Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias

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The online version of this article has a Supplementary Appendix.

ABSTRACT

Background
Following a clinical evaluation of deferasirox (Exjade®) it was concluded that, in addition to baseline body iron burden, ongoing transfusional iron intake should be considered when selecting doses. The 1-year EPIC study, the largest ever investigation conducted for an iron chelator, is the first to evaluate whether fixed starting doses of deferasirox, based on transfusional iron intake, with dose titration guided by serum ferritin trends and safety markers, provides clinically acceptable chelation in patients (aged ≥2 years) with transfusional hemosiderosis from various types of anemia.

Design and Methods
The recommended initial dose was 20 mg/kg/day for patients receiving 2-4 packed red blood cell units/month and 10 or 30 mg/kg/day was recommended for patients receiving less or more frequent transfusions, respectively. Dose adjustments were based on 3-month serum ferritin trends and continuous assessment of safety markers. The primary efficacy end-point was change in serum ferritin after 52 weeks compared with baseline.

Results
The 1744 patients enrolled had the following conditions; thalassemia (n=1115), myelodysplastic syndromes (n=341), aplastic anemia (n=116), sickle cell disease (n=80), rare anemias (n=43) and other transfused anemias (n=49). Overall, there was a significant reduction in serum ferritin from baseline (-264 ng/mL; $P<0.0001$), reflecting dosage adjustments and ongoing iron intake. The most common (>5%) adverse events were gastrointestinal disturbances (28%) and skin rash (10%).

Conclusions
Analysis of this large, prospectively collected data set confirms the response to chelation therapy across various anemias, supporting initial deferasirox doses based on transfusional iron intake, with subsequent dose titration guided by trends in serum ferritin and safety markers (*clinicaltrials.gov identifier: NCT00171821).*

Key words: transfusion medicine, iron chelation therapy, transfusion-dependent anemias.

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Introduction

Chronic iron overload is a serious complication of the repeated blood transfusions that are necessary for the treatment of patients with blood disorders such as thalassemia, sickle cell disease (SCD), myelodysplastic syndromes (MDS) and various other rare anemias, including aplastic anemia (AA). Without chelation therapy, excess iron accumulates in the body, leading to organ failure, particularly of the liver, heart and endocrine glands.[1,2] Following extensive clinical research in the management of iron overload, patients with thalassemia major receiving effective chelation therapy were found to have significant improvements in survival.[3] Preliminary data also suggest a potential survival benefit in lower-risk MDS patients receiving chelation therapy.[4,5]

In prior studies evaluating the efficacy and safety of deferasirox, dosing was based on baseline liver iron concentration (LIC) as assessed by either liver biopsy, superconducting quantum interference device (SQUID) or magnetic resonance imaging (MRI).[6-10] Biopsies are uncomfortable for the patient, particularly the elderly, and can lead to complications such as bleeding and infection, especially in MDS or AA patients with hemostatic impairment.[11,12] The consistency of results obtained from studies measuring the accuracy of LIC by SQUID is generally poor, with the underestimation of SQUID-determined LIC compared with biopsy-determined LIC being a critical factor.[13] Measurement of LIC by MRI is not used routinely as it requires special software and expertise and is often unavailable or relatively expensive in many regions worldwide. Hence, serum ferritin concentration remains a convenient, less expensive and widely used way of assessing body iron and, when followed serially, is a suitable alternative marker of trends in body iron burden as significant correlations between changes in LIC and serum ferritin have been identified in various types of anemia.[6,9,14] *Post-hoc* analyses of 1-year phase III deferasirox data suggested that, in addition to baseline LIC, ongoing transfusional iron intake is an important factor when selecting initial doses and making dose adjustments during the course of iron chelation therapy.[15] This is particularly important as the average transfusional iron intake in patients with thalassemia, MDS and SCD varies considerably; thus, the duration and rate of iron loading should also be considered.[9,10,15]

The multicenter Evaluation of Patients' Iron Chelation with Exjade (EPIC) study is the first prospective study to evaluate whether the practical approach of fixed starting doses of deferasirox, based on ongoing iron intake from blood transfusions, followed by subsequent dose titration every 3 months according to serum ferritin trends and safety markers, could provide effective chelation as assessed by a decline in serum ferritin. EPIC is the largest prospective study conducted on an iron chelator to date, providing data on diverse and large cohorts of iron-overloaded patients with thalassemia and other rare transfusion-dependent anemias.

Design and Methods

Inclusion and exclusion criteria

Male or female patients (aged ≥2 years) with transfusional iron overload (independently of the underlying condition) as shown by a serum ferritin level of 1000 ng/mL or more, or less than 1000 ng/mL but with a history of multiple transfusions (>20 transfusions or 100 mL/kg of red blood cells) and R2 MRI-confirmed LIC of or exceeding 2 mg of Fe/g dry weight (dw), were eligible for inclusion. Pediatric patients had to be of sufficient weight to receive the smallest strength tablet at their allocated dose (i.e. 125 mg). Patients with levels of alanine aminotransferase (ALT) above 300 U/L, uncontrolled systemic hypertension, serum creatinine above the upper limit of normal (ULN), a history of nephrotic syndrome, a previous history of clinically relevant ocular toxicity related to iron chelation, systemic diseases (cardiovascular, renal, hepatic) or any surgical or medical condition that could affect absorption of deferasirox were excluded from the study. Patients were also excluded if they had been treated with systemic or topical investigational drugs within the preceding 4 weeks or 7 days, respectively, or a had a history of drug or alcohol abuse within the past 12 months or a history of non-compliance to medical regimens. Patients (or parents/guardians) provided written, informed consent before entering the study. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. A Study Monitoring Committee supervised the trial conduct and made decisions regarding exceptional dose adjustments for individual patients. This study was conducted between April 2005 and June 2008.

