	20.0	23.6	21.9	23.8
5, %	8.5	3.3	–	2.4
10, %	14.9	10.0	4.5	9.4
20, %	25.5	26.7	45.5	25.9
30, %	51.1	60.0	50.0	62.4
Mean exposure, wk	38.6	51.6	46.8	51.2
Patients discontinued, %	38.3	3.3	22.7	9.4
Death	8.5	3.3	–	–
Withdrawal for safety	14.9	–	9.1	4.7
Withdrawal, other reasons[2]	14.9	–	13.6	4.7

[1]Two RBC units of blood/month = 0.263 mg/kg/d of iron (assuming that 1 unit = 185 mL packed RBC = 200 mg iron, and a patient weight of 50 kg); [2]Includes study drug no longer required and withdrawal of consent.

A total of 152 patients (82.6%) completed 1 yr of treatment, of whom 147 (79.9%) had baseline and end-of-study LIC measurements (101 by biopsy, 46 by SQUID). Of the 46 patients evaluated by SQUID, 15, 12, 4 and 15 were MDS, DBA, other anaemia and β-thalassaemia patients, respectively (53.6, 46.2, 23.5 and 19.7% of the respective populations).

Success rates

The overall success rate was 50.5% [n = 184, 95% CI (43.3, 57.8)]. However, excluding patients without a LIC assessment at end of study, the overall success rate was 63.3% [n = 147, 95% CI (55.5, 71.1)]. Success rates in the MDS, DBA, other anaemia and β-thalassaemia disease groups were 78.6% (63.4, 93.8), 53.8% (34.7, 73.0), 70.6% (48.9, 92.2) and 59.2% (48.2, 70.3), respectively, in patients with available LIC assessment at end of study (see Table 2 for sample sizes).

Changes in liver iron concentration

Table 2 shows changes in LIC in each disease group according to the initial dose received in patients with LIC measured at study end. The overall mean change in LIC in the 125 patients with baseline LIC ≥7 mg Fe/g dw who were treated with deferasirox 20 or 30 mg/kg/d was −6.0 ± 7.8 mg Fe/g dw ($P < 0.001$; 1-sample Student's t-test). The LIC decreases in these patients were also statistically significant in the MDS, DBA, other anaemia and β-thalassaemia disease groups [−9.9 ± 5.5 (n = 19), −3.7 ± 7.7 (n = 22), −3.8 ± 7.1 (n = 17) and −6.2 ± 8.2 (n = 67) mg Fe/g dw, respectively; $P < 0.001$ for MDS and β-thalassaemia, $P = 0.036$ for DBA and $P = 0.044$ for other anaemias]. A separate pooled analysis of all patients evaluated by SQUID (uncorrected) or biopsy demonstrated LIC changes of −1.9 ± 3.8 and −3.9 ± 4.4 mg Fe/g dw, respectively, for patients on 20 mg/kg/d and −3.6 ± 2.3 and −7.0 ± 8.5 mg Fe/g dw, respectively, for patients on 30 mg/kg/d. Changes in LIC over 1 yr were categorised as increase vs. no increase, which is independent of the absolute magnitude of change. All patients (19/19) with MDS who received 20 or 30 mg/kg/d had a reduction in LIC, while 44% (4/9) of the patients who were treated with 5 or 10 mg/kg/d also had a reduction. This compares with 55% (12/22) and 25% (1/4) of patients with DBA, respectively, the group which had highest iron intake during study.

Chelator efficiency was not statistically significantly different when compared across disease groups ($P = 0.19$; Table 2) or dose ($P = 0.24$, linear model with dose and disease group as main effects).

Changes in serum ferritin

Effects on mean serum ferritin levels over time paralleled the dose-dependent changes in LIC (Table 2). A correlation was observed between changes in serum ferritin and LIC, which was consistent across disease groups (correlation coefficient = 0.59, $P < 0.001$; Fig. 1). Change in ferritin was the only covariate which had a statistically significant effect on change in LIC ($P < 0.001$). Thus, the change in serum ferritin in relation to change in LIC follows a similar relationship for all disease groups treated with deferasirox. Monthly monitoring of serum ferritin levels also revealed a similar dose–response pattern in the MDS and β-thalassaemia groups: levels increased with deferasirox 5 mg/kg/d and decreased with deferasirox 30 mg/kg/d, with doses of 10 and 20 mg/kg/d generally showing intermediate effects. Although the number of patients receiving deferasirox doses of 5 and 10 mg/kg/d was small, an

