Continued improvement in myocardial T2* over two years of deferasirox therapy in β-thalassemia major patients with cardiac iron overload

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ABSTRACT

Background
The efficacy of cardiac iron chelation in transfusion-dependent patients has been demonstrated in one-year prospective trials. Since normalization of cardiac T2* takes several years, the efficacy and safety of deferasirox was assessed for two years in patients with β-thalassemia major in the cardiac sub-study of the EPIC trial.

Design and Methods
Eligible patients with myocardial T2* greater than 5 to less than 20 ms received deferasirox, with the primary endpoint being the change in T2* from baseline to two years.

Results
Baseline myocardial T2* was severe (>5 to <10 ms) in 39 patients, and moderate-to-mild (10 to <20 ms) in 62 patients. Mean deferasirox dose was 33.1±3.7 mg/kg/d in the one-year core study increasing to 36.1±7.7 mg/kg/d during the second year of treatment. Geometric mean myocardial T2* increased from a baseline of 11.2 to 14.8 ms at two years (P<0.001). In patients with moderate-to-mild baseline T2*, an increase was seen from 14.7 to 20.1 ms, with normalization (≥20 ms) in 56.7% of patients. In those with severe cardiac iron overload at baseline, 42.9% improved to the moderate-to-mild group. The incidence of drug-related adverse events did not increase during the extension relative to the core study and included (≥5%) increased serum creatinine, rash and increased alanine aminotransferase.

Conclusions
Continuous treatment with deferasirox for two years with a target dose of 40 mg/kg/d continued to remove iron from the heart in patients with β-thalassemia major and mild, moderate and severe cardiac siderosis. *(Clinicaltrials.gov identifier: NCT 00171821)*

Key words: β-thalassemia major, cardiac iron overload, deferasirox, iron chelation, myocardial T2*.

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Introduction

Iron chelation therapy has markedly improved survival for many patients with β-thalassemia major; however, heart failure due to myocardial iron deposition has, until recently, been the leading cause of death.[1-3] Accurate measurement of cardiac iron levels is important as common assessment methods of total body iron alone, such as measurement of serum ferritin and liver iron concentration (LIC), do not reliably predict myocardial iron status.[4,5] This may be due to different rates of iron entry/clearance from cardiomyocytes and hepatocytes,[6] or other as yet unidentified factors. T2* cardiovascular magnetic resonance (CMR) provides rapid and direct assessment of cardiac iron content and is useful in evaluating cardiac responses to iron chelation therapy.[7,8] Myocardial tissue iron concentration has a non-linear relationship with T2*.[9] Myocardial T2* values below 20 ms indicate myocardial iron overload and values less than 10 ms are associated with an increased likelihood of heart failure and arrhythmia.[8] As such, based on myocardial T2* assessments, patients requiring intensive iron chelation can be identified and treated earlier in an attempt to avoid the mortality associated with heart failure.[3]

The efficacy of iron chelation therapy in reducing cardiac iron levels based on myocardial T2* assessments has been demonstrated in several prospective clinical trials; however, all had a treatment duration of up to a maximum of one year.[10-13] As iron clears more slowly from the heart than the liver,[6] normalization of myocardial T2* may take several years of iron chelation therapy. It is, therefore, essential that the long-term efficacy and safety of any such therapy is assessed prospectively. In the EPIC (Evaluation of Patients' Iron Chelation with Exjade) cardiac sub-study, deferasirox significantly improved geometric mean myocardial T2* from a baseline of 11.2 to 12.9 ms (+16%, $P<0.0001$) with significant concomitant improvements in both serum ferritin and LIC over one year.[13] Patients in the cardiac substudy of the EPIC trial have now received deferasirox therapy for two years in an extension to the core trial.

Design and Methods

The cardiac substudy of EPIC was a prospective, open-label, multicenter study conducted over a core period of one year. The study was extended, allowing continuous treatment to all patients who completed the one-year core study. LIC was assessed by magnetic resonance (MR) measurements of the transverse relaxation parameter R2, a method that demonstrates a high degree of sensitivity and specificity compared with biopsy LIC measurements.[14] R2 scans were performed using FerriScan (Resonance Health, Perth, Australia) according to standardized procedures at individual sites. A full description of the study design and inclusion/exclusion criteria has been previously published;[13] however, the key information relevant to this analysis is summarized here.