Study design

EPIC was a prospective, 1-year, multicenter, open-label phase IIIb trial conducted by 136 investigators across 23 countries. Patients previously receiving deferiprone discontinued treatment at least 28 days before entering the study (washout period) but could switch to deferoxamine during this time. Patients were permitted deferoxamine until 1 day immediately prior to study entry.

The starting dose of deferasirox was individualized based on the frequency of blood transfusions. The recommended initial dose was 20 mg/kg/day for patients receiving approximately 2-4 units of packed red blood cells/month (7-14 mL/kg/month for a body weight of ~60 kg, equivalent to 0.3-0.5 mg/kg/day). An initial dose of 30 mg/kg/day could be considered for patients receiving blood transfusions more frequently and a reduced dose of 10 mg/kg/day could be considered for patients receiving blood transfusions less frequently. Dose increases were recommended in patients with baseline serum ferritin values of more than 500 ng/mL and demonstrating an increasing trend or with baseline serum ferritin values of more than 1000 ng/mL with no downward trend after 3 months. The increasing or decreasing trends were judged by the individual investigators. Specific dose adjustment recommendations were provided based on continuous assessment of safety markers including changes in serum creatinine, urinary protein:urinary creatinine ratio, liver function tests, development of skin rash, auditory and ocular disturbances, cytopenias and hypersensitivity reactions. These dose adjustments were recommended in steps of 5-10 mg/kg/day (in the range of 0-40 mg/kg/day). The dose could be escalated above 40 mg/kg/day in exceptional cases and this had to be approved on an individual basis by the Study Monitoring Committee. If serum ferritin levels were 500 ng/mL or below on two consecutive study visits, deferasirox treatment was suspended until levels returned to above 500 ng/mL.

Assessments

The primary efficacy end-point was the difference in serum ferritin concentration after 52 weeks of treatment compared with baseline. Serum ferritin was assessed at the beginning of the run-in period (days -35 to -1) and then every 4 weeks. Baseline serum ferritin was taken as the average of the available measurements within 28 days prior to the start of treatment. Secondary efficacy

end-points included the absolute change in serum ferritin levels from baseline to the end of the study in each disease cohort and evaluation of the relationship between dose adjustment regimens and transfusional iron overload. Safety was evaluated through the continuous monitoring and recording of adverse events and serious adverse events, as well as through routine laboratory assessments and physical examination. Records of study medication used, dosages administered, all dispensed and returned study medication and intervals between visits were kept during the study to determine treatment compliance.

Statistical methods

Power calculations indicated that a total sample size of 1541 patients was required to achieve a study power of 80% to demonstrate an overall one-sided α significance level of 0.025 that the mean value of serum ferritin decreased at the end of study compared to baseline. This was based on the assumption that the expected difference would be greater than 100 ng/mL and the standard deviation of the differences was 1400 ng/mL. Efficacy was assessed for the full analysis set, including all patients who had been successfully screened and started the study. If there was no serum ferritin value available at 52 weeks, the last available observation was used as the end of study assessment to calculate change from baseline (last-observation-carried-forward [LOCF] analysis) thus providing a robust, yet conservative end-point to cope with the intention-to-treat principle. Reported *P* values for the investigation are based on two-sided paired t-tests or the Kruskall Wallis test. All patients who received at least one dose of study medication were included in the safety analysis.

Results

Patients' characteristics

A total of 1744 patients were enrolled (Table 1). The underlying diseases necessitating chelation therapy were thalassemia (63.9%), MDS (19.6%), AA (6.7%), SCD (4.6%), other rare anemias (predominantly pure red cell aplasia and hemolytic anemias; 2.5%) and various conditions requiring transfusion, including malignant diseases [primarily acute myeloid leukemia (n=16) and congenital anemia; 2.8%]. Overall, 79.6% of patients (n=1389) completed 1 year of treatment. Treatment discontinuation rates (Figure 1) were lowest among thalassemia patients (9.4%), and highest among MDS patients (48.7%).

Baseline median serum ferritin levels in all subgroups were greater than 2500 ng/mL, which is a threshold known to be associated with significant negative outcomes (Table 1). The median length of time that patients had been transfusion-dependent was 9.0 years; however, this was longer in thalassemia patients (median 15.0 years). The duration of transfusion dependency was comparatively brief in MDS patients at a median of only 3.0 years. Although SCD patients had been transfusion dependent for a median of 10.0 years, the amount of blood received during the year prior to study entry was the lowest at 84±57 mL/kg. Most patients had received prior chelation therapy (Table 1); however, a large proportion of patients with AA, MDS and other anemias were chelation-naïve (68%, 48% and 61%, respectively).