Table 2 Changes in LIC and serum ferritin by initial dose and disease group (for patients with end-of-study LIC assessment, n = 147)

Initial dose, mg/kg/d	Change in iron burden (based on available values)	MDS (n = 28)	DBA (n = 26)	Other anaemias (n = 17)	β-Thalassaemia (n = 76)
5	Patients	3	1	0	1
	Change in serum ferritin, μg/L	2620 ± 2473	2473	–	2071
	Change in LIC, mg Fe/g dw	7.4 ± 4.9	7.6	–	11.4
10	Patients	6	3	0	8
	Change in serum ferritin, μg/L	196 ± 1097	1084 ± 392	–	1116 ± 642
	Change in LIC, mg Fe/g dw	−3.4 ± 5.6	5.7 ± 6.2	–	6.5 ± 3.2
20	Patients	7	7	8	17
	Change in serum ferritin, μg/L	−410 ± 1632	−364 ± 1002	−894 ± 957	385 ± 876
	Change in LIC, mg Fe/g dw	−10.7 ± 5.2	−4.6 ± 6.6	−3.2 ± 7.0	−1.1 ± 4.2
30	Patients	12	15	9	50
	Change in serum ferritin, μg/L	−1581 ± 1653	−143 ± 1328	−443 ± 1906	−1019 ± 1651
	Change in LIC, mg Fe/g dw	−9.4 ± 5.9	−3.2 ± 8.4	−4.4 ± 7.6	−8.0 ± 8.5
All	Chelation efficiency, %	33.9 ± 20.0	26.7 ± 16.1	26.6 ± 15.0	26.7 ± 12.3

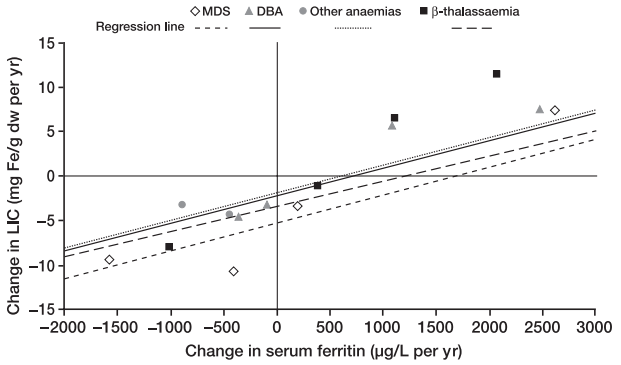

Figure 1 Separate regression lines derived from a linear model for each disease are shown in this figure together with symbols indicating the mean changes in LIC and ferritin by disease group and dose (as summarised in Table 2). When analysing the data across disease groups (regression line not shown), an overall LIC change over 1 yr is predicted as −3.36 + 0.003 times change in ferritin (Pearson's correlation coefficient = 0.59). Based on this linear model, a reduction in ferritin of 1000 μg/L predicts a reduction of approximately 6 mg Fe/g dw in LIC.

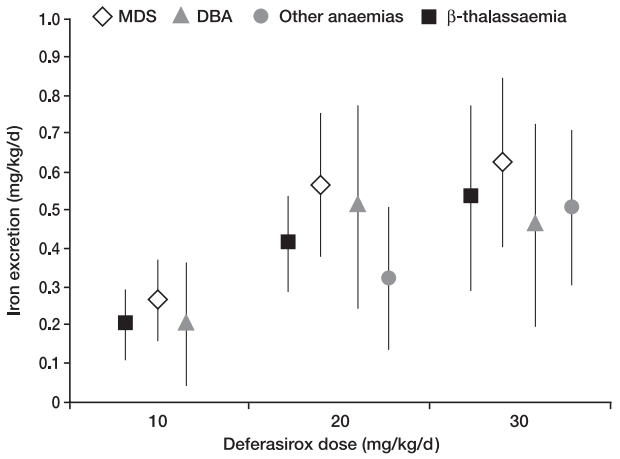

Figure 2 Iron excretion across dose and disease groups. The average iron excretion in mg/kg/d (±SD) is shown by disease group for doses above 5 mg/kg/d. There is a dose effect on iron excretion ($P < 0.001$), with no statistically significant difference in disease groups ($P = 0.14$). The overall average iron excretion is 0.22, 0.44 and 0.53 mg/kg/d for doses of 10, 20 and 30 mg/kg/d, respectively.

increase in LIC and serum ferritin levels was generally noted (Table 2). In contrast, patients receiving doses of 20 and 30 mg/kg/d generally experienced maintenance or reduction of iron burden.