Patient recruitment and dosing schedule

Patients with β-thalassemia aged 10 years or over with myocardial T2* greater than 5 to less than 20 ms (indicating cardiac siderosis) and left ventricular ejection fraction (LVEF) of 56% or over as assessed by CMR were eligible for enrollment. In addition, serum ferritin levels of greater than 2,500 ng/mL, MR-assessed (R2) LIC greater than 10 mg Fe/g dry weight (dw) and a lifetime minimum of 50 transfused blood units were required. At the end of the core one-year study, patients were invited to enter an extension study for an additional year of treatment with deferasirox; those who chose not to continue the study did not have to provide a reason. Patients continued to receive deferasirox in the extension based on the last dose received in the core one-year study. Dose adjustments were based on serum ferritin trends (assessed at 3-month intervals), myocardial T2* assessments every six months and safety parameters (serum creatinine, transaminases and adverse events [AEs]). Dose increases up to 45 mg/kg/d were considered in patients with minimal worsening of cardiac T2* (≤33% from baseline) or no improvement in T2* (≤25% from baseline) provided that LIC was at least 3 mg Fe/g dw at the 6-monthly follow-up assessments. Dose increases beyond 40 mg/kg/d had to be approved by the Study Monitoring Committee and study sponsor. Patients were withdrawn from the sub-study and treated with appropriate standard of care if they had a decrease in cardiac T2* by more than 33% from baseline or a decrease in LVEF to between 50% and less than 56% with no improvement to 56% or more on a repeat assessment within three months of the initial assessment. The study was approved by the Independent Ethics Committee at each participating center, and all patients (or parents/guardians) provided written, informed consent before being allowed to enter the extension study. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Assessments

The primary efficacy endpoint of the extension trial was change in myocardial T2* from baseline (of the core one-year study) to two years. Myocardial T2* was assessed at baseline, then every six months. Secondary efficacy endpoints included change from baseline in LVEF and LIC after 24 months. Serum ferritin levels were also measured at baseline and then monthly until the end of the extension study. Safety was evaluated monthly through monitoring and recording of AEs and routine laboratory testing, including hematology, blood chemistry and urine renal function assessments. A history of hepatitis was recorded as part of the patient history without serological testing.

Statistical methods

The primary efficacy endpoint was assessed in all patients who entered the extension and who received the study medication. Myocardial T2* measurements reported at the end of the extension included patients who had their last CMR scan performed at month 18 or month 24 (using last-observation-carried-forward [LOCF] analysis). The second year LOCF value was also used for the analysis of LVEF, LIC and serum ferritin data. LVEF and LIC are presented as mean ± standard deviation (SD), serum ferritin is presented as median (range), and myocardial T2* as the geometric mean (anti-log of the mean of the log data) ± the coefficient of variation (CV), equivalent to the variance of the mean in log scale. The correlation between change from baseline in LIC *versus* cardiac T2* was assessed using Pearson's correlation coefficient and regression analysis. Safety was assessed in all patients who received at least one dose of study medication. Statistical significance was established using a paired Student's t-test at a two-sided α level of 0.05; this was based on the log-transformed evaluations for myocardial T2* assessments.

Results

Patients' characteristics

In total, 105 patients with cardiac siderosis completed

the one-year core sub-study.[13] Of these patients, 101 chose to enter the one-year extension (for whom data are presented) and their baseline characteristics at enrollment are shown in Table 1. Baseline myocardial T2* was greater than 5 to less than 10 ms (severe cardiac siderosis) in 39 patients (38.6%) and 10 to less than 20 ms (moderate-to-mild cardiac siderosis) in 62 patients (61.4%).