Exposure to treatment

Overall, 27 patients (1.5%) started on 10 mg/kg/day, 1527 (87.6%) on 20 mg/kg/day and 189 (10.8%) on 30 mg/kg/day. The deferasirox dose was adjusted from the planned dose during the study in 1303/1744 patients (74.7%). Doses were increased in 672 patients (39%) at a median of 24 weeks after treatment initiation (range, 2-53). The first dose increase was performed at or less than 3 months of starting treatment in 82 patients (12.2%), between 3 and 6 months after starting treatment in 332 patients (49.4%), between 6 and 9 months in 158 patients (23.5%) and more than 9 months after starting treatment in 100 patients (14.9%). The most common dose increase was from 20 to 25 mg/kg/day (291 patients) (*Online Supplementary Figure S1*). Doses were reduced in 198 patients (11.4%) and temporarily interrupted in 425 patients (24.4%) due to laboratory abnormalities or adverse events. Fifteen patients (0.9%) discontinued treatment as they no longer required the study drug since their serum ferritin levels were 500 ng/mL or lower on two consecutive visits. Of the 1389 patients completing the study, 131 patients (9.4%) were receiving less than 20 mg/kg/day, 550 (39.6%) were receiving from 20 mg to less than 30 mg/kg/day, and 708 (51.0%) were receiving 30 mg/kg/day or more. Compliance was greater than 80% in 85.3% of the patients.

The mean actual dose received over the course of the study was 22.2±5.9 mg/kg/day for a median of 52.1 (range, 50.9-64.4) weeks. The mean dose and median change in serum ferritin during the 1-year treatment period by mean actual dose category are shown in Figure 2. The majority of patients (66%) in the thalassemia group received a higher daily deferasirox dose of from 20 mg to less than 30 mg/kg/day, whereas many patients (~50-60%) in all other disease cohorts received less than 20 mg/kg/day (*Online Supplementary Table S1*).

Transfusional iron intake

Over the course of the 1-year study, patients received a mean of 116.3±72.4 mL red blood cells/kg, equivalent to 0.41 mg/kg/day of iron. The mean transfusional iron intake was highest in the thalassemia, MDS and rare anemia groups (0.43, 0.42 and 0.49 mg/kg/day, respectively) and approximately 0.25 mg/kg/day in the SCD and AA groups (Table 2). Transfusional iron intake was significantly different across deferasirox dose cohorts in the total population of patients ($P<0.0001$, Kruskall Wallis test).

Effect of deferasirox on serum ferritin

LOCF data indicated that median serum ferritin levels decreased significantly from baseline by a median of 264 ng/mL ($P<0.0001$; Table 3) after 1 year of deferasirox treatment with a mean actual dose of 22.2 mg/kg/day and mean transfusional iron intake of 0.41 mg/kg/day. The extent of reduction in serum ferritin reflected the dosage adjustments applied at a median of 6 months after treatment initiation and iron intake over the course of the study. In patients with no initial drop in serum ferritin [i.e. requiring dose increases to above 20 mg/kg/day (n=9729 with a resulting mean actual dose of from 20 mg to less than 30 mg/kg/day over the course of the study], there was a significant reduction in serum ferritin of 198 ng/mL ($P=0.0130$) while receiving a mean transfusional iron intake of 0.44 mg/kg/day. Other patients (n=586) having drops in serum ferritin within 3 months received a mean actual dose of less than 20 mg/kg/day; at 12 months, median serum ferritin was significantly reduced in these patients (-279 ng/mL; $P<0.0001$) with a mean transfusional iron intake of 0.36 mg/kg/day. Patients receiving doses

of 30 mg/kg/day or more over the course of the study (n=149), had a more substantial reduction in serum ferritin of 882 ng/mL (P<0.0001) with a mean transfusional iron intake of 0.37 mg/kg/day. A similar pattern of serum ferritin changes, reflecting dose adjustments and mean iron intake, was seen across all underlying anemias. A similar response was noted in the full analysis set of patients including all patients who had been successfully screened and started the study (Figure 2A–D).

Safety

Adverse events, irrespective of their relation to the study drug, were reported in 1477 (84.7%) patients, with the most common being diarrhea (22.5%), rash (13.3%), abdominal pain (12.2%) and nausea (12.7%). The most common adverse events leading to discontinuation of the study drug were rash (n=22; 1.3%) and diarrhea (n=8; 0.5%). Adverse events considered to be drug-related by the investigator were reported in 877 (50.3%) patients; most of these events were of mild-to-moderate severity and resolved without treatment needing to be discontinued. The most common drug-related adverse events were diarrhea (14.4%), skin rash (10.0%), and nausea (7.7%) (Table 4). Drug-related adverse events were particularly common in patients with rare anemias (69.8%), other anemias (67.3%) and MDS (66.3%), with diarrhea being the most common adverse events in these patients. Deafness, hearing impairment or hypoacusis were reported as adverse events in 10 (0.6%) patients, irrespective of a relationship with the drug; two (0.1%) cases were considered by the investigators to be drug-related. Cataracts were reported as adverse events in two patients (0.1%); in both cases the adverse event was considered unrelated to the study drug. There were 90 reports of arthralgia, 10 of which (0.6%) were considered by the investigators to be drug-related. Serious adverse events, irrespective of causality, were reported in 336 patients (19.3%); the most common of these serious adverse events were pyrexia (n=51; 2.9%), abdominal pain (n=31; 1.8%), pneumonia (n=23; 1.3%) and sepsis (n=20; 1.1%). Drug-related serious adverse events (as assessed by the investigator) were reported in 30 patients (*Online Supplementary Table S2*), the most common being rash (n=7).

