Deferasirox for up to 3 years leads to continued improvement of myocardial T2* in patients with β-thalassemia major

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ABSTRACT

Background
Prospective data on cardiac iron removal are limited beyond one year and longer-term studies are, therefore, important.

Design and Methods
Seventy-one patients in the EPIC cardiac substudy elected to continue into the 3rd year, allowing cardiac iron removal to be analyzed over three years.

Results
Mean deferasirox dose during year 3 was 33.6±9.8 mg/kg per day. Myocardial T2*, assessed by cardiovascular magnetic resonance, significantly increased from 12.0 ms ±39.1% at baseline to 17.1 ms ±62.0% at end of study (P<0.001), corresponding to a decrease in cardiac iron concentration (based on ad hoc analysis of T2*) from 2.43±1.2 mg Fe/g dry weight (dw) at baseline to 1.80 ±1.4 mg Fe/g dw at end of study (P<0.001). After three years, 68.1% of patients with baseline T2* 10 to <20 ms normalized (≥20 ms) and 50.0% of patients with baseline T2* >5 to <10 ms improved to 10 to <20 ms. There was no significant variation in left ventricular ejection fraction over the three years. No deaths occurred and the most common investigator-assessed drug-related adverse event in year 3 was increased serum creatinine (n=9, 12.7%).

Conclusions
Three years of deferasirox treatment along with a clinically manageable safety profile significantly reduced cardiac iron overload *versus* baseline and normalized T2* in 68.1% (32 of 47) of patients with T2* 10 to <20 ms.

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

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Introduction

Siderotic cardiomyopathy is a leading cause of morbidity and mortality in transfused patients with β-thalassemia major.[1,2] Although all available iron chelators have demonstrated efficacy in removing cardiac iron, prospective data beyond one year of treatment are rather limited.[3-10] As removal of cardiac iron may take several years, it is imperative to assess the effects of longer-term iron chelation therapy in the context of efficacy, safety and cardiac function. Results from the EPIC (Evaluation of Patients' Iron Chelation with Exjade®) cardiac substudy have shown continued, significant reduction of cardiac iron, as assessed by T2* cardiovascular magnetic resonance (CMR) over two years of deferasirox treatment in patients with mild-to-moderate (T2* 10 to <20 ms) and severe (T2* >5 to <10 ms) myocardial siderosis.[7,8] Cardiac T2* <20 ms is considered to indicate cardiac iron levels below the normal range, whereas a value <10 ms is associated with reduction in left and right ventricular ejection fraction (LVEF and RVEF) and an increased risk of cardiac failure and arrythmia.[11-13] The study continued for a 3rd year and final end-of-study (EOS) results are reported here. Furthermore, the recent calibration of the relationship between CMR measurements and cardiac iron concentration[14] allows an additional assessment of chelator efficacy in terms of the actual concentration of iron in cardiac tissue. In an ad hoc analysis, the long-term effects of deferasirox on cardiac iron concentration are reported for the first time based on the formula provided by Carpenter *et al.*, allowing a direct assessment of chelator efficacy, independently of the characteristics of the T2* to tissue iron relationship.

Design and Methods

Patient recruitment

The methods and inclusion/exclusion criteria for the EPIC cardiac substudy have already been described (*ClinicalTrials.gov number NCT00171821*).[7,8] Patients who completed the 2nd year could enter the 3rd year of the study, continuing to receive deferasirox at the dose prescribed at the end of year 2. Dose adjustments could be made during the 3rd year according to criteria pre-specified in the study protocol as previously described.[7,8] Dose increases beyond 40 mg/kg per day had to be approved by the Study Monitoring Committee and study sponsor.

Assessments

The primary efficacy end point was change in myocardial T2*, presented in the text as geometric mean ± coefficient of variation (CV) and graphically as geometric mean ± 95% confidence intervals (CI), from baseline to 36 months. Secondary end points included changes in LVEF (expressed as mean ± standard deviation [SD]), liver iron concentration (LIC; presented as mean ± SD) and median serum ferritin levels over the same period. T2* and LVEF values were assessed by CMR every six months. LIC was also assessed every six months by MR imaging while serum ferritin levels were evaluated monthly. Safety was evaluated by monitoring adverse events (AEs) and routine laboratory parameters as previously described.[7,8] Creatinine clearance was calculated from serum creatinine levels using the Cockcroft–Gault formula[15] and the Modification of Diet in Renal Disease (MDRD) formula.[16] Compliance with deferasirox was assessed by tablet counts.

