Deferasirox (Exjade®) significantly improves cardiac T2* in heavily iron-overloaded patients with β-thalassemia major

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Abstract Noninvasive measurement of tissue iron levels can be assessed using T2* magnetic resonance imaging (MRI) to identify and monitor patients with iron overload. This study monitored cardiac siderosis using T2* MRI in a cohort of 19 heavily iron-overloaded patients with β-thalassemia major receiving iron chelation therapy with deferasirox over an 18-month period. Overall, deferasirox therapy significantly improved mean ± standard deviation cardiac T2* from a baseline of 17.2±10.8 to 21.5±12.8 ms (+25.0%; P=0.02). A concomitant reduction in median serum ferritin from a baseline of 5,497 to 4,235 ng/mL (−23.0%; P=0.001), and mean liver iron concentration from 24.2±9.0 to 17.6±12.9 mg Fe/g dry weight (−27.1%; P=0.01) was also seen. Improvements were seen in patients with various degrees of cardiac siderosis, including those patients with a baseline cardiac T2* of <10 ms, indicative of high cardiac iron burden. These findings therefore support previous observations that deferasirox is effective in the removal of myocardial iron with concomitant reduction in total body iron.

Keywords Iron overload · Iron chelation · β-thalassemia · T2* magnetic resonance imaging · Myocardial iron

Introduction

Myocardial siderosis is a leading cause of cardiac morbidity and mortality in regularly transfused patients with β-thalassemia [1, 2]. Adequate chelation therapy can reverse the deleterious effects of cardiac iron overload [3]; however, it is also important for an iron chelator to prevent myocardial iron accumulation while reducing total body iron burden. Measurement of cardiac T2* by magnetic resonance imaging (MRI) is a noninvasive direct method that has been developed for detecting and quantifying tissue iron levels and identifying patients with iron overload [4, 5].

Deferasirox (Exjade®; Novartis Pharma AG, Basel, Switzerland), a once-daily, oral iron chelator has demonstrated efficacy in reducing hepatic and body iron burden as assessed by liver iron concentration (LIC) and serum ferritin measurements in chronically transfused patients with a range of anemias [6–8]. Preclinical evaluation and initial clinical studies have demonstrated the efficacy of deferasirox in the removal of cardiac iron [9–11]. More recently, a prospective study of deferasirox in a large group of patients with β-thalassemia and a longitudinal analysis of myocardial T2* in iron-chelated patients have provided further evidence supporting the use of deferasirox in removing and preventing myocardial iron accumulation [12–14].

The efficacy and safety of long-term treatment with ICL670 in β-thalassemia patients with transfusional hemosiderosis (ESCALATOR) trial was conducted to evaluate the efficacy and safety of deferasirox specifically in regularly transfused patients with β-thalassemia who had previously received deferoxamine (DFO; Desferal®; Novartis Pharma AG, Basel,
Switzerland) and/or deferiprone (Ferriprox®; Apotex Inc., Toronto, ON, Canada) [15]. Sultan Qaboos University Hospital, Muscat Oman, was one of the participating sites, and cardiac T2* MRI was introduced at the center in 2006. Therefore, after completing the 1-year core phase of the ESCALATOR trial, cardiac iron was evaluated in Omani trial patients as part of standard-of-care practice. The aim of this study was to monitor the effects of deferasirox on myocardial siderosis in these patients enrolled at a single center in Oman using T2* MRI for a further 18-month period.

**Patients and methods**

This study was conducted on a subgroup of 19 patients, from the ESCALATOR trial to monitor the effects of deferasirox on myocardial siderosis in patients enrolled at the Sultan Qaboos University Hospital in Oman using T2* MRI over an 18-month period.

The ESCALATOR trial was a prospective, open-label, 1-year, multicenter, Phase IV study conducted in the Middle East. Details of the design and inclusion criteria for the ESCALATOR trial have been described in detail previously [15]. The ESCALATOR trial enrolled male or female patients (≥2 years old) with β-thalassemia and transfusional iron overload who had been unsuccessfully chelated with prior mono- or combination therapy with DFO and/or deferiprone (due to unacceptable toxicity, poor response to previous chelator, or documented noncompliance of taking <50% of prescribed doses in previous year). Patients were required to have a LIC of ≥2 mg Fe/g dry weight (dw), serum ferritin levels of ≥500 ng/mL, alanine aminotransferase levels of <300 U/L, and normal renal function.