Deferasirox dosing

In patients who continued in the extension study, the mean (± SD) actual deferasirox dose received over the 2-year treatment period was 34.5±4.8 mg/kg/d; this was 33.1±3.7 mg/kg/d during the one-year core study increasing to 36.1±7.7 mg/kg/d during the one-year extension. In patients with severe cardiac siderosis (baseline myocardial T2* >5 to <10 ms), the mean dose over two years was 34.8±4.7 mg/kg/d (32.6±4.0 mg/kg/d during the core and 37.5±6.6 mg/kg/d during the extension) and in patients with moderate-to-mild cardiac siderosis (baseline T2* 10 to <20 ms), the mean dose over two years was 34.3±4.8 mg/kg/d (33.5±3.5 mg/kg/d during the core and 35.3±8.2 mg/kg/d during the extension). During the 2-year study, several dose increases to 40 mg/kg/d or over were prescribed; 63 (62.4%) patients received dose increases from 30 to 40 mg/kg/d, 28 (27.7%) received an increase from 35 to 40 mg/kg/d, 13 (12.9%) received an increase from 40 to 45 mg/kg/d and one patient received an increase from 40 to 50 mg/kg/d. At the end of the one-year core phase, 71 patients (70.3%) were receiving deferasirox doses of 40 mg/kg/d and 2 (2.0%) were receiving 45 mg/kg/d. At the end of two years, 54 patients (53.5%) were receiving 40 mg/kg/d, 10 (9.9%) were receiving 45 mg/kg/d and 2 were receiving 47 and 51 mg/kg/d, respectively (Figure 1).

Table 1. Patients' characteristics at baseline.

	Myocardial T2* >5 to <10 ms (n=39)	Myocardial T2* 10 to <20 ms (n=62)	All patients (n=101)
Mean age ± SD, years	21.4±5.9	20.1±8.0	20.6±7.3
Age group in years, n (%)			
10–<16	7 (17.9)	22 (35.5)	29 (28.7)
≥16	32 (82.1)	40 (64.5)	72 (71.3)
Male:female, n	17:22	31:31	48:53
Race (Caucasian:Oriental:other), n	15:23:1	18:39:5	33:62:6
History of hepatitis B and/or C, n (%)	12 (30.8)	16 (25.8)	28 (27.7)
History of splenectomy, n (%)	20 (51.3)	30 (48.4)	50 (49.5)
Previous iron chelation therapy, n (%)			
Deferoxamine monotherapy	23 (59.0)	45 (72.6)	68 (67.3)
Deferoxamine + deferiprone	16 (41.0)	17 (27.4)	33 (32.7)
Mean time since first chelation ± SD, years	15.7±7.4	13.8±7.6	14.6±7.5
Mean number of transfusion sessions in the year prior to study entry ± SD (range)†	17.1±6.8 (10–34)	16.2±7.4 (8–44)	16.5±7.1 (8–44)
Geometric mean baseline myocardial T2* ± CV%, ms	7.3±19.4	14.7±20.6	11.2±40.8
Mean baseline LIC ± SD, mg Fe/g dw	28.4±10.2	28.1±10.2	28.2±10.2
Median baseline serum ferritin (range), ng/mL	7,185 (1,643–15,895)	4,893 (1,689–16,944)	5,350 (1,643–16,944)

†*Information on the number of transfusions is only available for the year prior to study entry.*

Over the two years, deferasirox dose was increased at least once in 97 of 101 (96.0%) patients, as per the study protocol. The overall median time to the first dose increase was 21.7 weeks (range 0–87), thus occurring during the core study. Once patients had entered the extension study, 42 (41.6%) patients had at least one dose increase; the median time to the first dose increase in the extension was 64 weeks (range 52–101). During the 2-year study, there were 89 dose reductions in 43 patients (42.6%); 59 (66.3%) of those were due to investigator-assessed clinically significant laboratory test abnormalities or AEs, 21 (23.6%) were according to protocol (e.g. changes in patient weight, serum ferritin, etc.), 8 (9.0%) were due to disease improvement and one (1.1%) due to dosing error. In all patients, the most common AEs requiring dose adjustments or interruptions included clinically significant increases in serum creatinine (n=23; 22.8%), increased alanine aminotransferase (n=6; 5.9%) and increased aspartate aminotransferase (n=6; 5.9%); 5 of the 6 patients with increased alanine aminotransferase also had increased aspartate aminotransferase. Mean transfusional iron intake in all patients was 0.34± 0.15 mg/kg/d over the 2-year treatment period (0.37±0.16 mg/kg/d for patients with T2* >5 to <10 ms; 0.32±0.13 mg/kg/d for patients with T2* 10 to <20 ms).