An ad hoc analysis of mean change in cardiac iron concentration was also conducted; cardiac iron concentration was calculated from T2* values using the formula described by Carpenter *et al.* as follows: $[Fe] = 45.0 \times (T2^*)^{-1.22}$ where [Fe] is measured in milligrams per gram dry weight (dw) and T2* is measured in milliseconds.[14]

Statistical analysis

Data are presented for an intent-to-treat population of patients who entered the 3rd year and received at least one deferasirox dose. Efficacy measurements are reported using last-observation-carried-forward analysis. End of study T2*, LVEF and LIC (month 36) values include patients who had their last MR scan at month 30 or 36. The EOS serum ferritin values include patients with their last serum ferritin assessment in year 3. 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) ± CV, equivalent to the variance of the mean in log scale. Safety was assessed in all patients who received at least one dose of study medication. Statistical significance was examined 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

Of the 114 patients initially enrolled,[7] 101 continued into the 2nd year and 86 completed two years of deferasirox treatment.[8] Seventy-one patients elected to continue into the 3rd year; baseline myocardial T2* was >5 to <10 ms in 24 patients and 10 to <20 ms in 47 patients (Table 1).

Deferasirox dosing and exposure

During year 3, average actual deferasirox dose was 33.6±9.8 mg/kg per day: 36.8±6.6 mg/kg per day in patients with baseline T2* >5 to <10 ms and 31.9±10.8 mg/kg per day in those with baseline T2* 10 to <20 ms. For the 71 patients entering the 3rd year of the study, the average actual deferasirox dose was 33.3±3.9 mg/kg per day during the one-year core study, increasing to 35.4±8.0 mg/kg per day (P=0.02 *vs.* year 1) during year 2 of the study and then decreasing to 33.6±9.8 mg/kg per day (P=0.01 *vs.* year 2) during the 3rd year. Deferasirox dose was increased to 45 mg/kg per day by the investigators in 6 (8.5%) patients. Final dose was 30 to 40 mg/kg per day in 48 (67.6%) patients, 45 mg/kg per day in 6 (8.5%) patients, while the remaining patients had less than 30 mg/kg per day. Overall drug exposure during the study was 211 patient-years: 72 and 140 patient-years in patients with baseline T2* >5 to <10 ms and 10 to <20 ms, respectively.

Effect of deferasirox on cardiac T2*

During deferasirox treatment for up to three years, overall geometric mean cardiac T2* significantly increased from 12.0 ms ±39.1% at baseline to 17.1 ms ±62.0% at EOS (Figure 1A), corresponding to mean annual cumulative increases from baseline of 18.3% in year 1, 36.7% in year 2 and 52.1% in year 3 (P<0.001 *vs.* baseline for each year). In patients with T2* 10 to <20 ms at baseline, geometric mean T2* increased significantly from 15.0 ms ±21.7% at baseline to 22.3 ms ±48.8% at EOS (55.6% increase from baseline; P<0.001). In patients with baseline T2* >5 to <10 ms, geometric mean T2* also sig-

nificantly increased from 7.7 ms ±18.5% at baseline to 10.5 ms ±42.5% at EOS (45.7% increase from baseline; *P*<0.001).

After three years, 68.1% of patients with baseline T2* 10 to <20 ms normalized to ≥20 ms. Of the remaining patients, 23.4% remained in the same T2* range and 8.5% of patients worsened to T2* >5 to <10 ms. Of those with baseline T2* >5 to <10 ms, 50.0% improved to the mild-to-moderate range and one patient normalized (Figure 1B). Compliance with deferasirox was high and comparable in patients that did and did not move cardiac T2* subgroups by EOS (95.0% in patients remaining in the same cardiac T2* subgroup *vs.* 92.9% in patients moving from either >5 to <10 ms to 10 to <20 ms or from 10 to <20 ms to ≥20 ms). Similar findings were observed in patients with baseline T2* >5 to <10 ms (93.6% compliance in patients remaining within the T2* >5 to <10 ms subgroup *vs.* 92.0% compliance in patients moving to T2* 10 to <20 ms) and baseline T2* 10 to <20 ms (96.1% compliance in patients remaining within T2* 10 to <20 ms *vs.* 93.2% compliance in patients moving to ≥20 ms). The overall mean cardiac iron concentration, calculated from T2*, showed a continual, significant decrease during deferasirox treatment for up to three years, from 2.43±1.2 mg Fe/g dw at baseline to 1.80±1.4 mg Fe/g dw at EOS (*P*<0.001). The reductions in mean cardiac iron concentration over three years were significant both in patients with baseline cardiac T2* >5 to <10 ms (mean change from baseline, -0.97±1.2 mg Fe/g dw; *P*<0.001) and in those with baseline cardiac T2* 10 to <20 ms (mean change from baseline, -0.46±0.8 mg Fe/g dw; *P*<0.001; Figure 2).