Measurement of cardiac T2* by MRI was performed using the single breath-hold, multi-echo T2* protocol described by Westwood et al. [16]. A 10-mm thick single slice was obtained in the short axis through the midventricle during a single breath-hold. The T2* sequence was acquired at eight echo times from 2.5 to 18.0 ms in 2.18 ms increments. For analysis, a full-thickness region was chosen through the interventricular septum. The T2* values were calculated using CMRtools (Cardiovascular Imaging Solutions, London, UK). LIC was measured by a R2 MRI technique as described by St. Pierre et al. [17]. Echo times of 6, 9, 12, 15, and 18 ms were obtained in the short axis through the midventricle during a single breath-hold. The T2* sequence was acquired at eight echo times from 2.5 to 18.0 ms in 2.18 ms increments. For analysis, a full-thickness region was chosen through the interventricular septum. The T2* values were calculated using CMRtools (Cardiovascular Imaging Solutions, London, UK). LIC was measured by a R2 MRI technique as described by St. Pierre et al. [17]. Echo times of 6, 9, 12, 15, and 18 ms were collected with a slice thickness of 5 mm.

All patients received deferasirox 20 mg/kg/day as a starting dose with routine dose adjustments performed in response to changes in serum ferritin levels and safety markers. Patients had therefore been receiving once-daily deferasirox for 12 months prior to the first cardiac T2* assessment (baseline). Patients continued on deferasirox throughout the 18-month period of this present evaluation with dose adjustments conducted as per the ESCALATOR trial protocol [15]. Dose adjustments in increments of 5 or 10 mg/kg/day were performed based on efficacy (serum ferritin levels) and safety markers (dose range 0–40 mg/kg/day). Doses were increased if serum ferritin rose to ≥1,000 ng/mL above baseline on two consecutive visits or to >2,500 ng/mL without a decreasing trend. Deferasirox was interrupted if serum ferritin fell to ≤500 ng/mL on two consecutive visits and resumed if serum ferritin rose to ≥1,000 ng/mL. Doses were reduced for elevated serum creatinine, urinary protein/creatinine ratio, and transaminases and in response to adverse events.

**Statistical analysis**

Markers of deferasirox efficacy, cardiac T2*, LIC, and serum ferritin were measured at 6 and 18 months. Baseline characteristics of patients were compared at 6 months and at 18 months using one-way analysis of variance for continuous variables and Student’s t test for paired variables. All P values are two-sided and considered significant with P≤0.05. Statistical analysis was performed using SPSS statistical software v14 (SPSS, Inc., Chicago, IL).

**Results**

All 19 patients who participated in this study were assessed for myocardial iron loading by T2* MRI and total body iron load using serum ferritin measurements and LIC by biopsy (Table 1). All patients completed 18 months of extended evaluation.

Baseline cardiac T2* (mean ± standard deviation, 17.2±10.8 ms) was indicative of myocardial iron accumulation (normal T2* is considered to be >20 ms), and baseline serum ferritin (median 5,497 ng/mL) signified a high total

**Table 1  Baseline patient characteristics**

| Characteristic                                      | All patients (n=19) |
|-----------------------------------------------------|---------------------|
| Mean age (range; years)                             | 18 (10–29)          |
| Female: male (n)                                    | 11:8                |
| Race (caucasian:oriental:other; n)                  | 19:0:0              |
| History of hepatitis C* (%, n (%))                  | 5 (26.3)            |
| Splenectomy, n (%)                                  | 7 (36.8)            |
| Mean ± SD baseline cardiac T2*, ms                  | 17.2±10.8           |
| Median baseline serum ferritin (range; ng/mL)       | 5,497 (2,560–16,378) |
| Mean ± SD prebaseline LIC* (mg Fe/g dw)             | 24.2±9.0            |

