

# Update on the use of deferasirox in the management of iron overload

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**Abstract:** Regular blood transfusions as supportive care for patients with chronic anemia inevitably lead to iron overload as humans cannot actively remove excess iron. The cumulative effects of iron overload cause significant morbidity and mortality if not effectively treated with chelation therapy. Based on a comprehensive clinical development program, the once-daily, oral iron chelator deferasirox (Exjade<sup>®</sup>) is approved for the treatment of transfusional iron overload in adult and pediatric patients with various transfusion-dependent anemias, including  $\beta$ -thalassemia and the myelodysplastic syndromes. Deferasirox dose should be titrated for each individual patient based on transfusional iron intake, current iron burden and whether the goal is to decrease or maintain body iron levels. Doses of  $>30$  mg/kg/day have been shown to be effective with a safety profile consistent with that observed at doses  $<30$  mg/kg/day. Recent data have highlighted the ability of deferasirox to decrease cardiac iron levels and to prevent the accumulation of iron in the heart. The long-term efficacy and safety of deferasirox for up to 5 years of treatment have now been established. The availability of this effective and generally well tolerated oral therapy represents a significant advance in the management of transfusional iron overload.

**Keywords:** deferasirox, Exjade, oral, iron chelation, iron overload, cardiac iron

## Iron overload and chelation therapy

The human body has many mechanisms to absorb, transfer and store essential dietary iron, but none to excrete excess amounts. It is therefore inevitable that patients who undergo regular transfusion therapy to treat chronic anemia, such as those with  $\beta$ -thalassemia and the myelodysplastic syndromes (MDS), will develop iron overload, since every unit of blood contains approximately 200 mg of iron.<sup>1</sup> Iron overload from transfusions may be exacerbated in some patients due to increased absorption of iron from the diet in response to ineffective erythropoiesis.<sup>2</sup> Excess iron is deposited in parenchymal tissue, including the liver, heart and endocrine system, which leads to ongoing damage and, ultimately, to organ failure.

Iron chelation therapy is the only viable option for the treatment of transfusional iron overload and can prevent further cellular iron uptake and reduce levels of morbidity and mortality in regularly transfused patients.<sup>3-5</sup> Deferoxamine (DFO; Desferal<sup>®</sup>) is the current standard of care for iron chelation therapy; however, as DFO is a large molecule with a short half-life (20 to 30 minutes), treatment requires a demanding regimen of slow continuous infusion over 8 to 12 hours, 5 to 7 days/week, which often results in poor compliance.<sup>6</sup> The 3-times daily chelator deferriprone (Ferriprox<sup>®</sup>) was the first oral chelator to reach market and it is currently available in a number of countries outside

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the USA and Canada for the second-line treatment of iron overload in adult patients with thalassemia major for whom DFO therapy is contraindicated or inadequate.<sup>7</sup> The use of deferasiprone has partly been restricted due to the occurrence of serious adverse events such as arthropathy (common), neutropenia and agranulocytosis (rare).<sup>8,9</sup>

Deferasirox (Exjade®), which became available in 2005, is an oral iron chelator that requires once-daily administration. It is currently approved in more than 90 countries for the treatment of chronic iron overload due to blood transfusions in pediatric and adult patients.<sup>10</sup> Deferasirox has been evaluated in patients with a wide range of underlying anemias and a wealth of clinical data is now available. This review will provide an update on the use of deferasirox, primarily focusing on the recent long-term efficacy and safety data available from the extension studies, new analyses in patients with MDS, aplastic anemia (AA) and Diamond-Blackfan anemia (DBA), as well as updates on the effects of deferasirox on cardiac iron levels.

## Pharmacodynamics and pharmacokinetics of deferasirox

### Chemistry and pharmacodynamic properties

Deferasirox represents a new class of tridentate iron chelators, the N-substituted bis-hydroxyphenyl-triazoles.<sup>11</sup> As a tridentate iron chelator, two molecules are required to form a stable complex with each iron ( $\text{Fe}^{3+}$ ) atom; the active molecule in deferasirox (ICL670) is highly lipophilic and 99% protein bound. Deferasirox has a high affinity and selectivity for  $\text{Fe}^{3+}$ , which is approximately 14 and 21 orders of magnitude greater than its affinity for copper or zinc, respectively, which minimizes the potential for depletion of these trace elements.<sup>12</sup> Animal models in several species, such as rats, gerbils and marmosets, demonstrated that deferasirox could efficiently and selectively mobilize iron from various tissues such as hepatocytes and cardiomyocytes, and could also promote iron excretion.<sup>11,13,14</sup> Deferasirox is primarily metabolized by glucuronidation, with subsequent biliary excretion, and the deferasirox–iron complex is excreted in the feces.<sup>15</sup>

### Pharmacokinetic properties

Deferasirox is rapidly absorbed with a median  $t_{\text{max}}$  of 1 to 2 hours and a mean elimination half-life of 7 to 16 hours.<sup>16</sup> The plasma concentration of deferasirox is proportional to the administered dose<sup>17,18</sup> and plasma levels

are maintained within the therapeutic range over 24 hours following once-daily administration.<sup>16</sup>  $C_{\text{max}}$ , area-under-curve and half-life are similar in children (aged < 12 years) and adolescents (aged  $\geq$  12 years). Exposure to deferasirox is approximately 20% to 30% lower in children and adolescents than in adults,<sup>17</sup> and is significantly lower in pediatric patients aged <6 years compared with older pediatric patients. These factors may add an additional margin for tolerability and mean that pediatric patients require higher deferasirox doses than adults to achieve comparable efficacy. As the bioavailability of deferasirox is affected by food when consumed concomitantly, it is recommended that it is administered at least 30 minutes before eating.<sup>19</sup>

## Efficacy of deferasirox

### Introduction to deferasirox clinical trials

The clinical efficacy of deferasirox has been thoroughly evaluated in patients with a wide range of transfusion-dependent anemias, including  $\beta$ -thalassemia, MDS, sickle cell disease (SCD), AA, DBA and other rare anemias. Five pivotal 1-year core studies were conducted in more than 1000 patients,<sup>16,20–23</sup> while more than 900 patients were enrolled into subsequent extension studies and will receive treatment with deferasirox for up to a further 4 years. A wealth of data are also now available from a global program of additional studies, the largest of which include ESCALATOR (237 patients with  $\beta$ -thalassemia)<sup>24,25</sup> and EPIC (1744 patients with various underlying anemias)<sup>26</sup> (Table 1).