Effect of deferasirox on LVEF

There was no variation in mean LVEF throughout the 3-year study; no significant fluctuations from baseline levels were observed in the mean values of patients with baseline T2* >5 to <10 ms or 10 to <20 ms (Figure 3).

Effect of deferasirox on LIC and serum ferritin

Deferasirox treatment for up to three years led to a significant decrease in mean LIC from 28.6±10.0 mg Fe/g dw at baseline to 14.8±14.0 mg Fe/g dw at EOS (-49.3%; *P*<0.001). Continued, annual reductions were observed in patients with severe and mild-to-moderate myocardial siderosis (Figure 4A). LIC also decreased in patients with severe myocardial T2* at baseline who did not improve to the mild-to-moderate category (n=11); findings showed a reduction in mean LIC from 31.0±7.6 mg Fe/g dw at baseline to 17.1±14.4 mg Fe/g dw at EOS (-47.8%).

A significant reduction in median serum ferritin levels was also observed each year, from 5575 ng/mL at baseline

Table 1. Baseline characteristics of patients who entered the 3rd year of the EPIC cardiac substudy.

Characteristic	Baseline T2* >5 to <10 ms (n = 24)	Baseline T2* 10 to <20 ms (n = 47)	All patients (n = 71)
Mean age ± SD, years	21.3±6.3	20.0±8.0	20.5±7.4
Age group, n (%)			
10 to <16 years	5 (20.8)	15 (31.9)	20 (28.2)
≥16 years	19 (79.2)	32 (68.1)	51 (71.8)
Male:female, n.	8:16	20:27	28:43
Race (Caucasian:Oriental:other), n.	9:14:1	14:31:2	23:45:3
History of hepatitis B and/or C, n. (%)	8 (33.3)	10 (21.3)	18 (25.4)
History of splenectomy, n. (%)	12 (50.0)	23 (48.9)	35 (49.3)
Prior chelation therapy, n. (%)			
Deferoxamine	13 (54.2)	35 (74.5)	48 (67.6)
Deferoxamine + deferiprone†	11 (45.8)	12 (25.5)	23 (32.4)
Mean time since first chelation ± SD, years	15.2±8.4	13.1±7.4	13.8±7.8
Mean number of transfusions in year prior to study entry ± SD (range)‡	17.5±6.4 (11–32)	15.5±7.9 (8–44)	16.2±7.4 (8–44)
Geometric mean baseline cardiac T2* ± CV%, ms	7.7±18.5	15.0±21.7	12.0±39.1
Mean baseline cardiac iron concentration ± SD, mg Fe/g dw	3.8±0.9	1.7±0.5	2.4±1.2
Mean baseline LVEF ± SD, %	66.0±5.1	68.4±6.3	67.6±6.0
Mean baseline LIC ± SD, mg Fe/g dw	31.0±9.0	27.4±10.3	28.6±10.0
Median baseline serum ferritin (range), ng/mL	8059 (2904–15,895)	4869 (1689–16,944)	5575 (1689–16,944)

†*Both deferoxamine and deferiprone received either as monotherapy or in combination;* ‡*Information on the number of transfusions is only available for the year prior to study entry.*