Outcome of chelation by disease group: impact of blood transfusion and dose

Average iron intake per kilogram of body weight varied widely both within and between disease groups (Table 1). On an average, patients with MDS had the lowest transfusional iron intake (0.28 mg/kg/d), while those with DBA had the highest (0.40 mg/kg/d). These differences in transfusional iron intake were also reflected in the proportions of patients having the lowest transfusional iron intake, with 53% of MDS patients, but only 20% of DBA patients requiring <0.3 mg/kg/d. At 20 and 30 mg/kg/d, deferasirox stabilised or reduced mean LIC and serum ferritin levels across a variety of transfusion-dependent anaemias (Table 2). However, changes in LIC were most pronounced in MDS (−9.4 mg Fe/g dw at 30 mg/kg/d) and least pronounced in DBA (−3.2 mg Fe/g dw at 30 mg/kg/d) and paralleled the relative changes in serum ferritin of −1581 and −143 μg/L, respectively. When including dose, iron intake category, disease group and the interaction of iron intake and disease group into an exploratory linear regression model, only dose ($P < 0.001$) and iron intake category ($P < 0.01$) had a statistically significant effect on change in LIC ($P = 0.15$ for disease group, $P = 0.61$ for interaction term). The same was observed when evaluating iron excretion (mg/kg/d) as the dependent variable, with no difference between disease groups but a statistically significant dose effect ($P < 0.001$, Fig. 2). Furthermore, iron-chelating efficiency is essentially the same in MDS and other patient groups (Table 2). These results therefore show that in addition to dose, the degree of transfusional iron intake is a key factor governing the outcome of iron chelation therapy across different diseases.

Safety

Deferasirox treatment was associated with a defined safety profile that was clinically manageable with regular patient monitoring. Dose was temporarily interrupted in 24 (51.1%), 7 (23.3%), 10 (45.5%) and 30 (35.3%) patients, and adjusted on at least one occasion in 28 (59.6%), 9 (30.0%), 14 (63.6%) and 38 (44.7%) patients in the MDS, DBA, other anaemia and β-thalassaemia groups, respectively. Dose adjustments and interruptions were primarily due to adverse events or based on laboratory test results and had little impact on the overall exposure to deferasirox, as shown by the overall relative dose intensity (dose during study divided by initial dose) of 0.95. The proportions of patients who permanently discontinued treatment are shown in Table 1. Five deaths were reported during the study (four patients with MDS and one with DBA); three were due to a combination of neutropenia and sepsis [two patients had neutropenia at study entry (including the patient with DBA), and one developed neutropenia following chemotherapy with 5-azacytidine], one was due to pulmonary embolism and one was due to cardio-respiratory arrest. None of the deaths were considered by the independent Program Safety Board to be related to administration of study drug.

The most common adverse events with a reported relationship to study drug were transient gastrointestinal events in 45.6% of patients, including abdominal pain, nausea, vomiting, diarrhoea and constipation, as well as skin rash in 8.7% of patients. These symptoms rarely required prolonged dose adjustment or interruption. Increases in serum creatinine >33% above baseline were observed in 73 patients (39.7%), most frequently at doses of 20 and 30 mg/kg/d. These increases were typically seen at the start of treatment, were non-progressive and generally remained within the normal range. No patient had a progressive increase in serum creatinine and no patient developed a serum creatinine level that was >2 times the ULN. Increases in serum creatinine led to dose reductions in 32 patients (17.4%; all treated at 20 or 30 mg/kg/d), and contributed to discontinuation in four patients (2.1%). Serum creatinine levels declined following dose reduction in 14 patients and were non-progressive in the remaining patients. Elevated alanine aminotransferase (ALT) levels (>5 times the ULN at ≥2 consecutive postbaseline visits) were observed in 14 patients (7.6%), all but one of whom had elevated levels at baseline. At baseline, median ALT values were 18, 23, 39 and 60 U/L in the four dose groups, respectively, with the highest values observed in patients with the highest LIC who then received the highest deferasirox dose. At study end, the overall median changes in ALT (61, 19, −6 and −20 U/L, respectively) corresponded to the observed iron accumulation, iron balance and iron reduction observed with deferasirox doses of 5, 10, 20 and 30 mg/kg/d, respectively. No patient underwent dose reduction/interruption or discontinued because of increases in transaminase levels.