### Factors impacting on deferasirox efficacy

The pivotal 1-year clinical studies demonstrated that the efficacy of deferasirox is dependent on both dose and ongoing transfusional iron intake.<sup>16,20–23,27</sup> Although doses of 5 and 10 mg/kg/day are able to effectively remove iron they are generally insufficient to balance the iron uptake from regular blood transfusions. Doses of 20 to 30 mg/kg/day are able to maintain or reduce body iron burden depending on iron intake.

For most patients the recommended starting dose for deferasirox is 20 mg/kg/day,<sup>18</sup> however this dose can be modified based on iron intake, current iron burden and a patient's individual therapeutic goal (ie, whether the aim is to decrease or maintain body iron levels);<sup>10</sup> local prescribing information should be consulted. If necessary, deferasirox dose adjustments should be made in steps of 5 to 10 mg/kg/day every 3 to 6 months based on serum ferritin trends. Data from the ESCALATOR study suggested that a starting dose of 20 mg/kg/day is insufficient to decrease

**Table 1** Trial design and key efficacy results from the ESCALATOR and EPIC studies

Design	Population	Treatment	Key results
ESCALATOR: Open-label, 1 year <sup>24</sup>  Subsequent extension study of at least 1 additional year <sup>25</sup>	Pediatric ( $\geq 2$ years) and adult patients with $\beta$ -thalassemia, n = 237 (n = 233 in extension study)  All patients were previously unsuccessfully chelated with DFO and/or deferiprone	Deferasirox 20 mg/kg/day* (initial dose); dose adjustments in steps of 5–10 mg/kg/day based on serum ferritin and safety markers	<ul style="list-style-type: none"> <li>• After 1 year: 57% of patients had treatment success (<math>P = 0.016</math>)<sup>†</sup> Mean reduction in LIC: 3.4 mg Fe/g dw (<math>P &lt; 0.001</math>)</li> <li>• Proportion of patients with LIC &lt; 7 mg Fe/g dw had risen from 9.9% at baseline to 26.2% In patients whose therapeutic goal was reduction, significant decrease in serum ferritin (<math>-517</math> mg/mL; <math>P &lt; 0.001</math>)</li> </ul>
EPIC: Open-label, 1-year <sup>26</sup>	Pediatric ( $\geq 2$ years) and adult patients with $\beta$ -thalassemia, MDS, DBA, SCD, AA and other rare anemias, n = 1744	Deferasirox 10–30 mg/kg/day (initial dose dependent on blood transfusion frequency); dose adjustments in steps of 5–10 every 3 months based on serum ferritin and safety markers	<ul style="list-style-type: none"> <li>• At end of study: Proportion of patients with LIC &lt; 7 mg Fe/g dw had risen to 44.4%. Further decreases in LIC and serum ferritin observed</li> <li>• Significant reduction in serum ferritin from baseline in overall population (<math>-264</math> ng/mL; <math>P &lt; 0.0001</math>), reflective of dosage adjustments and ongoing iron intake</li> <li>• Significant reduction in serum ferritin in each disease cohort</li> </ul>

**Abbreviations:** AA, aplastic anemia; DBA, Diamond-Blackfan anemia; DFO, deferoxamine; dw, dry weight; LIC, liver iron concentration; MDS, myelodysplastic syndromes; SCD, sickle cell disease.

iron burden in heavily iron-overloaded patients, since dose increases above 20 mg/kg/day were required in 185/237 patients (78%) in the initial 1-year treatment period.<sup>24</sup> Further dose increases were performed in 137/233 patients (59%) in the extension study, with increases to >30 mg/kg/day necessary in 112 patients; significant improvements in liver iron concentration (LIC) and serum ferritin were observed following these dose increases (Figure 1).<sup>25</sup> The importance of timely and appropriate deferasirox dose adjustments to enable patients to achieve target serum ferritin levels has also been highlighted in the extension phases of the pivotal studies. Patients who initially received deferasirox 5/10 mg/kg/day had increases in serum ferritin during the core 1-year treatment period, however a gradual decline in iron burden to below baseline levels was observed once doses were subsequently increased.<sup>28,29</sup> Figure 2 shows that doses of >20 mg/kg/day were necessary before patients were able to achieve a significant reduction in serum ferritin.<sup>28</sup>

The dosing approach used in the EPIC study accounted for iron intake as patients received initial deferasirox doses of 10 to 30 mg/kg/day depending on transfusion history, followed by dose titration in steps of 5 to 10 mg/kg/day every 3 months according to serum ferritin trends and safety markers.<sup>26,27</sup> Changes in serum ferritin over the 1-year treatment period were reflective of dosage adjustments and mean iron intake (Figure 3).<sup>26</sup> Significant