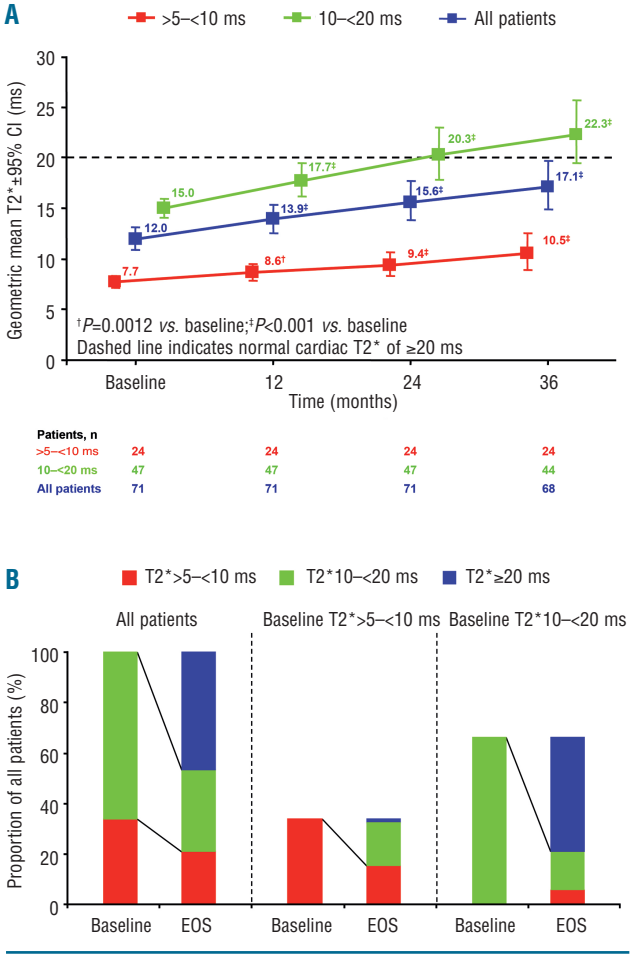

Figure 1. (A) Geometric mean cardiac T2* ± 95% CI during deferasirox treatment for three years; and (B) shift in proportion of patients with severe, mild-to-moderate and normalized cardiac T2* values at baseline and EOS.

to 2917 ng/mL at EOS (-45.7%; *P*<0.001). Similar relative reductions were observed in patients with baseline T2* >5 to <10 ms (-46.1%; *P*<0.001) and those with baseline T2* 10 to <20 ms (-44.2%; *P*<0.001; Figure 4B). Median serum ferritin level for the T2* >5 to <10 ms group increased from 3369 ng/mL at 24 months to 3721 ng/mL at 36 months (*P*=0.16), although LIC continued to decrease in this group. This appears to be related to individual patient responses, including 3 patients who experienced increases in median serum ferritin from baseline to 36 months (increases ranged from 1141 to 4203 ng/mL), 2 of whom had concomitant increases in LIC (+4.0 and +1.1 mg Fe/g dw) and decreases in heart T2* (-2.2 and -0.8 ms).

Safety

No deaths were reported in patients who entered the 3rd year of the study. Five of 71 (7.0%) patients who entered year 3 discontinued, citing either unsatisfactory therapeutic effect (n = 3; 4.2%) or withdrawal of consent (n = 2; 2.8%).

One patient (with baseline T2* 10 to <20 ms) was reported to have a serious cardiac AE (atrial fibrillation) during the 3rd year. This was the only cardiac event to result in hospitalization during the study, and it did not result in discontinuation. This patient had an increase in cardiac T2* from 11.8 to 17.8 ms, while LIC decreased from 48 to 24 mg Fe/g dw and serum ferritin decreased from 3417 to 2979 ng/mL. Other serious AEs reported in the 3rd year included chronic sinusitis, femur fracture, gastritis, muscle abscess and rheumatic fever (each n = 1). None of the serious AEs reported in the 3rd year, or throughout the entire study, were considered to be related to deferasirox.

Throughout the study, incidences of the most common investigator-assessed drug-related AEs (≥5% in any year) decreased incrementally each year in patients who entered the 3rd year of the study (Figure 5A). The most frequently reported drug-related AE during the 3rd year was increased serum creatinine (n = 9; 12.7%). No patient who entered year 3 discontinued as a result of increased creatinine.