Effect of deferasirox on myocardial iron and cardiac function

Myocardial T2* improved significantly from a core baseline of 11.2 ms±40.8% to 14.8 ms±61.2% at two years (Figure 2; $P<0.001$ LOCF). This represents an overall mean relative increase from baseline of 17.7% in the first year and 36.8% in the second year for all patients. Significant increases in myocardial T2* were noted both in the subgroup with severe myocardial iron overload (baseline myocardial T2* >5 to <10 ms) from 7.3 ms±19.2% to 8.7 ms±34.8% and in the subgroup with moderate-to-mild myocardial iron overload (baseline myocardial T2* 10 to <20 ms) from 14.7 ms±20.6% to 20.1 ms±44.1% ($P<0.001$ LOCF for both). For patients with data in the extension (myocardial T2* values at 18 or 24 months), improvement in cardiac T2* (defined as >4% increase) was reported in 72 patients (75.8%), no change in T2* was

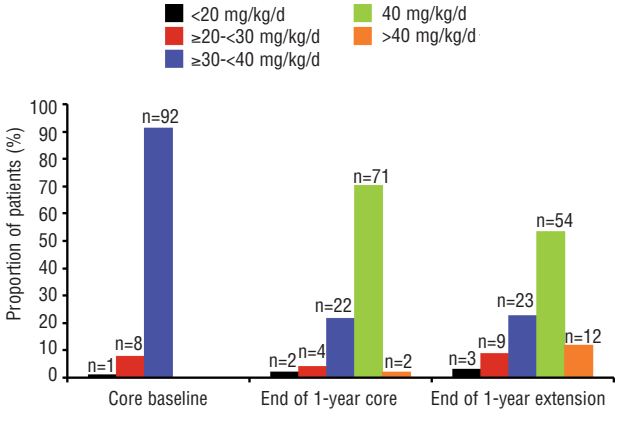

Figure 1. Planned deferasirox doses at core baseline, end of the one-year core and end of the one-year extension study in all patients.

reported in 9 patients (9.5%), and worsening of T2* (>4% decrease) in 14 patients (14.7%). Improvement in myocardial T2* was seen in 71.4% and 78.3% of patients with severe and moderate-to-mild cardiac siderosis (baseline T2* >5 to <10 ms and 10 to <20 ms), respectively. In patients with severe baseline myocardial iron overload, 42.9% improved to myocardial T2* 10 to less than 20 ms at two years, and 56.7% of patients with moderate-to-mild baseline myocardial iron overload achieved a normal myocardial T2* (≥20 ms). Cardiac T2* also continued to improve in patients receiving at least one dose decrease due to laboratory test abnormalities (11.2 ms±41.7% at baseline; 14.7 ms±52.0% after two years).

LVEF remained stable and in the normal range over the two years (Figure 3; baseline: 67.5±5.7%; two years: 67.7±5.1%; *P*=0.72 LOCF). Comparable results were observed in both subgroups of patients with baseline T2* greater than 5 to less than 10 ms (baseline: 66.1±5.3%; two years: 66.5±5.5%, *P*=0.57 LOCF) and 10 to less than 20 ms (baseline: 68.4±5.8%; two years: 68.4±4.7%, *P*=0.98 LOCF). Five patients developed LVEF less than 56% during the trial, 4 of whom had myocardial T2* greater than 5 to less than 10 ms and one with myocardial T2* 10 to less than 20 ms at baseline. This occurred at month 12 and month 18 in 2 of these patients, respectively, one of whom was noted to be non-compliant with therapy. Both patients subsequently discontinued the trial due to unsatisfactory therapeutic effect. The remaining 3 patients completed the trial; LVEF had improved to at least 56% in 2 patients by month 24 and was reduced by 5% from baseline to 55% in one patient only at month 24.