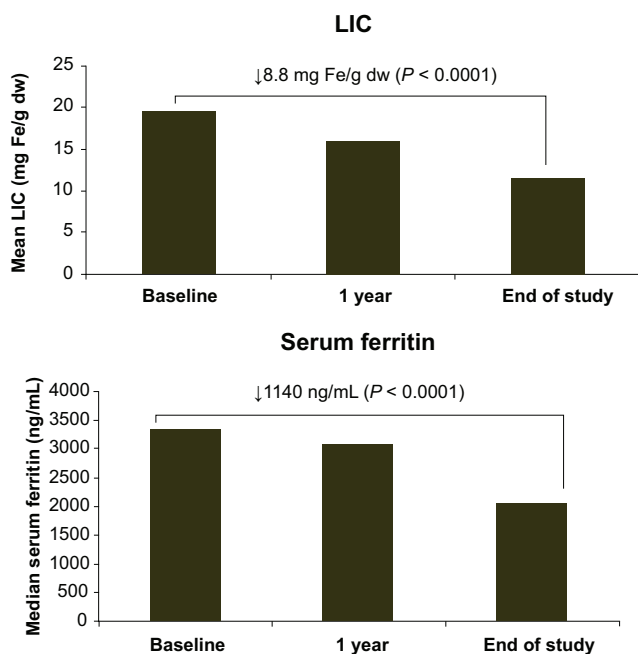
decreases in serum ferritin were observed in each overall disease cohort (Table 2).<sup>30–34</sup> These data from the EPIC study show that it is important to regularly monitor transfusional iron intake and serum ferritin levels during deferasirox therapy in order to optimize dosing.

Some patients will require escalation to >30 mg/kg/day to achieve therapeutic goals. A retrospective analysis of 228 patients who received deferasirox doses of >30 mg/kg/day in the extension studies and ESCALATOR demonstrated a significant reduction in median serum ferritin of 370 ng/mL ( $P < 0.001$ ) from pre-dose-escalation to the time-of-analysis.<sup>35</sup> These findings have important implications for patients who are heavily transfused and may require higher doses of deferasirox to reduce body iron burden.

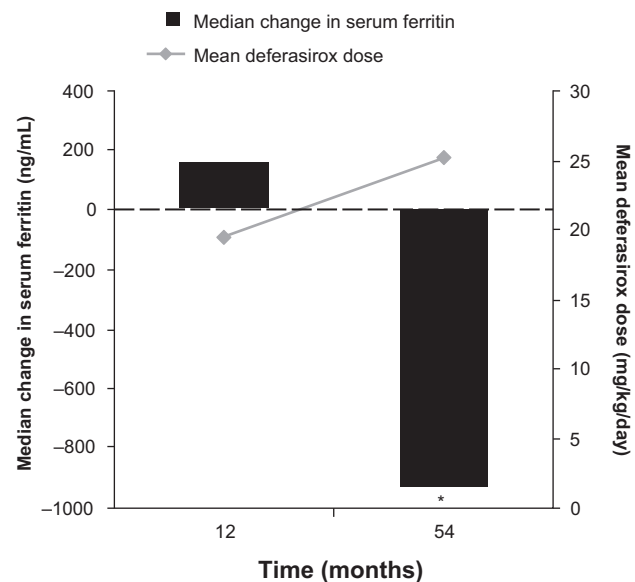
## Efficacy across different underlying anemias

### $\beta$ -thalassemia major

As complications of iron overload have been most widely studied in  $\beta$ -thalassemia major, this population was the primary focus of the deferasirox clinical trial program. The efficacy of deferasirox in this population was clearly demonstrated in the pivotal 1-year Phase III study (n = 296), where doses of 20 or 30 mg/kg/day provided dose-dependent changes in LIC and serum ferritin.<sup>20</sup> These data were confirmed in several trials including EPIC, where



**Figure 1** Mean liver iron concentration (LIC) and median serum ferritin at 1 year and end of study. Reproduced with permission. Taher A, El-Beshlawy A, Elalfy M, et al. *Haematologica*. 2009;94(Suppl 2):abstr 209.<sup>25</sup> Obtained from *Haematologica*/the Hematology Journal website <http://www.haematologica.org> with kind permission of the Ferrata Storti foundation, Pavia, Italy.



\*P < 0.0001 versus baseline

**Figure 2** Mean dose and median serum ferritin during long-term deferasirox treatment in patients with  $\beta$ -thalassemia.<sup>28</sup>

937 patients with  $\beta$ -thalassemia major were enrolled and where a significant decrease in serum ferritin was observed after 1 year of deferasirox treatment (Table 2).<sup>30</sup> In the ESCALATOR study, the proportion of  $\beta$ -thalassemia major patients with a LIC of <7 mg Fe/g dry weight (dw) increased from 9.9% at baseline, to 26.2% at 1 year and 44.4% at the end of study (median of 2.7 years).<sup>25</sup> With appropriate dose adjustments, deferasirox continues to be effective over the long term in patients with  $\beta$ -thalassemia major, a finding that is supported by data from the extension studies over a median treatment period of 4.5 years (Figure 2).<sup>28</sup>

Cardiac failure related to myocardial iron overload is the leading cause of death in regularly transfused patients with  $\beta$ -thalassemia major.<sup>4,36</sup> Evidence for the ability of deferasirox to remove cardiac iron in patients with  $\beta$ -thalassemia major has been demonstrated in a number of studies.<sup>37-41</sup> The largest of these was a substudy of EPIC, where deferasirox significantly improved myocardial T2\* in patients with mild, moderate and severe myocardial siderosis (11.2 ms at baseline to 12.9 ms at 12 months; P < 0.0001) (Figure 4a).<sup>41</sup> Left ventricular ejection fraction (LVEF) is a useful surrogate marker of cardiac function and is often used when evaluating the cardiac efficacy of an iron chelator. It was evaluated in the EPIC and ESCALATOR trials, which enrolled patients with baseline LVEF within the reference range for healthy