There were no cases of arthralgia considered by the investigators to be related to study drug. Deafness, hypoacusis or sudden hearing loss was reported in five patients, two cases of which (1.1%) were considered by the investigators to be possibly related to study drug. Cataract formation was reported as an adverse event in two patients (1.1%); both cases were considered by the investigators to be unrelated to study drug.

In total, nine patients with a normal absolute neutrophil count (ANC) at study start developed neutropenia (ANC $< 1.50 \times 10^9$/L at ≥2 consecutive postbaseline visits) during the study (three with MDS, two with DBA, three with another anaemia and one with β-thalassaemia). The patient with β-thalassaemia had an ANC of approximately 1.0×10^9/L on two occasions, which normalised without either dose interruption or reduction, making a relationship to study drug extremely unlikely. There were no cases of neutropenia, agranulocytosis or thrombocytopenia considered by the investigators to be related to study drug. There were no clinically significant changes in serum copper and zinc levels. A single episode of QT prolongation, not assessed as drug related, occurred in association with hypocalcaemia in a patient with β-thalassaemia. Paediatric growth and development proceeded normally, although the small number of paediatric patients and the absence of a comparator group do not allow definitive conclusions.

Discussion

This is the first study to compare the response to iron chelation therapy in MDS, DBA and other rare anaemias with that seen in β-thalassaemia. Treatment with deferasirox resulted in a similar pattern of dose-dependent iron excretion in patients with MDS, rare anaemias and β-thalassaemia (Fig. 2). This is consistent with the similar efficiency of iron chelation observed across each of these disease groups (Table 2).

The influence of transfusional iron intake on iron balance is consistent with the differences in LIC changes across the different disease groups. Patients with MDS, who had the lowest mean iron intake, also showed the largest dose-dependent reductions in LIC. Conversely, patients with DBA, who had the highest average transfusional iron intake, showed the smallest reductions in LIC. Therefore, provided the differences in transfusional iron loading rate are accounted for, the response to chelation with deferasirox is similar across the different types of transfusion-dependent anaemia studied.

Patients with β-thalassaemia had higher LIC values at study start compared with a recent study (9). This is likely because β-thalassaemia patients enrolled in this study were selected on the basis of the previous poor chelation with DFO, whereas previously compliant β-thalassaemia patients were included in the published study. Nevertheless, the response to treatment with deferasirox is similar in both studies.

The change in serum ferritin over time correlated with changes in LIC across all disease groups (Fig. 1). This is in line with previous findings in patients with β-thalassaemia treated with DFO or deferasirox (9, 20). As LIC has been shown to accurately predict total body iron levels (16), these findings support the use of regular serum ferritin assessments for the monitoring of deferasirox therapy. Thus, while a single serum ferritin level has limitations for the accurate prediction of total body iron burden, the trend in ferritin levels with deferasirox treatment correlates with the change in LIC values. Monthly changes in serum ferritin showed a similar trend across all the disease groups studied, suggesting that the chelatable iron pools in the liver and their relationship to changes in serum ferritin are similar in patients with MDS and β-thalassaemia. Thus, a downward trend in serum ferritin levels with deferasirox therapy is likely due to a decrease in body iron burden. However, we

acknowledge the large variability in serum ferritin observed in this study. The high SDs associated with mean serum ferritin change (Table 2) show that even at a deferasirox dose of 30 mg/kg/d, some individual patients may not experience a reduction in serum ferritin. Despite this variability, the overall results suggest that serum ferritin trends over time may be used to inform decisions about dose adjustment in MDS as well as β-thalassaemia and rare transfusion-dependent anaemias.