Of the 71 patients who entered the 3rd year, 6 (8.5%) reported two consecutive increases in serum creatinine levels over 33% above baseline and the upper limit of normal (ULN); 3 during year 1 and 3 during year 3. Serum creatinine levels returned to the normal range spontaneously

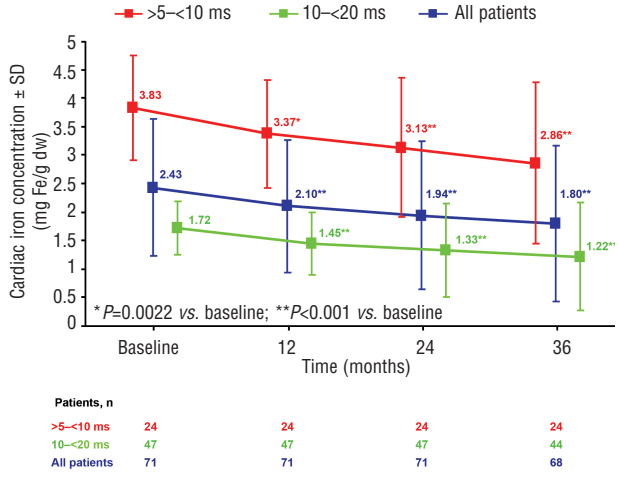

Figure 2. Mean cardiac iron concentration ± SD during 3-year deferasirox treatment.

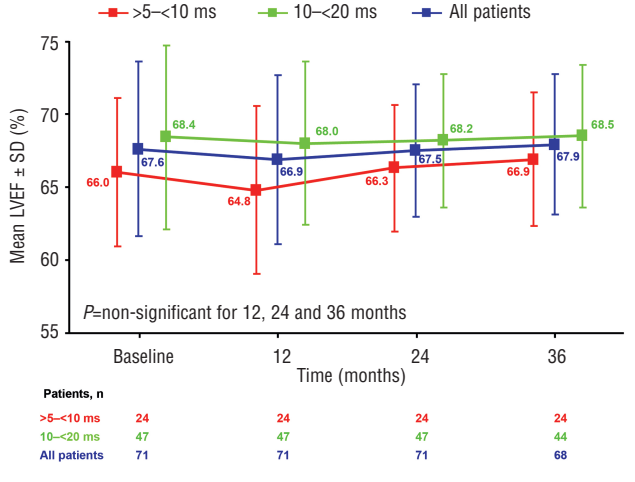

Figure 3. Mean LVEF ± SD during 3-year deferasirox treatment.

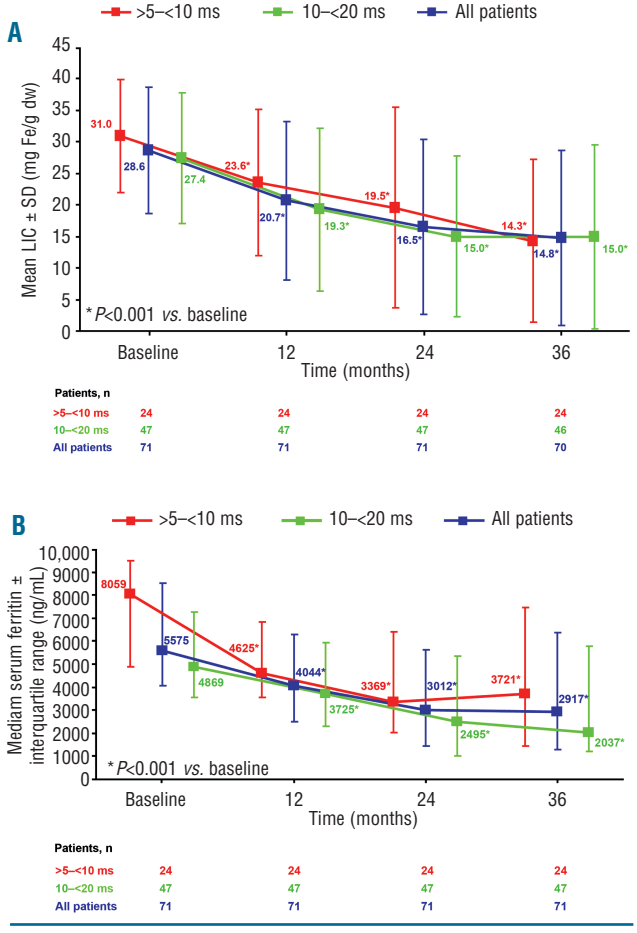

Figure 4. (A) Mean LIC ± SD; and (B) median serum ferritin ± interquartile range during deferasirox treatment for up to three years.