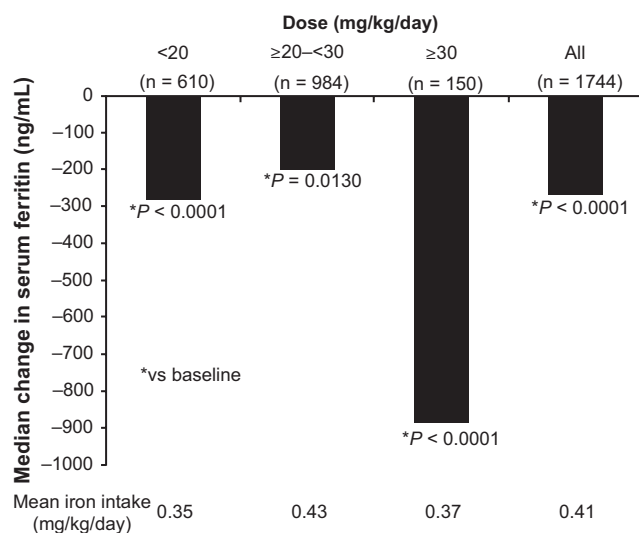
adults (ie,  $\geq 56\%$ ). LVEF, as measured by echocardiogram or cardiovascular magnetic resonance, was maintained at approximately 67% in the EPIC substudy,<sup>41</sup> and improved significantly from 65.1% to 66.8% (P = 0.0002) in the 1-year core ESCALATOR study.<sup>24</sup> As well as removing iron from the heart, deferasirox may also prevent the accumulation of cardiac iron in iron-overloaded patients with normal cardiac iron levels (Figure 4b).<sup>42</sup> This ability may potentially help in preventing future cardiac failure associated with myocardial siderosis in patients with  $\beta$ -thalassemia major.

### $\beta$ -thalassemia intermedia

Although patients with  $\beta$ -thalassemia intermedia are rarely transfused they are still at risk for developing iron overload due to increased intestinal iron absorption secondary to chronic anemia. Few studies with chelation therapy have been conducted in this population to date. However, data are emerging from small numbers of patients demonstrating that deferasirox can significantly decrease mean serum ferritin levels over 1 year of treatment (1356 to 914 ng/mL, P < 0.05;<sup>43</sup> 2030 to 1165 ng/mL, P = 0.02,<sup>44</sup> at doses of 10 to 20 mg/kg/day, respectively). A large prospective study is underway to fully evaluate the use of deferasirox in patients with thalassemia intermedia.

### Myelodysplastic syndromes

Several studies have demonstrated the efficacy of deferasirox in maintaining or reducing body iron burden in patients



**Figure 3** Median change from baseline in serum ferritin in patients enrolled in the EPIC study.<sup>26</sup>

with MDS.<sup>22,31,45-48</sup> As in the  $\beta$ -thalassemia population, deferasirox has dose-dependent efficacy in patients with MDS.<sup>22</sup> The largest cohort of MDS patients ( $n = 341$ ) ever assessed with iron chelation therapy were enrolled in the EPIC study; with appropriate dose adjustments, significant reductions in serum ferritin were noted after 1 year of deferasirox treatment (Table 2).<sup>26,31</sup> Another large study in 176 heavily iron-overloaded MDS patients also showed decreases in serum ferritin.<sup>46</sup> Preliminary data suggest that in addition to decreases in serum ferritin, improvements in hematological parameters can occur with deferasirox treatment in patients with MDS.<sup>49</sup> Serum ferritin decreases during deferasirox treatment in patients with MDS have been shown to be associated with significant improvements in alanine aminotransferase (ALT), which is an indicator of hepatocellular injury.<sup>47,50</sup> This is of importance given that liver dysfunction is a common complication in MDS;<sup>51,52</sup> prospective studies are warranted to further investigate this observation. MDS patients who are most likely to benefit from receiving chelation therapy are transfusion-dependent patients with lower-risk MDS (ie, Low or Int-1 International Prognostic Scoring System) and life expectancy  $>1$  year, who have serum ferritin levels of  $>1000$  ng/mL.<sup>53,54</sup>

### Sickle cell disease

Deferasirox has also demonstrated dose-dependent efficacy in the SCD population.<sup>23</sup> In one Phase II study in adult and pediatric patients, LIC was significantly reduced from baseline after 1 year of deferasirox treatment ( $P < 0.05$ ).<sup>23</sup> Serum ferritin levels were also decreased, although there

was substantial inpatient variability. Deferasirox doses of 10 to 30 mg/kg/day were shown to have similar efficacy to DFO. Of 195 patients enrolled in this 1-year study, 132 entered the ongoing extension phase. To date, these patients have received deferasirox for a median treatment period of 3.1 years and have shown continued reduction in serum ferritin levels ( $-651$  ng/mL from baseline;  $P = 0.0533$ ).<sup>55</sup> Further evidence for the efficacy of deferasirox in SCD is emerging from smaller studies that have demonstrated substantial reductions in serum ferritin and liver iron levels over 1 year.<sup>56,57</sup>

### Aplastic anemia, Diamond-Blackfan anemia, and other rare anemias

Patients with AA, DBA and other types of rare anemia often require blood transfusions as supportive therapy; however, the efficacy of chelation therapy has rarely been evaluated in these populations. A 1-year prospective Phase II trial with deferasirox included 30 patients with DBA and 22 patients with other rare anemias (including AA,  $\alpha$ -thalassemia and sideroblastic anemia).<sup>22</sup> Significant, dose-dependent effects on LIC and serum ferritin were observed in both groups over the 1-year treatment period.<sup>22,58,59</sup> Patients with AA ( $n = 116$ ), DBA ( $n = 14$ ) and rare anemias ( $n = 43$ ) were also enrolled in the EPIC study and significant overall reductions in serum ferritin from baseline to 1 year were observed in each of the disease groups (Table 2).<sup>32-34</sup> As with the overall EPIC population, changes in serum ferritin were reflective of dose adjustments and iron intake during the study. A similar observation has been made based on interim data from 50 patients with AA in Korea, where significant reductions in mean LIC ( $P = 0.01$ ) and serum ferritin ( $4185$  to  $2913$  ng/mL,  $P < 0.01$ ) were noted over the 1-year treatment period.<sup>48</sup>