SD standard deviation, LIC* liver iron concentration, dw dry weight
*Arab including some of Indian genetic background
*Investigator-reported patient history
*These values were measured 3–6 months prior to baseline T2* MRI
body iron burden. Patients also had high mean prebaseline LIC, which moderately correlated with both baseline cardiac T2* and serum ferritin levels ($r=−0.52$ and 0.53, respectively). Mean deferasirox dose in all patients was 25.9±2.3 mg/kg/day at baseline in this extended study, which increased to 32.0±4.4 mg/kg/day at 6 months and 37.7±5.5 mg/kg/day at 18 months. When the data were analyzed by baseline cardiac T2* subgroups (<10 ms [n=6], 10–20 ms [n=7], and >20 ms [n=6]), all subgroups demonstrated high baseline serum ferritin levels and prebaseline LIC (Fig. 1). Mean prebaseline LIC had a stronger positive correlation with baseline cardiac T2* in the >20-ms cardiac T2* subgroup ($r=0.72$) than the 10–20 ms ($r=0.18$) and <10-ms subgroups ($r=−0.64$). Conversely, mean prebaseline LIC correlated more strongly with serum ferritin levels in the <10-ms cardiac T2* subgroup ($r=0.60$) than the 10–20-ms ($r=0.20$) and >20-ms subgroups ($r=0.18$).

Myocardial iron: cardiac T2*

After 6 months of deferasirox therapy, a significant improvement in mean cardiac T2* from 17.2 to 20.8 ms (+20.9%; $P=0.007$) was seen. The observed improvement continued through to 18 months with a mean cardiac T2* of 21.5 ms (+25.0%; $P=0.02$; Fig. 1a). There were significant improvements in T2* ($P<0.05$) at 18 months in both the <10-ms subgroup (cardiac T2* improved from a mean of 6.3 to 7.8 ms [+23.8%]) and the 10–20-ms subgroup (cardiac T2* improved from a mean of 14.9 to 21.4 ms [+43.6%]; Fig. 1a). There was also a significant improvement in T2* after 6 months in the >20-ms subgroup (cardiac T2* improved from a mean of 30.8 to 37.2 ms [+20.8%]); after 18 months, cardiac T2* was 35.2 ms (Fig. 1a), representing an average improvement of 14.3% compared with baseline.

Total body iron: LIC and serum ferritin

Deferasirox treatment significantly reduced LIC from 24.2±9.0 mg Fe/g dw prebaseline to 17.6±12.9 mg Fe/g dw at 18 months (−27.1%; $P=0.01$) in the overall study population (Fig. 1b). The reductions in LIC (−56.6%) were also significant after 18 months in the >20-ms cardiac T2* subgroup; LIC was reduced by 8.1 and 10.2 mg Fe/g dw at 6 ($P<0.01$) and 18 months ($P<0.05$, respectively, from a prebaseline value of 18.0 mg Fe/g dw (Fig. 1b). Although not statistically significant, LIC was reduced in both the <10-ms and 10–20-ms cardiac T2* subgroups after 18 months of therapy (−32.3% and −3.4%, respectively); however, in the 10–20-ms subgroup after 6 months, there was a marginal rise (Fig. 1b); whereas, the trend in the other two subgroups and overall was downwards. Serum ferritin was also significantly reduced from baseline median 5,497 to 4,235 ng/mL (−23.0%; $P=0.001$) after 18 months of deferasirox treatment in the overall study population (Fig. 1c). In the >20-ms cardiac T2* subgroup, serum ferritin was reduced (−62.1%) after 18 months; serum ferritin fell by 1,703 and 2,940 ng/mL at 6 and 18 months ($P<0.01$ for both), respectively, from a baseline value of 4,733 ng/mL (Fig. 1c). After 18 months of therapy, serum ferritin was reduced by 7.0% and 15.3% in the <10-ms and 10–20-ms cardiac T2* subgroups, respectively (not statistically significant).
Discussion