There were 42 (2.4%) deaths after the start of study treatment, none of which was considered, by the investigators, to be related to the study drug. Twenty-six deaths occurred in MDS patients, with the causes including hemorrhage (n=4) and septic shock (n=3) (*Online Supplementary Table S3*); five occurred in AA patients and were caused by sepsis (n=3), pneumonia (n=1) and rupture of a hepatic adenoma (n=1); four occurred in thalassemia patients and were due to heart failure (n=3) and septicemia following surgery (n=1), and seven occurred in patients with other rare anemias, in whom the causes were acute respiratory failure, bladder tumor, sepsis, heart failure, hemolytic anemia, progressive (malignant) disease and septic shock (all n=1).

Overall, 175 (10.0%) patients had two consecutive serum creatinine increases of more than 33% above base-

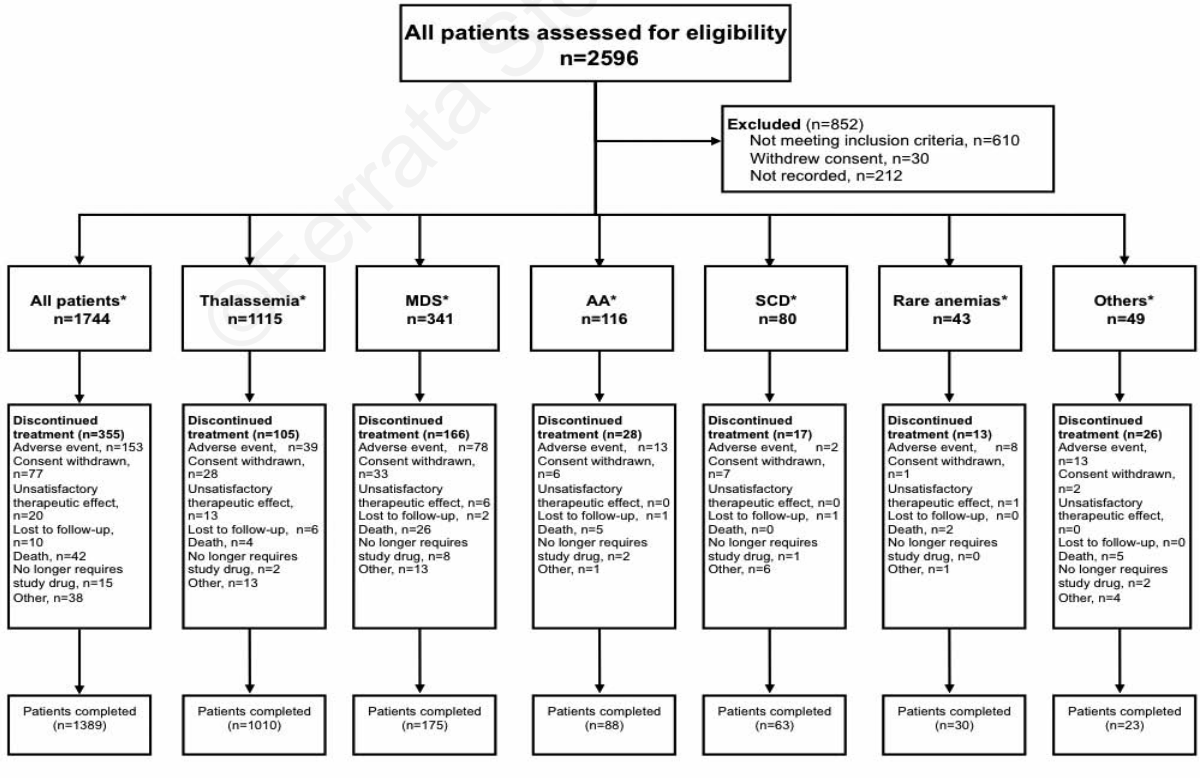

Figure 1. Disposition of patients. *All patients who were successfully screened and started treatment were included in the intent-to-treat analysis and last-observation-carried-forward (LOCF) analysis was used as the end of study efficacy assessment.

line and above the ULN; there was no progressive increase in mean serum creatinine (Table 4). The risk of having two consecutive serum creatinine increases of more than 33% above baseline and above the ULN was higher if the baseline serum creatinine concentration was high. The deferasirox dose was decreased within 30 days of the creatinine increase episode in 58/175 patients (33.1%) and temporarily interrupted in 19/175 patients (10.9%). Three patients discontinued treatment with the study drug because of increases in serum creatinine. Overall, 11 cases of drug-related proteinuria (0.6%) were reported during the study (thalassemia n=6; MDS n=3; AA n=1; rare anemias n=1). There was one case of acute renal failure assessed as a drug-related serious adverse event (*Online Supplementary Table S2*). Thirteen (0.7%) patients experienced two consecutive increases in ALT over ten times the ULN; however, levels were already elevated at baseline in 11 of these patients (Table 4). Dose adjustments based on elevated ALT at baseline and after deferasirox therapy were not performed in eight of these 11 patients; ALT levels resolved in six of these patients (ALT levels were less than the ULN by the last observation). Deferasirox dose was decreased and/or temporarily interrupted in five patients; the abnormality in ALT level resolved in two of these patients, two had initial signs of improvement, but ALT levels increased when deferasirox was resumed or increased and one patient had no improvement in ALT levels.