### Pediatric patients

The deferasirox clinical trial program included patients with a wide range of ages. Pediatric patients (aged 2 to 16 years) were well represented, comprising approximately 40% of all patients enrolled in the five pivotal studies. When used at appropriate doses for the degree of iron burden and the ongoing transfusional iron intake, deferasirox provides dose-dependent efficacy in pediatric patients for up to 5 years of treatment;<sup>29,60</sup> these effects are similar to those observed in adult patients.<sup>28</sup> Efficacy data have been confirmed by the large number of pediatric patients ( $n = 166$ ) enrolled in the ESCALATOR study.<sup>24</sup> In this heavily iron-overloaded pediatric population, significant decreases in mean LIC ( $-7.9 \pm 8.7$  mg Fe/g dw;  $P < 0.0001$ ) and median serum

**Table 2** Efficacy of deferasirox across various transfusion-dependent anemias: data from the EPIC trial

	$\beta$ -thalassemia major (n = 937) <sup>30</sup>	MDS (n = 341) <sup>31</sup>	AA (n = 116) <sup>32</sup>	Rare anemias (n = 43) <sup>33</sup>	DBA (n = 14) <sup>34</sup>
Baseline, ng/mL*	3157	2730	3254	3161	2289
Change at 1 year, ng/mL*	-129	-253	-964	-832	-790
P value	0.0007	0.0019	0.0003	0.0275	0.0121
Deferasirox dose, mg/kg/day**	24.2 ± 5.6	19.2 ± 5.4	17.6 ± 4.8	18.6 ± 5.6	21.0 ± 4.8

\*Serum ferritin data are presented as median; \*\*Dose data are presented as mean ± SD.

**Abbreviations:** AA, aplastic anemia; DBA, Diamond-Blackfan anemia; MDS, myelodysplastic syndromes.

ferritin (−1126 ng/mL;  $P < 0.0001$ ) were observed after a median of 2.8 years' treatment.<sup>61</sup>

### Effect of deferasirox on labile plasma Iron

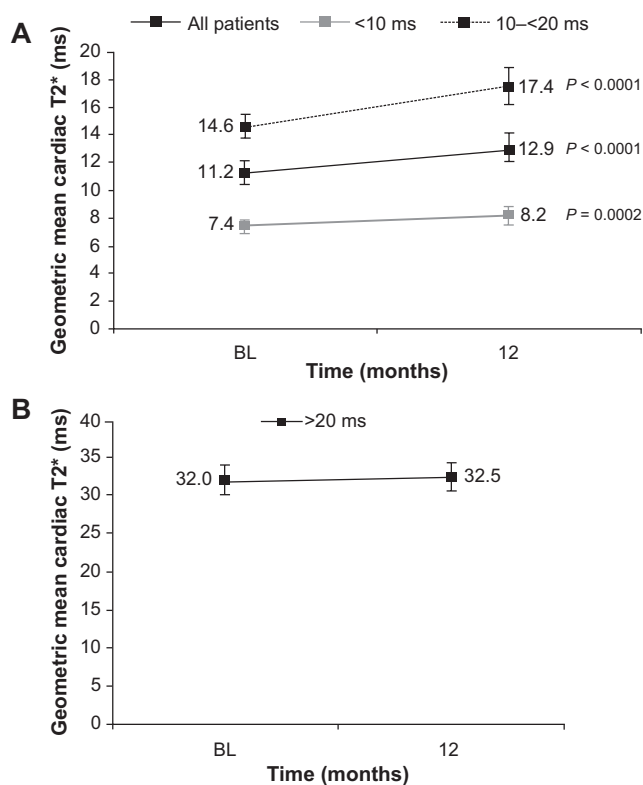
Excess iron in the blood saturates the iron-binding protein transferrin leading to non-transferrin-bound iron (NTBI) in the plasma. The cellular uptake of NTBI is uncontrolled, which can potentially lead to excessive accumulation of labile iron in tissues such as the heart, liver and endocrine system. This labile iron may be a key mediator of iron toxicity due to its ability to catalyze production of reactive oxygen species.<sup>62</sup> Control of labile plasma iron (LPI) is therefore an important aim of chelation therapy. In the ESCALATOR study in patients with  $\beta$ -thalassemia, LPI levels were analyzed using an assay that measured iron-specific redox cycling capacity in the presence of low ascorbate concentrations.<sup>63</sup> Redox reactions were detected by the oxidation of a fluorogenic probe to its fluorescent form, which allowed distinction of chelator-bound from chelator-free LPI. Data from this study demonstrated that daily trough levels of deferasirox are sufficient to maintain suppression of LPI (Figure 5).<sup>64</sup> After 4 weeks of treatment and throughout the remainder of the 1-year treatment period, peak LPI levels observed just before deferasirox dosing were significantly decreased compared with baseline and remained within normal values. Similar sustained reductions in LPI with deferasirox have been observed in other disease cohorts, including MDS and AA.<sup>46,65,66</sup> These findings support the concept that once-daily deferasirox therapy may decrease unregulated tissue iron loading and prevent further end-organ damage across various transfusion-dependent anemias.