Effect of deferasirox on LIC and serum ferritin levels

At two years, mean LIC was significantly reduced from a baseline of 28.2±10.2 to 17.6±14.3 mg Fe/g dw in the overall population, representing a reduction of 38.8% (Figure 4; absolute change from baseline –10.7±12.7 mg Fe/g dw; *P*<0.001 LOCF). Mean LIC was also significantly reduced in patients with baseline myocardial T2* greater than 5 to less than 10 ms from 28.4±10.2 to 20.9±15.6 mg Fe/g dw representing a 28.0% reduction (absolute change from baseline –7.7±12.8 mg Fe/g dw; *P*=0.0012 LOCF) and in patients with baseline myocardial T2* 10 to less than 20 ms from 28.1±10.2 to 15.8±13.3 mg Fe/g dw representing 44.9% reduction (absolute change from baseline –12.4±12.4 mg Fe/g dw; *P*<0.001 LOCF). There was a significant negative correlation between the change in LIC and change in cardiac T2* (r=–0.47, *P*<0.0001). For patients with LIC data in the extension, 32 patients (33.3%) achieved a LIC of less than 7 mg Fe/g dw.

Similarly, median serum ferritin was significantly decreased from a baseline of 5,350 ng/mL (range 1,643–16,944 ng/mL) to 3,267 ng/mL (range 197–29,681 ng/mL) at two years in the overall population, representing a median reduction of 42.8% (Figure 5; absolute

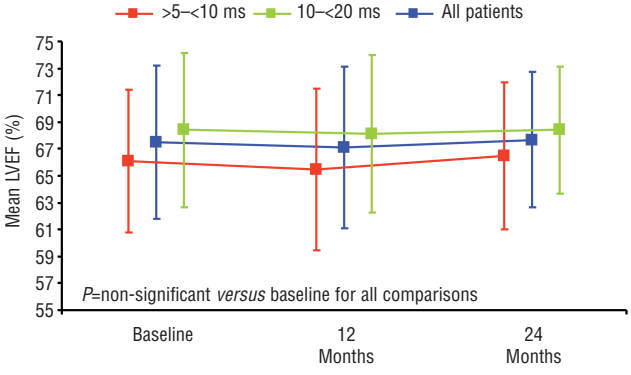

Figure 3. Changes in LVEF (mean ± SD) over two years in all patients (n=101) and in subgroups with baseline T2* >5 to <10 ms (n=39), and T2* 10 to <20 ms (n=62). The 24-month value includes all patients who received study medication and had an MR LVEF measurement at baseline and post-month 12, analyzed using LOCF analysis (n=95; 35 patients with baseline T2* >5 to <10 ms and 60 patients with baseline T2* 10 to <20 ms).

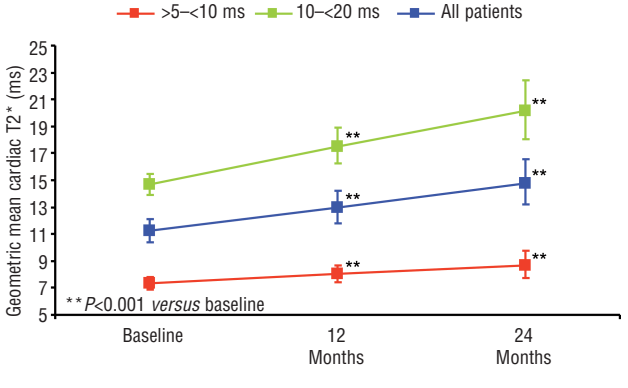

Figure 2. Changes in myocardial T2* (geometric mean ± 95% CI) over two years in all patients (n=101) and in subgroups with baseline T2* >5 to <10 ms (n=39), and T2* 10 to <20 ms (n=62). The 24-month value includes all patients who received study medication and had an MR myocardial T2* measurement at baseline and post-month 12, analyzed using LOCF analysis (n=95; 35 patients with baseline T2* >5 to <10 ms and 60 patients with baseline T2* 10 to <20 ms).