Deferasirox therapy significantly improved cardiac T2* in this group of heavily iron-overloaded β-thalassemia patients at doses that were progressively escalated to >30 mg/kg/day over a period of 18 months of continued therapy. In our study group, we observed that although 65% of patients had significant myocardial iron overload as defined by T2*< 20 ms, improvements in cardiac T2* were seen in patients with various degrees of cardiac siderosis, including those patients with baseline cardiac T2* of <10 ms. This indicates that deferasirox is effective in removing iron from the heart in patients with mild, moderate, and severe cardiac siderosis. Overall serum ferritin and LIC were also significantly reduced in all patients. When data were analyzed by baseline T2* subgroup, the reduction in these markers of total body iron did not reach statistical significance in the <10-ms and 10–20-ms subgroups. This was possibly due to the small number of patients in the study and the extremely heavy prebaseline iron burden in these patients; however, measurements of LIC and serum ferritin were reduced from baseline. These data suggest that deferasirox is capable of removing cardiac iron in cardiac iron-overloaded patients while also decreasing total body iron burden. Deferasirox was also shown to continue removal of total body iron in iron-overloaded patients while protecting them from developing cardiac overload as demonstrated in the cardiac T2* >20-ms subgroup.

Statistically significant improvements in myocardial T2* have recently been reported as part of the deferasirox evaluation of patients iron chelation (EPIC) trial in a larger group of β-thalassemia patients (n=114) treated with deferasirox over a 1-year period [12]. A subgroup of β-thalassemia patients (n=78) with normal cardiac iron levels were also shown to maintain normal cardiac iron while reducing total body iron levels [13]. In our study, there was differential improvement in the first 6 months versus the last 12 months of treatment based on the slope of mean LIC and mean serum ferritin plots. The slope was steeper in the first 6 months, which may reflect better chelator efficiency when the iron overload was higher. Interestingly, this is also correlated with the slope of improvement in the mean cardiac T2* plot (Fig. 1a) which is indicative of congruous and simultaneous cardiac and liver iron overload chelation. Our study results, although obtained on a small sample size, are reflective of similar results already reported by the much larger EPIC study [12].

However, longitudinal analyses of cardiac and liver iron content in response to chelation therapy have indicated that iron is removed from the heart at a slower rate as compared with the liver [18], highlighting the importance of long-term studies to observe changes in iron content in these organs. Our study also shows a similar trend. When comparing the slope of change in mean LIC and serum ferritin plots against the slope of mean cardiac T2*, the slope appears steeper in the former as compared with the latter for the two corresponding study periods in the subgroup analysis (Fig. 1a, b, and c). This would seem to indicate that iron is being chelated at a faster rate from the liver than the heart, although an unidirectional trend would confirm that chelation is being achieved at both sites. The only aberration was noticed in the 10–20-ms subgroup where, after an initial improvement, there was a marginally opposite trend, one explanation for which may be due to poor compliance in a few patients.

A further point of consideration is that these results were achieved based on an ongoing dynamic strategy to adjust the chelator dose to meet the level of iron overload at any given point in the study period. This was done by looking at the trends seen with markers of iron overload namely serial serum ferritin levels and LIC values. Thus, the chelator dose was progressively increased if parameters of iron overload showed a rising trend and reduced progressively if an opposite trend was seen at any time point in the study. This was done with the dual aim of providing optimal chelation and minimizing the precipitation of any side effects. In this context, looking at the subgroups, the >20-ms group remained within the normal range with the maximal benefit seen in the first 6 months. The 10–20 ms subgroup showed a steady improvement, which was better than the <10-ms subgroup, although both improved. The comparatively poorer improvement in the <10-ms subgroup may be due to the very severe cardiac siderosis and very high iron overload in this subgroup. Recently, few published studies have shown that cardiac T2* does not correlate with the degree of LIC and serum ferritin [19–21]. However, this was not so in our study patients. None of our patients with high LIC had normal myocardial iron, and all received the same single oral chelator. Currently, therefore, although deferiprone alone or in combination with DFO has a proven efficacy to remove myocardial iron, in our study patients, the improvement in the cardiac T2* was purely following deferasirox therapy. Overall, these initial results are encouraging for the use of deferasirox in the treatment and prevention of cardiac iron overload as well as in the reduction of total body iron. Additional, longer-term studies with larger groups of patients will contribute further to our understanding of the efficacy of deferasirox in the removal and prevention of cardiac iron overload.

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409