### Safety and tolerability of deferasirox

Deferasirox has a well characterized and manageable safety profile in adult and pediatric patients as young as 2 years with various transfusion-dependent anemias.<sup>20–23</sup> Most patients remain on deferasirox therapy and adverse events

are not a common reason for study discontinuation; eg, only 74 of >1000 patients enrolled in the core clinical studies discontinued treatment with deferasirox due to the occurrence of adverse events.<sup>16,20–23</sup> The most common drug-related adverse events reported during deferasirox treatment include transient, mild-to-moderate gastrointestinal disturbances (such as nausea, vomiting, abdominal pain and diarrhea) and skin rash; these events generally resolved spontaneously. For severe skin rash deferasirox should be interrupted until the rash has resolved; reintroduction at a lower dose with subsequent gradual escalation may then be considered in combination with a short period of oral steroid administration. Mild, non-progressive increases in serum creatinine, generally within the upper limit of normal (ULN), were observed in approximately one-third of patients in the pivotal 1-year clinical trials.<sup>16,20–23</sup> Serum creatinine levels spontaneously returned to baseline in approximately two-thirds of patients who experienced these increases.<sup>67</sup> There were no cases of moderate-to-severe renal insufficiency or renal failure and no patients permanently discontinued treatment due to creatinine increases. If there is an increase in serum creatinine beyond the age-appropriate ULN, deferasirox should be interrupted until levels have returned to the normal range. Treatment may then be restarted at a lower dose with gradual escalation. In the 1-year studies elevations of liver transaminases were reported in about 2% of patients; these were not dependent on dose and most patients had elevated baseline levels. Elevations greater than  $10 \times$  ULN, suggestive of hepatitis, were uncommon (0.3%).<sup>10</sup> Following any unexplained, persistent, or progressive increases in serum transaminases, deferasirox treatment should be interrupted. Once the cause of the transaminase increases has been established or when levels have returned to normal, deferasirox may be restarted at a lower dose followed by gradual escalation.

The tolerability and safety profile of deferasirox in pediatric patients is similar to that observed in adults.<sup>29</sup> As growth retardation and hypogonadism remain significant



**Figure 4** The effect of deferasirox on the mean cardiac T2\* by baseline T2\* in patients **A)** with cardiac iron overload; **B)** with normal cardiac levels.<sup>41,42</sup>

clinical problems in pediatric patients with  $\beta$ -thalassemia, it is important to note that growth and sexual development proceed normally during deferasirox therapy.<sup>24,29</sup> In the ESCALATOR study, growth in pediatric patients was assessed based on height standard deviation score (h-SDS).<sup>68</sup> At baseline, both boys and girls were initially smaller than the reference group across all ages (2 to <6, 6 to <12 and 12 to <16 years).<sup>24</sup> Over the 1-year study period, the observed growth as evaluated by change from baseline in h-SDS showed growth improvements (>0.5 SDS) in 18.1% of patients, worsening in growth in 9.4% of patients, and no change from baseline in 72.5% of patients. In this population, girls aged 12 to <16 years showed a notable improvement in growth, with 66.7% of this cohort exhibiting a net increase in h-SDS (25% percentile or first quartile = -0.06).<sup>24</sup>

### Long-term safety of deferasirox

Safety data with deferasirox has now been reported for up to 5 years of treatment (Table 3).<sup>28,60,69</sup> Based on 472 patients with  $\beta$ -thalassemia who received deferasirox for a median of 4.5 years, 50 (10.6%) discontinued due to adverse events. The types of drug-related adverse events reported in the extension studies were similar to those reported in the initial

**Table 3** Most common drug-related adverse events during a median 4.5-year treatment period with deferasirox in 472 patients with  $\beta$ -thalassemia<sup>28\*</sup>

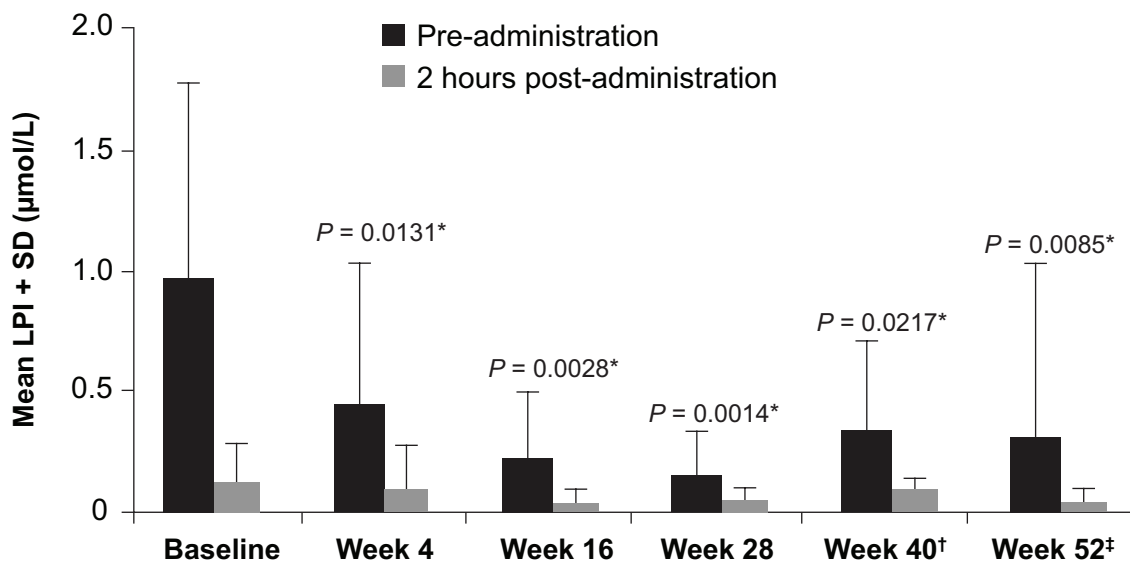
Adverse event	Frequency, n (%)
Abdominal pain	62 (13.1)
Nausea	55 (11.7)
Diarrhea	40 (8.5)
Vomiting	32 (6.8)
Rash	23 (4.9)

\*Pooled data from core and extension phases of 4 pivotal studies.