in 2 of the patients and following dose reduction in the remaining 4. Calculated creatinine clearance showed a slight decrease in the first 12 weeks of deferasirox treatment before leveling off for the remainder of the study. Mean creatinine clearance was in the normal range for the duration of deferasirox treatment as calculated using both the Cockcroft–Gault (Figure 5B) and the MDRD formula (Figure 5C). Creatinine clearance data were comparable for patients with T2* >5 to <10 ms and 10 to <20 ms at baseline.

Two patients (2.8%) had two consecutive increases in alanine aminotransferase over 10 x ULN, both during the 2nd year. These were managed with dose decreases and/or temporary interruptions.

Discussion

Over three years of follow up, treatment with deferasirox resulted in a significant and continued reduction of cardiac iron *versus* baseline levels at the start of the trial. Improvements in T2* were observed with a mean deferasirox dose of 33.6 mg/kg per day during year 3. This average actual dose was slightly lower compared with that in year 2, which may have been driven by the reduction of deferasirox doses in patients with baseline T2* 10 to <20 ms and is likely a reflection of downward titration of deferasirox dose as more patients reached their therapeutic objective of normalized heart T2*. Deferasirox dose was increased to 45 mg/kg per day by the investigators in only 6 patients; 3 had a baseline cardiac T2* of 5 to <10 ms (one had worsening of both cardiac T2* and LIC compared with baseline, one stabilized and one improved cardiac T2*, both with clinically relevant LIC decreases) and 3 patients had cardiac T2* 10 to <20 ms (cardiac T2* improved in 2 and remained stable in one patient, LIC decreased in all 3 patients, although serum ferritin levels remained high in 2 patients at the end of the study). Therefore, iron overload was managed in the majority of patients at doses of up to 40 mg/kg per day.

Annual increases in cardiac T2* were observed at a constant rate in patients with severe and mild-to-moderate myocardial siderosis at baseline. The change in cardiac iron concentration (Figure 2) shows that deferasirox is equally efficacious in both the baseline T2* >5 to <10 ms and T2* 10 to <20 ms groups. In patients with baseline T2* >5 to <10 ms, geometric mean T2* increased to above the severe threshold (≥10 ms) by EOS. In those with baseline T2* 10 to <20 ms, geometric mean T2* reached normal levels (≥20 ms) after two years and continued to increase above this threshold during the 3rd year. By EOS, deferasirox treatment for up to three years had enabled 50% of patients with severe myocardial siderosis to improve to mild-to-moderate levels, hence decreasing their risk of potential cardiac complications. In addition, the majority (68.1%) of patients with mild-to-moderate cardiac iron overload normalized their cardiac T2*, although a small percentage (8.5%) of patients worsened to T2* >5 to <10 ms (2 patients had a reduction in cardiac T2* from 10 and 10.1 to 9.4 and 9.1 ms, respectively, and 2 reduced from 10.4 and 12.3 to 6.6 and 6.1, respectively). Compliance with deferasirox was high and comparable in patients that did and did not change cardiac T2* subgroups by the end of the study. This suggests that achievement of higher cardiac T2* was not necessarily the result of better compliance with treatment.

Improvements in cardiac T2* values were associated with concomitant decreases in LIC and total body iron, as assessed by serum ferritin level, in this heavily iron-over-