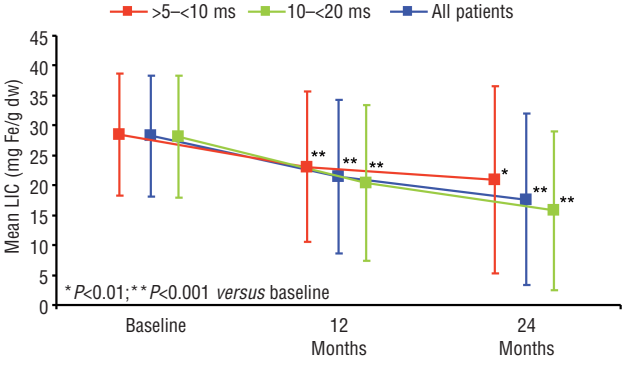

Figure 4. Changes in LIC (mean ± SD) over two years in all patients (n=101) and in subgroups with baseline T2* >5 to <10 ms (n=39), and T2* 10 to <20 ms (n=62). The 24-month value includes all patients who received study medication and had an MR LIC measurement at baseline and post-month 12, analyzed using LOCF analysis (n=96; 35 patients with baseline T2* >5 to <10 ms and 61 patients with baseline T2* 10 to <20 ms).

change from baseline –2,358 [range –12,795 to 25,127 ng/mL; *P*<0.001 LOCF). Decreases in serum ferritin were observed in patient subgroups with baseline myocardial T2* greater than 5 to less than 10 ms (7,185 at baseline and 3,614 ng/mL at two years, 42.8% reduction; absolute change from baseline –2,707 [range –12,795 to 2,404 ng/mL]; *P*<0.001 LOCF) and T2* 10 to less than 20 ms (4,893 at baseline to 2,565 ng/mL at two years, 44.8% reduction; absolute change from baseline –1,868 [range –7,872 to 25,127 ng/mL]; *P*<0.001 LOCF). For patients with serum ferritin data in the extension, 16 patients (15.8%) achieved serum ferritin levels of less than 1,000 ng/mL.

Safety

During the one-year core study, 9 patients discontinued therapy as previously described.[13] Of 101 patients who entered the extension study, 86 (85.1%) completed two years of treatment with deferasirox and 15 (14.9%) discontinued. Of these patients, 9 (23.1%) had myocardial T2* greater than 5 to less than 10 ms and 6 (9.7%) had a T2* 10 to less than 20 ms at baseline. Reasons for discontinuation included unsatisfactory therapeutic effect (n=7), consent withdrawal (n=4), abnormal laboratory result (n=1, no improvement in myocardial T2* and raised alanine aminotransferase), abnormal test procedure result (n=1, worsened myocardial T2*), protocol violation (n=1) and lost to follow up (n=1). Of the patients discontinuing due to unsatisfactory therapeutic effect, the treating physician noted a worsening of cardiac function or cardiac siderosis in 2 patients. Furthermore, one patient listed as discontinuing due to consent withdrawal was noted to report no improvement in liver or cardiac scan results prior to discontinuation. No patients died during the 2-year study period. The incidence of investigator-assessed drug-related AEs occurring in over 5% of patients did not increase in the one-year extension study relative to the one-year core study even though the mean deferasirox dose in the extension study was higher than in the core study: increased blood creatinine (extension: n=19 [18.8%] *vs.* core: n=22 [21.8%]), rash (extension: n=0 *vs*. core: n=15 [14.9%]) and increased alanine aminotransferase (extension: n=4 [4.0%] *vs*. core: n=6 [5.9%]). In patients receiving at least one deferasirox dose increase to at least 40 mg/kg/d in either the core or extension study, the most common drug-related AEs and incidences were similar: increased blood creatinine (n=19 [21.1%]), increased alanine aminotransferase (n=4 [4.4%]) and increased aspartate aminotransferase (n=3 [3.3%]). There was no increase in the proportion of drug-related AEs reported in patients achieving LIC less than 7 mg Fe/g dw or serum ferritin levels of less than 1,000 ng/mL as compared with patients with higher iron burdens (53.1% *vs.* 54.7% and 56.3% *vs*. 54.1%, respectively). Two drug-related serious AEs were reported during the one-year core study as previously reported (one nephritis leading to acute renal failure and one renal tubular disorder, both resolved following drug discontinuation during the core study).[13] No drug-related serious AEs were reported during the one-year extension. In total, 4 patients (4.0%) had an increase in serum creatinine of greater than 33% above baseline and the upper limit of normal (ULN) on two consecutive visits (3 patients during the core and one during the extension); there were no progressive increases in these patients. The patient who had increased serum creatinine greater than 33% above baseline and the ULN on two consecutive visits during the extension, was receiving deferasirox at 30 mg/kg/d and subsequently discontinued by withdrawal of consent. Four patients (4.0%) had an increase in alanine aminotransferase greater than 10 x ULN on two consecutive visits (one patient during the core, 2 patients during the extension and one patient during both the core and extension studies); alanine aminotransferase levels were already elevated at baseline in all these patients. For the 2 patients experiencing alanine aminotransferase increases greater than 10 x ULN during the extension, the percentage change in alanine aminotransferase levels from core baseline ranged from 159 to 260% and 23 to 72%, respectively. Both patients were managed with dose interruptions/decreases followed by dose titration back up to 40 mg/kg/d. The one patient with increases in alanine aminotransferase greater than 10 x ULN in both the core and extension discontinued the study due to an unsatisfactory therapeutic effect; the percentage change in alanine aminotransferase ranged from –42 to 49%.