1-year treatment period, and the annual frequency generally decreased from year to year, ranging from 0% to 2.3% in years 2 to 5.<sup>28</sup> In addition, there were no progressive increases in serum creatinine over longer-term deferasirox treatment.<sup>28</sup> The long-term safety profile of deferasirox in diseases other than  $\beta$ -thalassemia is also available. Deferasirox has a well characterized and manageable safety profile in SCD patients for up to 3.5 years of treatment and no progressive increases in serum creatinine were observed, demonstrating a favorable renal safety profile in these patients who are at risk of progressive renal disease.<sup>69</sup> In MDS patients the most common adverse events are gastrointestinal disturbances and skin rash, similar to that observed with  $\beta$ -thalassemia patients.<sup>31</sup>

### Drug interactions and post-marketing surveillance

Deferasirox inhibits CYP3A4 and CYP2C8 *in vitro*, therefore caution should be used when administering deferasirox with drugs metabolized by these enzymes. Deferasirox also inhibits CYP1A2, CYP2A6, CYP2D6, and CYP2C19, however the clinical significance of this is unknown. The concomitant use of deferasirox with potent UDP-glucuronosyltransferase inducers (eg, rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in deferasirox efficacy. The concomitant administration of deferasirox with other iron chelators, aluminum-containing antacid preparations, vitamin C or hydroxyurea has not been formally studied. There have been post-marketing reports of cytopenias (both spontaneous and from clinical trials) in patients treated with deferasirox, although all of these patients had either pre-existing hematologic disorders that are commonly associated with bone-marrow failure or complications of the underlying disease that are associated with cytopenias (eg, hypersplenism, sickle cell crisis, administration of chemotherapy). The relationship of these episodes to treatment with deferasirox is uncertain. As with the standard



**Figure 5** Mean labile plasma iron (LPI) taken pre-administration and 2 hours post-administration of deferasirox reproduced with permission. Daar S, Pathare A, Nick H, et al. Reduction in labile plasma iron during treatment with deferasirox, a once-daily oral iron chelator, in heavily iron-overloaded patients with  $\beta$ -thalassaemia. *Eur J Haematol.* 2009;82(5):454–457. © Wiley-Blackwell 2009.

\*Versus pre-administration at baseline.

LPI data are from 13 patients except †n = 11 ‡n = 12 due to lost samples.

clinical management of such hematological disorders, blood counts should be monitored regularly. Post-marketing cases of acute renal failure, some with a fatal outcome, have also been reported. Most of the fatalities occurred in patients with severe complications related to the underlying disease (eg, patients with multiple co-morbidities who were in advanced stages of disease). It is therefore recommended that particular attention is given to monitoring serum creatinine levels in patients who have preexisting renal conditions, are elderly, have co-morbid conditions that may affect renal function, or are receiving medicinal products that depress renal function. There have also been post-marketing reports of hepatic failure, some with a fatal outcome, in patients treated with deferasirox. Most of these events occurred in patients with significant comorbidities, including liver cirrhosis and multi-organ failure. In addition, upper gastrointestinal ulceration and hemorrhage have been reported in some patients, including children and adolescents, receiving deferasirox. Physicians and patients should remain alert for signs and symptoms of these events and promptly initiate additional evaluation and treatment if a serious gastrointestinal adverse event is suspected.

### Safety at low iron burden and high deferasirox doses

Maintaining serum ferritin levels below 1000 ng/mL is known to be associated with a reduced risk of iron-overload-related complications, such as heart failure, in patients with

thalassaemia.<sup>5</sup> However, as the use of DFO has been associated with increased toxicity at low serum ferritin levels, it is of interest to assess the adverse event profile of patients enrolled in the deferasirox studies who achieved serum ferritin levels of <1000 ng/mL.<sup>5,70,71</sup> An analysis of 174 patients demonstrated a similar safety profile to that observed in patients who did not achieve serum ferritin levels of <1000 ng/mL (n = 300).<sup>72</sup> For example, the frequency of drug-related adverse events such as nausea (14.9% vs 12.7%), vomiting (8.0% vs 8.3%) and skin rash (5.2% vs 5.3%), were comparable. In addition, similar proportions of patients experienced increases in serum creatinine >33% above baseline and ULN (14.9% vs 12.0%) and increases in ALT > 10 × ULN (6.9% vs 6.7%). These data suggest that when appropriately dosed, serum ferritin can be maintained at levels lower than 1000 ng/mL during deferasirox treatment without increases in the frequency or type of adverse event reported.<sup>73</sup>

Data from patients who have received deferasirox doses of >30 mg/kg/day demonstrate that the safety profile is consistent with that observed at doses of <30 mg/kg/day.<sup>35</sup> The most common drug-related adverse events were gastrointestinal events such as vomiting (n = 7, 3.1%), abdominal pain and nausea (n = 4, 1.8% for both).<sup>35</sup>

### Health economics of deferasirox

It is well established that compliance is a key factor determining outcome of iron chelation therapy,<sup>3,74</sup> and