Discussion

The results of this large-scale study confirm the efficacy of deferasirox in reducing serum ferritin levels in patients with a wide range of transfusion-dependent anemias.[6,9,10] Serum ferritin was significantly decreased in the overall population and in all disease subgroups, except for SCD. The observed reduction in serum ferritin reflected the

Table 1. Demographic and baseline characteristics of the patients.

	Thalassemia (n=1115)	MDS (n=341)	AA (n=116)	SCD (n=80)	Rare anemias (n=43)	Others (n=49)	All patients (n=1744)
Mean age (range), years	18.2 (2-72)	67.9 (11-89)	33.3 (2-79)	23.9 (4-60)	39.5 (2-82)	50.3 (4-83)	30.6 (2-89)
Male:female, n	538:577	204:137	67:49	39:41	20:23	33:16	901:843
Race (Caucasian:oriental:other), n	468:594:53	309:30:2	32:80:4	18:15:47	30:11:2	38:10:1	895:740:109
History of hepatitis B and/or C, n (%)	275 (24.7)	11 (3.2)	8 (6.9)	19 (23.8)	4 (9.3)	2 (4.1)	319 (18.3)
Splenectomy, n (%)	395 (35.4)	13 (3.8)	–	22 (27.5)	12 (27.9)	6 (12.2)	448 (25.7)
Previous chelation therapy, n (%)							
DFO monotherapy	763 (68.4)	137 (40.2)	31 (26.7)	50 (62.5)	24 (55.8)	17 (34.7)	1022 (58.6)
Deferiprone monotherapy	12 (1.1)	14 (4.1)	–	1 (1.3)	1 (2.3)	–	28 (1.6)
DFO + deferiprone	245 (22.0)	24 (7.0)	6 (5.2)	10 (12.5)	5 (11.6)	2 (4.1)	292 (16.7)
Deferasirox	4 (0.4)	1 (0.3)	–	–	–	–	5 (0.3)
None	95 (8.5)	165 (48.4)	79 (68.1)	19 (23.8)	13 (30.2)	30 (61.2)	401 (23.0)
Median duration of previous ICT (25th, 75th percentiles), years	7.8 (2.9,16.1)	1.4 (0.5, 2.6)	2.2 (0.7, 4.4)	6.3 (3.2, 12.4)	1.1 (0.4, 7.0)	1.1 (0.5, 4.5)	5.7 (1.8, 13.5)
Median duration of transfusion therapy (25th, 75th percentiles), years	15.0 (8.0, 23.0)	3.0 (1.0, 4.0)	5.0 (2.0, 8.0)	10.0 (6.5, 17.0)	5.5 (2.0, 14.0)	2.0 (1.0, 6.0)	9.0 (3.0, 19.0)
Mean±SD transfusion sessions in year prior to study entry*	16.6±8.6	24.3±17.7	12.5±13.0	10.7±8.2	21.0±18.7	23.6±20.7	17.8±12.5
Mean±SD total volume of red blood cells transfused in year prior to study entry*, mL/kg	183±133	116±123	116±179	84±57	153±142	148±124	159±136
Median baseline serum ferritin, ng/mL (range)	3188 (462-22320)	2730 (951-9465)	3254 (908-25346)	3163 (579-12835)	3161 (568-13078)	3010 (1173-17053)	3135 (462-25346)

**Information on the number of transfusions is only available for the year prior to study entry. DFO, deferoxamine; ICT, iron chelation therapy.*

Table 2. Mean transfusional iron intake (mg/kg/day) by mean actual dose.

Mean average actual dose (mg/kg/day)	Thalassemia	MDS	AA	SCD	Rare anemias	Others	All patients
<20 Mean iron intake±SD, mg/kg/day (n)	0.38±0.28 (n=238)	0.38±0.4 (n=196)	0.21±0.18 (n=75)	0.28±0.24 (n=41)	0.43±0.55 (n=26)	0.42±0.34 (n=23)	0.36±0.34 (n=609)
≥20-<30 Mean iron intake±SD, mg/kg/day (n)	0.45±0.22 (n=736)	0.47±0.45 (n=135)	0.31±0.2 (n=41)	0.24±0.13 (n=39)	0.56±0.86 (n=17)	0.41±0.52 (n=12)	0.44±0.29 (n=984)
≥30 Mean iron intake±SD, mg/kg/day (n)	0.35±0.15 (n=141)	0.64±0.34 (n=9)	–	–	–	–	0.37±0.17 (n=150)
All patients Mean iron intake±SD, mg/kg/day (n)	0.43±0.23 (n=1115)	0.42±0.43 (n=340)	0.25±0.19 (n=116)	0.26±0.19 (n=80)	0.49±0.7 (n=43)	0.42±0.4 (n=35)	0.41±0.3 (n=1743)