Deferasirox had a defined, clinically manageable safety profile across all disease groups and age ranges studied. As some patients with LIC assessed by SQUID may have been assigned to a lower deferasirox dose than if they had been assessed by biopsy, they may therefore have been at a lower risk of treatment-related adverse events. The most common adverse events considered to be treatment related were gastrointestinal symptoms, which were mild to moderate in severity and generally resolved spontaneously without the need for discontinuing treatment. In line with the findings from a previous study (9), the observed elevations in serum creatinine levels were dose-related, non-progressive and most responded to dose reduction or interruption. These findings provide no evidence for an increased risk of progressive renal dysfunction with deferasirox therapy in patients with MDS. Increases in serum creatinine level may reflect a haemodynamic effect on the kidney induced by the chelating activity of deferasirox; investigations are ongoing to explore the effects of deferasirox on the kidney. Meanwhile, deferasirox should be used with caution in patients with renal impairment and serum creatinine should be monitored monthly in all patients. The nine cases of neutropenia observed in this study were considered by the investigators to be related to the underlying disease. The observation that there were no drug-induced cases of neutropenia, agranulocytosis or thrombocytopenia is of particular importance in patients with rare anaemia who may have multiple and often progressive bone marrow defects in addition to ineffective erythropoiesis. Thus, there is no evidence in this study of disease-specific toxicity or tolerability issues with deferasirox and, in particular, no evidence of a toxicity profile that is unusual to patients with MDS.

As there are currently no published reports on intra- and inter-centre variability of SQUID, nor any published multicentre validation studies, in order to evaluate any potential bias in the results, we performed additional analyses evaluating the impact of the SQUID data on the overall findings of the study. Both this study and a previous cross-validation substudy (19) have observed that LIC values obtained using SQUID are approximately half those obtained by biopsy. As such, in this analysis LIC data from SQUID were multiplied by a factor of two, which was considered appropriate to correct for the discrepancy. Therefore, combined with the wet-to-dry weight conversion factor of 3.33 (21), the overall conversion factor was 6.66. A subsequent sensitivity analysis has demonstrated that the use of slightly different conversion factors [e.g. 2.17 (1/0.46) based on the previous study (19), or 2.3 based on the two average baseline LICs reported in this study] does not affect the significance of the results or, therefore, the overall conclusions that have been drawn. Importantly, the significance also remains unaffected if SQUID data are excluded from the analyses altogether and only LIC data derived from biopsy are included. Further, if changes in LIC over 1 yr are categorised as increase vs. no increase, which is independent of the absolute magnitude of change, all patients with MDS and 55% of DBA patients who received 20 or 30 mg/kg/d had a reduction, while 44% of MDS patients and 25% of DBA patients who were treated with 5 or 10 mg/kg/d also had a reduction. It can therefore be concluded that despite the known limitations of the SQUID technique and the lack of published validation studies, inclusion of these data does not introduce undue bias into the overall findings of this study.

In conclusion, this 1-yr prospective trial shows that iron-overloaded patients with MDS, DBA and other rare anaemias respond to deferasirox in a similar dose-dependent manner as patients with β-thalassaemia, both with respect to efficacy and safety parameters. Changes in serum ferritin and LIC correlated, supporting the use of regular serum ferritin assessments to monitor deferasirox therapy. Deferasirox dosing should be guided by the therapeutic goal, accounting for both the existing iron burden and ongoing transfusional iron loading. The availability of a convenient, once-daily, oral iron chelator that has predictable, dose-dependent effects on iron balance and a defined, clinically manageable safety profile across a range of transfusion-dependent anaemias, including MDS, should allow a greater number of regularly transfused patients to gain benefit from iron chelation therapy.

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Author statement

JP, CR, RG, GS, EJN, EV, MDC, NO, AP, MJC, DS, NG, GT, JM, PG, JK, GQ, MJ, GLF, MS, HC, LD, MDP, MC and GA served as investigators on this trial, enrolling patients. They also reviewed and contributed their comments on this manuscript. CR, RG, GS and EJN served as Study Monitoring Committee members overseeing the conduct of the trial. DA, BR, IG and JMF coordinated the design and execution of the trial and contributed to the analysis of the trial data. JP/BR drafted the manuscript. IG served as the trial statistician.

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Supplementary Material

The following supplementary material is available for this article:

Appendix S1. Participating centres and investigators

This material is available as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.1600-0609.2007.0985.x

(This link will take you to the article abstract).

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