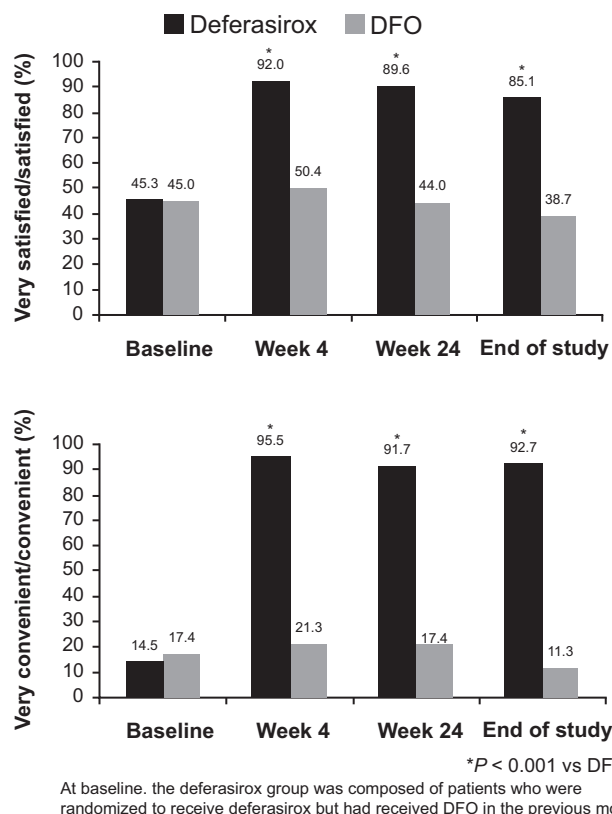
the route of administration has an impact on compliance. Due to the need for 8- to 12-hour infusions, 5 to 7 times per week, compliance with DFO is suboptimal, ranging from 59% to 78%.<sup>6</sup> Poor compliance with treatment can lead to serious morbidities and have a significant impact on cost, for example complications of iron overload such as heart disease or diabetes may increase annual costs by US\$40,000.<sup>75</sup> As deferasirox is a once-daily oral treatment, improvements in compliance compared with DFO may lead to improved patient outcomes and lower treatment costs. These have been evaluated in a number of analyses.

### Cost effectiveness of deferasirox

Two separate studies have compared the cost-effectiveness of DFO and deferasirox.<sup>76,77</sup> In a US model, treatment with deferasirox resulted in an additional 4.5 quality adjusted life years (QALYs) per patient at an additional lifetime cost of US\$126,018 per patient, translating into a cost-effectiveness ratio of US\$28,255 per QALY gained.<sup>76</sup> Deferasirox was also associated with lower net costs and higher QALYs than DFO in a UK-based model.<sup>77</sup> In this analysis drug dose and cost was related to patient weight; for patients with a mean weight of 62 kg the incremental cost per QALY gained was £7775.<sup>77</sup>

### Effect of deferasirox on patient-reported outcomes

A number of deferasirox studies have evaluated patient-reported satisfaction, convenience and treatment preference, which may provide surrogate measures for treatment compliance, in patients with  $\beta$ -thalassemia, SCD and MDS.<sup>78–81</sup> In one study, 97% of patients with  $\beta$ -thalassemia who switched from DFO to deferasirox reported that they preferred deferasirox to DFO, primarily due to convenience (37%), no injection-site soreness (25%) and less daily disruption (23%).<sup>78</sup> Most patients were more satisfied with deferasirox therapy and found it to be more convenient than DFO (Figure 6).<sup>78</sup> Similarly, another study found that 91% of 252 patients with  $\beta$ -thalassemia were 'satisfied/very satisfied' with treatment after 1 year compared with 23% at baseline (all patients had received DFO and/or deferiprone prior to initiation of deferasirox).<sup>80</sup> Time lost for normal activities due to chelation therapy was substantially reduced with deferasirox treatment compared with prior treatments (from 28.8 hours/month at baseline to 3.0 hours/month after 1 year).<sup>80</sup> Similar results have been observed in patients with SCD.<sup>81</sup> Improvements in health-related quality of life, based on SF-36 domain scores (eg, physical functioning and general health), were



**Figure 6** Overall treatment satisfaction with iron chelation therapy in patients previously treated with deferoxamine (DFO). Reprinted from *Clinical Therapeutics*. Cappellini MD, Bejaoui M, Agaoglu L, et al. Prospective evaluation of patient-reported outcomes during treatment with deferasirox or deferoxamine for iron overload in patients with  $\beta$ -thalassemia. *Clin Ther*. 2007;29(5):909–917<sup>78</sup> with permission from Excerpta Medica, Inc.

observed during 1 year of deferasirox treatment in patients with  $\beta$ -thalassemia (n = 274), MDS (n = 168) and SCD (n = 50) who were enrolled in the EPIC study.<sup>82</sup>

### Conclusions and place in therapy

This article demonstrates the efficacy and safety profile of the oral iron chelator deferasirox, which has specific advantages over the other available chelators due to its formulation and route of administration. The large clinical development program including patients with various underlying anemias has demonstrated the ability of deferasirox to remove iron from the liver and heart. The efficacy of deferasirox is dependent on appropriate dosing according to current iron burden, ongoing transfusional iron intake and safety markers,<sup>27,30</sup> and regular monitoring of these parameters is necessary to ensure dose adjustments are made in a timely manner.<sup>10</sup> Recent data from a substudy of EPIC have confirmed the findings of previous smaller studies demonstrating that deferasirox can remove cardiac iron and maintain cardiac function based on LVEF.<sup>39,41,42</sup> Data from this substudy also show that deferasirox

can prevent the accumulation of cardiac iron, highlighting the importance of early intervention to aid in the prevention of future cardiac events resulting from myocardial siderosis.<sup>83–85</sup> Data from several studies of up to 5 years' duration provide support for the long-term efficacy of deferasirox in maintaining or reducing overall iron burden across a range of anemias.<sup>28,55</sup> Deferasirox is well tolerated with a manageable safety profile over long-term treatment in both pediatric and adult patients. The frequency of treatment-related adverse events generally decreases over time; the most common adverse events reported are mild-to-moderate gastrointestinal disorders and skin rash.<sup>28,29,35</sup> The safety profile is similar at doses above and below 30 mg/kg/day and at serum ferritin levels above and below 1000 ng/mL.<sup>72</sup> Improved satisfaction with, and convenience of, deferasirox compared with DFO has also been shown,<sup>78–81</sup> which may translate into improved compliance and subsequent cost savings. In conclusion, once-daily oral therapy with deferasirox provides a significant development in the treatment of iron overload in patients with transfusion-dependent anemias.

## Disclosures

Ali Taher has received research grants and honoraria from Novartis Pharmaceuticals. Maria Domenica Cappellini has received honoraria from Novartis Pharmaceuticals, and is a member of their Speaker's Bureau.

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