dosage adjustments (which occurred relatively late at a median of 24 weeks) and mean iron intake over the course of the study. Patients who received an average actual deferasirox dose of less than 20 mg/kg/day during the study had a lower transfusional iron intake than those who received an average actual dose of from 20 to less than 30 mg/kg/day. Gradual dose up-titration was required in many patients to achieve a negative iron balance and a reduction in serum ferritin below baseline by 12 months. Patients who received an average actual dose of 30 mg/kg/day or more had the greatest reduction in serum ferritin levels, which reflects more appropriate dosing from the start of the study in patients with higher iron burden and transfusional iron intake. These data therefore support the clinical approach of initial dose selection of deferasirox according to transfusion requirements and highlights the need for prompt dose titration every 3 months based on trends in serum ferritin levels and markers of safety. Patients with thalassemia formed the largest cohort (63.9%) included in this study and had a significant (P<0.0001) reduction in serum ferritin levels, primarily driven by the significant reduction in the levels among patients who received an average actual dose of 30 mg/kg/day or more. Modest reductions in serum ferritin in the two lower dose groups may have resulted from delayed dose adjustments (median of 24 weeks) and the fact that dose increases were recommended, and not mandated, in the protocol at every 3 months. These findings are consistent with previous studies of deferasirox in thalassemia patients showing that higher doses are needed because of high iron burden and transfusional requirements in this population of patients.[16,17] The ESCALATOR study in heavily transfused and iron-overloaded patients with β-thalassemia showed that significant reductions in serum ferritin to below 2500 ng/mL were achieved following longer-term treatment with optimal doses of 25-30 mg/kg/day.[17]

Our study also enabled an evaluation of chelation therapy in reducing serum ferritin in large groups of patients with MDS, AA and other rare anemias, in whom studies have been limited to date.[18-20] Data from the 341 MDS patients enrolled demonstrated that a mean deferasirox

Table 3. Median (range) change from baseline in serum ferritin (ng/mL) by mean actual dose.

Mean actual dose (mg/kg/day)	Thalassemia	MDS	AA	SCD	Rare anemias	Others	All patients
<20							
Baseline	2356 (462-20788)	2535 (951-9193)	3263 (908-18635)	2615 (579-7274)	2572 (568-13078)	2976 (1173-17053)	2608 (462-20788)
Change from baseline*	-45 (-6010 to 9501) n=231	274 (-6040 to 6124) n=183	-970 (-11753 to 7883) n=75	-235 (-2315 to 2707) n=39	-846 (-4466 to 3939) n=25	-434 (-8846 to 4285) n=33	-279 (-11753 to 9501) n=586
P versus baseline*	0.2884	0.0012	<0.0001	0.4356	0.0174	0.1073	<0.0001
≥20-<30							
Baseline	3160 (480-22320)	2995 (1086-9465)	3238 (1129-25346)	3596 (1547-12835)	4248 (1321-10832)	3154 (1873-8067)	3165 (480-25346)
Change from baseline*	-93 (-7837 to 7933) n=732	-219 (-7125 to 14145) n=130	-884 (-15704 to 13894) n=40	-72 (-3728 to 2846) n=39	-771 (-4522 to 7064) n=17	-881 (-3509 to 2166) n=14	-198 (-15704 to 14145) n=972
P versus baseline*	0.2062	0.1730	0.2777	0.4161	0.4452	0.0543	0.0130
≥30							
Baseline	5093 (1326-16944)	4279 (1922-8980)	–	–	–	–	5048 (1326-16944)
Change from baseline*	-926 (-10282 to 7680) n=141	-638 (-1623 to 2580) n=8	–	–	–	–	-882 (-10282 to 7680) n=149
P versus baseline*	<0.0001	0.6266	–	–	–	–	<0.0001
All patients							
Baseline	3188 (462-22320)	2730 (951-9465)	3254 (908-25346)	3163 (579-12835)	3161 (568-13078)	3010 (1173-17053)	3135 (462-25346)
Change from baseline*	-163 (-10282 to 9501) n=1104	-253 (-7125 to 14145) n=321	-964 (-15704 to 13894) n=115	-225 (-3728 to 2846) n=78	-832 (-4522 to 7064) n=42	-620 (-8846 to 4285) n=47	-264 (-15704 to 14145) n=1707
P versus baseline*	<0.0001	0.0019	0.0003	0.2588	0.0275	0.0235	<0.0001

**Based on last-observation-carried-forward (LOCF) analysis. Presented serum ferritin values are median (range).*

dose of 19.2 mg/kg/day was associated with a significant reduction in serum ferritin ($P<0.05$). Data from the large groups with AA and rare anemias were also encouraging, indicating a reduction in serum ferritin from baseline with a mean deferasirox dose of 17.6 and 18.6 mg/kg/day, respectively. Many patients with MDS, AA and rare anemias were chelation-naïve despite being heavily iron overloaded, indicating a need for greater awareness of the potential impact of iron overload in these groups of patients.

SCD patients had received transfusion therapy for more than 50% of their lifetime, with elevated serum ferritin levels. The reduction in serum ferritin after 1 year of deferasirox was not statistically significant, possibly because of the small number of patients. In addition, serum ferritin levels can be affected by inflammatory processes,[21] which SCD patients are prone to as a consequence of sickling crises, and these may cause intra-patient variability in serum ferritin results.[10,22-24] Measurement of LIC by biopsy or MRI may, therefore, be a more reliable measure for monitoring tissue iron burden in these patients, as recommended in the UK guidelines.[23]

While assessment of LIC by biopsy provides a direct measurement of body iron, this invasive procedure does have limitations. MRI, although non-invasive, is not widely available worldwide. Serial measurements of serum ferritin provide a simple, generally reliable, indirect measure of total body iron which is accessible worldwide and inexpensive and has also been shown in several studies to correlate with LIC measurements in patients with thalassemia major.[6,14] The data reported in the present study indicate that serial measurements are useful for monitoring chelation therapy with deferasirox to alter doses according to ongoing iron loading through transfusion. The deferasirox prescribing information recommends that serum ferritin be monitored monthly to assess the patient's response to therapy and that the dose of deferasirox be adjusted if necessary every 3 to 6 months based on these trends.[25] Data from this trial are based on the pre-planned analysis of absolute change in serum ferritin from baseline. However, the clinical relevance of such changes may vary depending on a patient's baseline serum ferritin levels. It would be valuable to evaluate serum ferritin trends relative to grouped baseline serum ferritin values. These analyses are planned to be run in the near future.