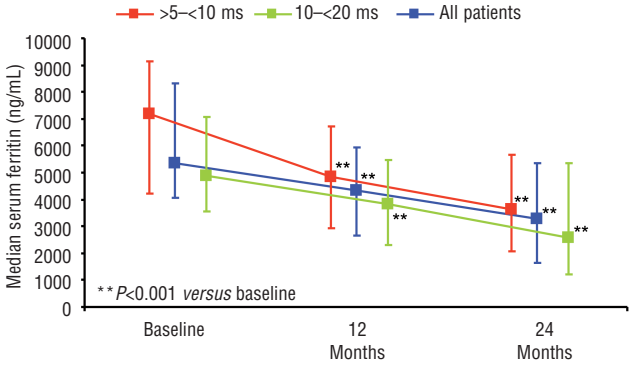

Figure 5. Changes in serum ferritin (median ± 25th/75th percentiles) over two years in all patients (n=101) and in subgroups with baseline T2* >5 to <10 ms (n=39), and T2* 10 to <20 ms (n=62). The 24-month value includes all patients who received study medication and had a serum ferritin measurement at baseline and post-month 12, analyzed using LOCF analysis (n=101).

Discussion

This large study is the first to report prospective 2-year data on cardiac iron removal for any iron-chelating agent. Data show that continued treatment with deferasirox at mean doses of over 30 mg/kg/d continued to significantly increase myocardial T2* over the 2-year treatment period compared with that achieved in the first year (17.7% in the first year, 36.8% over two years). These improvements in T2* resulted from a mean prescribed deferasirox dose of 33.1±3.7 mg/kg/d during the 1-year core study and 36.1±7.7 mg/kg/d during the 1-year extension. The improvement in cardiac T2* by using higher doses of deferasirox is comparable with high-dose data obtained for deferiprone, as reported from a different trial.[10] Of the patients with moderate-to-mild myocardial iron overload at baseline in the present study (cardiac T2* 10 to <20 ms), 57% achieved normal T2* of 20 ms or over at the end of two years. Of interest, patients with severe myocardial iron overload at baseline (T2* >5 to <10 ms) reached a geometric mean of 8.7 ms, with 43% of patients achieving

moderate-to-mild myocardial T2* levels (10 to <20 ms) at the end of two years, which is clinically important since a myocardial T2* less than 10 ms compared with T2* greater than 10 ms carries a significantly higher risk of heart failure (relative risk of 160).[8] For those with severe cardiac iron overload at baseline who did not improve to moderate-to-mild levels, or who required deferasirox doses above the approved label dose (doses up to 40 mg/kg/d are currently approved by the US Food and Drug Administration and the European Medicines Agency in patients not adequately treated with doses of 30 mg/kg/d), combination chelation therapy may offer an alternative regimen for faster removal of cardiac iron compared with monotherapies.[11] Combination regimens of deferasirox with deferoxamine are being investigated[15] and a Phase II multicenter study is being initiated. This notion supports recent similar findings by Wood *et al.* who concluded that more intensive combined iron chelation therapy may be warranted in patients with severe cardiac and liver iron overload.[16] As all patients had previously received chelation therapy, these results also suggest that deferasirox may be a useful treatment for cardiac iron overload in patients on other chelation therapies that have failed to control cardiac iron accumulation.