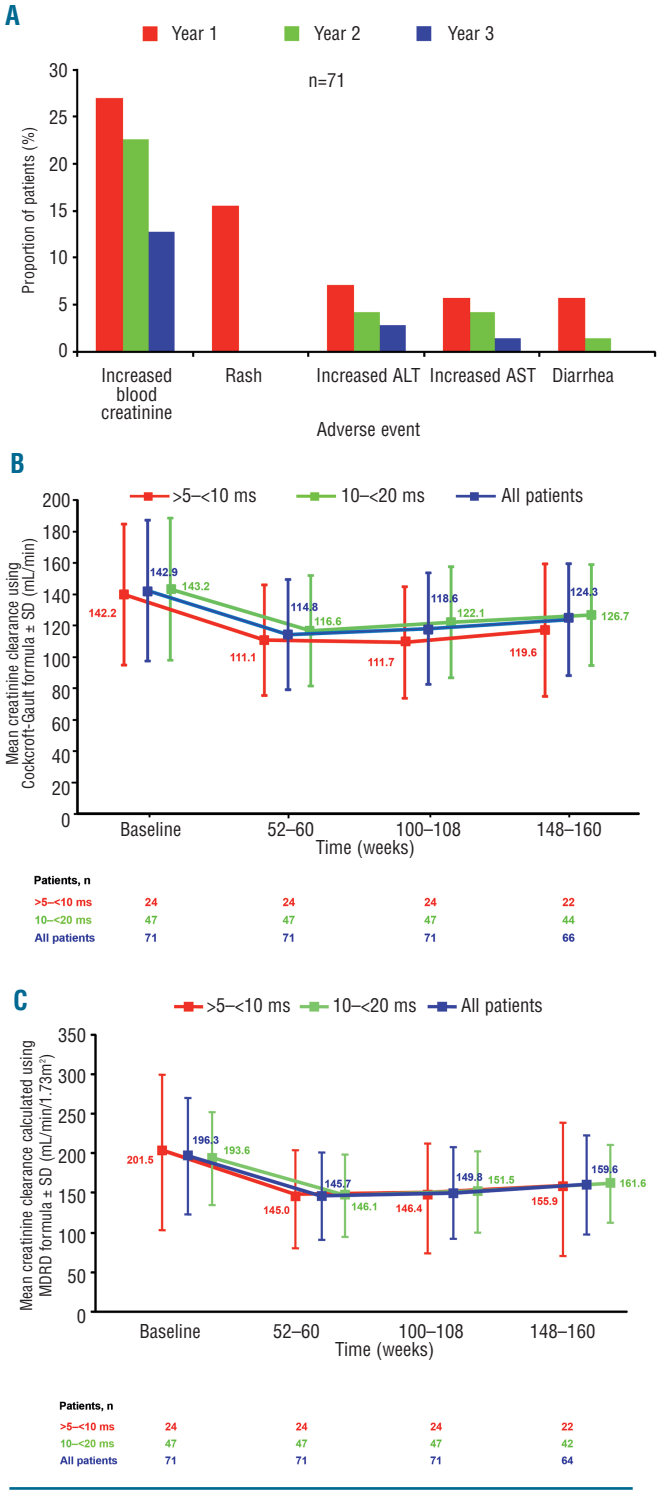

Figure 5. (A) Frequency of the most common (≥5%) investigator-assessed drug-related AEs; (B) mean creatinine clearance ± SD over time during deferasirox treatment for up to three years (Cockcroft–Gault formula); (C) mean creatinine clearance ± SD over time during deferasirox treatment for up to three years (MDRD formula).

loaded population. Mean LIC and median serum ferritin levels were halved from baseline levels in patients who received deferasirox for up to three years. LIC levels also decreased in those patients with baseline severe myocardial T2* that did not show an improvement to the mild-to-moderate T2* range. Therefore, although there is an association between LIC and improvements in cardiac T2*, LIC reductions cannot be used as a direct correlation for cardiac T2* improvement. Wood *et al.* suggest that the absolute level of LIC rather than the change in LIC may be of greatest relevance as a predictor of cardiac response.[17] Indeed, these authors speculate that iron chelation with deferasirox may be a competitive process with cardiac effectiveness improving once liver iron is depleted. These observations highlight the need to track and control both cardiac and total body iron concentrations.

Of note, patients with mild-to-moderate cardiac iron attained serum ferritin levels <2500 ng/mL, a threshold associated with improved cardiac disease-free survival,[18] after two years of deferasirox treatment. The serum ferritin levels of these patients continued to decrease during the final year of the study. Within the subgroup of patients with baseline T2* >5 to <10 ms, serum ferritin levels were slightly higher at 36 *versus* 24 months, although this difference was not significant and LIC continued to decrease. Closer analysis of this population suggested these findings were related to individual patient responses as 3 patients experienced increases in serum ferritin, 2 of whom had concomitant increases in LIC and decreases in T2*. These findings highlight the importance of individual patient care and ongoing monitoring of chelation therapy.