The safety of deferasirox has been shown in patients with a variety of underlying anemias in a number of studies.[6,7,9,10] In the present study, deferasirox was generally well tolerated with a clinically manageable side-effect profile. The adverse events reported in this 1-year study were predominantly gastrointestinal disturbances and skin rashes, which are consistent with previous observations from deferasirox trials.[6-10] A recent analysis of data from four deferasirox studies showed that the safety profile of deferasirox in patients who received more than 30

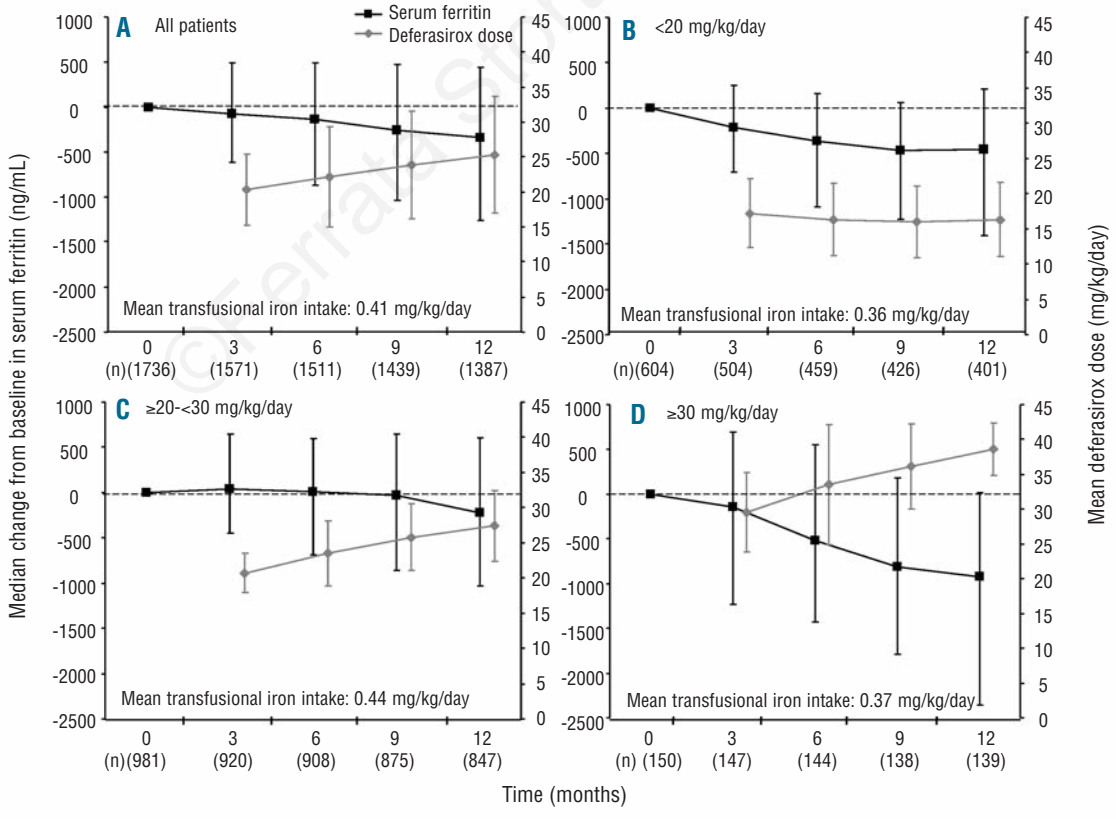

Figure 2. Mean actual deferasirox dose±SD (mg/kg/day) and median change in serum ferritin±25th and 75th percentiles (ng/mL) during the study by average actual dose categories in the full analysis set of patients. (A) All patients. (B) Patients on a dose <20 mg/kg/day. (C) Patients on a dose ≥20–<30 mg/kg/day. (D) Patients on a dose ≥30 mg/kg/day.

mg/kg/day is consistent with that of patients who received doses below 30 mg/kg/day.[26] Importantly this analysis also showed that there were no adverse events observed following escalation to over 30 mg/kg/day that were not observed at lower doses.[26] This is the first study to specifically assess the safety profile of deferasirox according to the underlying anemia in larger numbers of patients than previously reported[9] and the findings suggest that there may be differences in side-effect profiles between patients with different types of anemia. There was a higher incidence of drug-related adverse events and higher treatment discontinuation rates in patients in the MDS cohort than in patients with other underlying anemias, although this adverse event profile was consistent with data from previous studies in MDS patients.[9,27] This may be related to the risk of disease progression, pre-existing co-morbidities, concomitant medication use and the advanced age of patients with MDS. Drug-related adverse events were also more frequently reported in patients with rare anemias perhaps because the majority of patients were chelation-naïve and more prone to reporting mild symptoms such as diarrhea, nausea and abdominal pain. Evaluating adverse event frequency by underlying anemia and dose would, therefore, be of interest and warrants further analysis.