The improvement in myocardial T2* was associated with maintenance of normal cardiac function as determined by LVEF, as also shown in the 1-year core study.[13] A similar finding was also reported in an 18-month prospective study in severely iron-overloaded patients with β-thalassemia.[16] Maintenance of LVEF within the normal range is different to the response seen with deferiprone or combination therapy (deferiprone plus deferoxamine). The exact reason for this difference remains to be elucidated, although one explanation could be the greater access of the small molecule deferiprone to mitochondria,[17] where iron overload may suppress activity of the respiratory chain enzymes involved in the production of ATP. Interestingly, however, an increase in right ventricular ejection fraction measurements was seen with deferasirox,[18] but the relation of this change to the absence of left ventricular functional improvement is not currently understood. The data from the present study suggest that improvement in LVEF with deferasirox may occur after myocardial iron clearance is more complete, but further studies are required to examine this issue. In addition, as only patients with baseline LVEF within the reference range for healthy adults were enrolled in the cardiac substudy, further studies would be required to evaluate deferasirox therapy in patients with lower LVEF.

Significant reductions in cardiac iron levels were associated with concomitant continued decreases in serum ferritin and hepatic iron burden over two years of deferasirox therapy. In the 1-year core study, median serum ferritin and mean LIC were reduced from baseline by 1,257 ng/mL and 6.6 mg Fe/g dw[13] compared with a reduction from core baseline of 2,358 ng/mL and 10.7 mg Fe/g dw, respectively, in patients included in this 2-year extension study. This represented a 42.8% and 38.8% reduction in serum ferritin and LIC over two years of deferasirox treatment, respectively. In patients with moderate-to-mild baseline myocardial T2* (10 to <20 ms) completing two years of treatment, median serum ferritin levels were reduced from nearly 5,000 ng/mL to near the threshold of 2,500 ng/mL (2,565 ng/mL) that is associated with increased morbidity and mortality.[19,20] Furthermore, the correlation between changes in LIC and myocardial T2* suggests that patients with larger reductions in LIC show better improvements in myocardial T2*, supporting prior observations of a relationship between LIC and potential cardiac risks.[16,21]

Deferasirox treatment was well tolerated, with the most common drug-related AEs being increases in laboratory parameters (blood creatinine and alanine aminotransferase) and rash. Notably, no deaths were reported over this 2-year period of deferasirox therapy. Although patients received mean deferasirox doses at the higher end of the approved dose range (30–40 mg/kg/d), there was no change in the AE profile, further supporting the positive risk-benefit of high-dose deferasirox therapy for patients with high cardiac and/or hepatic iron burden.[16,22]

The current study has some limitations. Inclusion criteria for this trial enrolled only patients with LIC values greater than 10 mg Fe/g dw and serum ferritin levels of greater than 2,500 ng/mL. These criteria precluded the assessment of efficacy of deferasirox in patients with lower body iron burden. Other studies have, however, shown favorable cardiac T2* responses in patients with lower iron burden (LIC 10.7 mg Fe/g dw; serum ferritin 3,005 ng/mL).[16] Due to dose escalation, by the end of the second year, 66 (65.3%) patients were receiving deferasirox doses of between 40 mg/kg/d and 51 mg/kg/d, which are doses that are greater than the 40 mg/kg/d maximum currently approved by health authorities. Further studies assessing the safety profile at higher doses are warranted.

In conclusion, continued treatment with deferasirox monotherapy for two years was effective in increasing myocardial T2* by 36.8%, allowing 56.7% of patients with moderate-to-mild baseline T2* to achieve normalization of myocardial iron. Furthermore, 42.9% of patients with severe myocardial iron overload were able to achieve reduced myocardial iron levels corresponding to the moderate-to-mild range, which is associated with a much lower risk of cardiac complications. The ongoing extension of the EPIC cardiac substudy for an additional year will further characterize the long-term cardiac efficacy and safety of deferasirox for a total of three years.

Authorship and Disclosures

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Appendix

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