The efficacy demonstrated by deferasirox over three years is notable considering the high iron burden of the patients enrolled (cardiac T2* >5 to <20 ms; LIC >10 mg Fe/g dw; serum ferritin >2500 ng/mL), given that several published analyses of myocardial T2* or cardiac events during treatment with other chelators included patients with lower iron burden at baseline.[6,10,19-23] Baseline iron overload may impact the time taken to remove cardiac iron.[17,24] Although the relevance of this observation has not yet been confirmed for chelators other than deferasirox, it nevertheless highlights the importance of determining long-term efficacy and safety of iron chelation therapy in patients with myocardial and total body iron overload.

This is the first time the effects of long-term iron chelation on cardiac iron concentration have been reported. As observed for T2*, cardiac iron concentration showed significant decreases from baseline after 12, 24 and 36 months of deferasirox treatment in patients with mild-to-moderate and severe myocardial siderosis at baseline. The mean concentration of iron in cardiac tissue was much lower than that in the liver of the patients studied, in agreement with previous suggestions that heart function is more sensitive to the effects of iron loading.[14] Also, the rate at which cardiac iron was removed appeared to be slower than that for liver iron, further emphasizing the need for long-term chelation and ongoing monitoring of cardiac iron in patients with evidence of cardiac iron overload. These cardiac iron data, derived from T2* values according to Carpenter *et al.*,[14] provide information to support the cardiac T2* findings.

The improvement in myocardial T2* was associated with maintenance of cardiac function, as assessed by LVEF, consistent with the one and 2-year studies.[7,8] LVEF was also maintained in an 18-month prospective study in severely iron-overloaded patients with β-thalassemia.[17] However, in patients with baseline T2* >20 ms from the EPIC cardiac substudy, there was a significant increase in LVEF by an absolute mean of 1.8%.[7] In all these studies, LVEF remained within the normal range (>56%). Patients with cardiac siderosis treated with deferiprone have shown increases in LVEF.[6,10] We have previously suggested that one explanation for this difference could be the greater access of deferiprone to mitochondria,[25] where iron overload may suppress activity of the respiratory chain enzymes involved in the production of adenosine triphosphate.[7,25,26]

Deferasirox treatment for up to three years appeared to be well tolerated in patients with severe and mild-to-moderate myocardial iron overload. There were no deaths or drug-related serious AEs during 211 patient-years of deferasirox exposure and only one patient reported a serious cardiac AE. Although the one report of gastritis as a serious AE was not considered to be related to deferasirox by the investigator at the time, gastritis is an uncommon recognized adverse reaction. The rate of patients completing the study was high (93%).

Over the course of the study, there was an annual decrease in the incidence of the most common AEs reported by investigators to have a suspected relationship to deferasirox in patients who entered the 3rd year. Gastrointestinal AEs, in particular, were less prevalent with extended deferasirox exposure, while drug-related rash was only reported in the 1st year of the study, suggesting improved tolerance over time. The most frequently reported drug-related AE during the final year was increased serum creatinine. Mild, non-progressive increases in serum creatinine were observed in registration studies of deferasirox in patients with β-thalassemia major, most frequently in patients receiving doses at the higher end of the assessed range; the increases resolved either spontaneously or with dose reduction.[27] In the current study, creatinine clearance reduced slightly during the first 12 weeks of deferasirox treatment, before leveling off and remaining consistently in the normal range for the remainder of the 3-year study, demonstrating that doses of ≥30 mg/kg per day can be tolerated over the long term without a clinically significant reduction in creatinine clearance.

There are some limitations to the EPIC cardiac substudy design. The study was not randomized and there were no direct comparisons made with other iron chelators. The present study was specifically designed to prospectively evaluate deferasirox in the removal of cardiac iron in a large patient population with transfusion-dependent iron overload. A randomized study comparing deferasirox with deferoxamine is ongoing (NCT00600938).

To conclude, deferasirox at mean doses of 30 to 40 mg/kg per day and ranging up to 48.6 mg/kg per day significantly and continually decreased cardiac iron overload *versus* baseline with a manageable safety profile over three years. There was no significant variation in LVEF over the study period, which remained within the normal range. Two-thirds of patients with mild-to-moderate T2* at baseline reached normal levels and half of patients with severe cardiac disease at baseline improved to the mild-to-moderate range after three years of deferasirox treatment.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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