Increases in mean serum creatinine or liver transaminases were managed effectively in this large study and there were no progressive increases. Reported increases in these laboratory parameters were similar to those observed in previous studies irrespective of different dose interventions between trials, confirming the renal and hepatic safety profile of deferasirox across various types of anemias and at a range of doses.[6,9]

In conclusion, this large study is the first to support the clinical approach of using a specified starting dose of deferasirox based on transfusion requirements, and highlighting the need for timely individual dose titration every 3 months according to serum ferritin trends and markers of safety, underscoring the importance of early and prompt dose increases to achieve a therapeutic goal of reduction in serum ferritin. This study confirms that with appropriate dosing, deferasirox is generally well tolerated and effective in reducing serum ferritin levels in iron-overloaded, regularly transfused patients with a wide range of underlying anemias, including thalassemia, MDS, AA and other rare anemias. The results should provide clinicians using deferasirox with a framework for evaluating chelation requirements, using serum ferritin and safety markers, to make decisions on dose adjustments and tailoring deferasirox treatment to achieve therapeutic goals of reduction or maintenance of body iron levels.

Authorship and Disclosures

MDC drafted the manuscript. JP, AE-B, C-KL, JFS, ME, NG, SG, J-WL, LLC, K-HL, CR, AT, SLT, VV and AK served as investigators in this trial, enrolled patients, contributed to interpreting the data, reviewed the manuscript

Table 4. Safety results by underlying disease.

Adverse events, n (%)	Thalassemia (n=1115)	MDS (n=341)	AA (n=116)	SCD (n=80)	Rare anemias (n=43)	Others (n=49)	All patients (n=1744)
	Most common (>3%) drug-related adverse events						
Diarrhea	87 (7.8)	111 (32.6)	18 (15.5)	9 (11.3)	13 (30.2)	13 (26.5)	251 (14.4)
Skin rash	129 (11.5)	23 (6.7)	13 (11.2)	3 (3.7)	4 (9.3)	2 (4.1)	174 (10.0)
Nausea	42 (3.8)	45 (13.2)	26 (22.4)	5 (6.3)	9 (20.9)	8 (16.3)	135 (7.7)
Abdominal pain	54 (4.8)	26 (7.6)	7 (6.0)	1 (1.3)	6 (14.0)	3 (6.1)	97 (5.6)
Upper abdominal pain	25 (2.2)	25 (7.3)	7 (6.0)	5 (6.3)	4 (9.3)	2 (4.1)	68 (3.9)
Vomiting	20 (1.8)	26 (7.6)	10 (8.6)	3 (3.7)	4 (9.3)	3 (6.1)	66 (3.8)

Baseline creatinine, n (%)*	Thalassemia (n=1115)	MDS (n=341)	AA (n=116)	SCD (n=80)	Rare anemias (n=43)	Others (n=49)	All patients (n=1744)
	Patients with two consecutive serum creatinine increases >33% above baseline and ULN						
Low	3	3	–	–	–	–	6
Normal	37	75	28	2	7	11	160
High	–	7	1	–	1	–	9
Total	40 (3.6)	85 (24.9)	29 (25.0)	2 (2.5)	8 (18.6)	11 (22.4)	175 (10.0)

Baseline ALT, n (%)	Thalassemia (n=1115)	MDS (n=341)	AA (n=116)	SCD (n=80)	Rare anemias (n=43)	Others (n=49)	All patients (n=1744)
	Patients with two consecutive increases in ALT >10 x ULN						
Normal (<45 U/L)	1	1	–	–	–	–	2
High (>45 U/L)	6	–	2	1	1	1	11
Total	7 (0.6)	1 (0.3)	2 (1.7)	1 (1.3)	1 (2.3)	1 (2.0)	13 (0.7)

**Baseline creatinine levels were considered low, normal and high compared with the normal age– and gender–dependent range.*

and provided their comments on it. MDC, AE-B, C-KL, JS and AK served as Study Monitoring Committee members overseeing the conduct of the trial. DH and GD coordinated the execution of the trial and contributed to the analysis, interpretation, and reporting of the trial data. BR served as the trial statistician.

MDC and K-HL report receiving lecture fees from Novartis Pharmaceuticals. JP reports receiving consulting fees, research grant funding and lecture fees from Novartis Pharmaceuticals and consulting fees from Vifor International and Mundipharma. AE-B reports receiving research grant support, consulting fees and lecture fees from Novartis Pharmaceuticals and research support and honoraria from ApoPharma Inc. NG, SLT, AT and CR report receiving research grant support and lecture fees from Novartis Pharmaceuticals. LLC reports receiving research grant support and lecture fees from Novartis Pharmaceuticals and research grant support from ApoPharma Inc. VV reports receiving research grant support and lecture fees from Novartis Pharmaceuticals and research grant support from Government Pharmaceutical. AK reports receiving research grant support, consulting fees and lecture fees from Novartis Pharmaceuticals and consulting fees and lecture fees from Apotex Research Inc. C-KL reported receiving consulting and lecture fees from Novartis Pharmaceuticals. DH, GD and BR are full-time employees of Novartis Pharmaceuticals. No other potential conflicts of interests relevant to this article were reported.

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