One-year results from a prospective randomized trial comparing phlebotomy with deferasirox for the treatment of iron overload in pediatric patients with thalassemia major following curative stem cell transplantation

Adlette Inati1,2 | Mario Kahale2∗ | Nada Sbeiti3 | Maria Domenica Cappellini4 | Ali T. Taher5 | Suzanne Koussa6 | Therese A. Nasr6 | Khaled M. Musallam5† | Hussein A. Abbas7 | John B. Porter8

1Lebanese American University and University Medical Center Rizk Hospital | 2Rafik Hariri University Hospital, Beirut, Lebanon | 3Zahraa University Hospital, Beirut, Lebanon | 4Università di Milano, Ca Granda Foundation IRCCS, Milan, Italy | 5American University of Beirut, Beirut, Lebanon | 6Chronic Care Center, Hazmieh, Lebanon | 7University of Texas MD Anderson Cancer Center, Houston, Texas | 8University College London, London, UK

Correspondence Adlette Inati, Division of Pediatric Hematology/Oncology, Rafik Hariri University Hospital, Beirut, Lebanon. Email: adlette.inati@lau.edu.lb

Present address Mario Kahale, Novartis Pharma AG, Basel, Switzerland.

Present address Khaled M. Musallam, Evidamedical, London, UK.

Abstract

Background: Iron overload is well documented in patients with β-thalassemia major, and patients who have undergone hematopoietic stem cell transplantation (HSCT) remain at risk as a result of pre- and immediate post-HSCT transfusions.

Procedure: This is a prospective, randomized, 1-year clinical trial that compares the efficacy and safety of the once-daily oral iron chelator deferasirox versus phlebotomy for the treatment of iron overload in children with β-thalassemia major following HSCT.

Results: Patients (aged 12.4 years) received deferasirox (n = 12, 10 mg/kg/day starting dose) or phlebotomy (n = 14, 6 ml/kg/2 weeks) for 1 year. In two and five patients, deferasirox dose was increased to 15 and 20 mg/kg/day, respectively. Magnetic resonance imaging (MRI)–assessed liver iron concentration (LIC) decreased with deferasirox (mean 12.5 ± 10.1 to 8.5 ± 9.3 mg Fe/g dry weight [dw]; P = 0.0005 vs. baseline) and phlebotomy (10.2 ± 6.8 to 8.3 ± 9.2 mg Fe/g dw; P = 0.05). LIC reductions were greater with deferasirox than with phlebotomy for patients with base-line serum ferritin 1,000 ng/ml or higher (–8.1 ± 1.5 vs. –3.5 ± 5.7 mg Fe/g dw; P = 0.048). Serum ferritin and non-transferrin-bound iron also decreased significantly. In two patients with severe cardiac siderosis, a clinically relevant improvement in myocardial T2* was seen, following phlebotomy and deferasirox therapy (n = 1 each). Adverse effects with deferasirox were skin rash, gastrointestinal upset, and increased liver function tests (all n = 1), while those for phlebotomy were difficulty with venous access (n = 4) and distress during procedure (n = 1). Parents of 13/14 children receiving phlebotomy wished to switch to deferasirox, with 1/14 being satisfied with phlebotomy.

Conclusions: Deferasirox treatment or phlebotomy reduces iron burden in pediatric patients with β-thalassemia major post-HSCT, with a manageable safety profile.

KEYWORDS
deferasirox, hematopoietic stem cell transplant, phlebotomy, randomized controlled trial, thalassemia

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; CMR, cardiovascular magnetic resonance; dw, dry weight; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; LIC, liver iron concentration; LPI, labile plasma iron; MRI, magnetic resonance imaging; NTBI, non-transferrin-bound iron; SD, standard deviation; TIBC, total iron-binding capacity; UIBC, unsaturated iron-binding capacity
With increasing success of allogeneic hematopoietic stem cell transplantation (HSCT) as a curative therapy for \(\beta\)-thalassemia major, it is becoming more relevant to follow-up and assess patient care in the long term.\(^1\) Iron overload is well documented in patients with \(\beta\)-thalassemia major,\(^5\) and those who have undergone HSCT remain at risk as a result of pre- and immediate post-HSCT transfusions.\(^8,9\) Additionally, the HSCT conditioning regimen involves ablation of hematopoietic stem cells, causing decreased clearance of transferrin iron by the bone marrow cells expressing transferrin receptors, with the formation of non-transferrin-bound iron (NTBI).\(^10–12\) With the regeneration of bone marrow and transferrin receptor-bearing erythropoietic cells, transferrin iron clearance returns and transferrin saturation and NTBI fall but remain raised in those patients who have accumulated a transfusional iron load.\(^10\) NTBI is cleared by and accumulated in extra-hepatic tissues such as the myocardium,\(^13,14\) catalyzing the formation of free radicals and oxidative stress, ultimately culminating in end-organ damage.\(^15\) NTBI availability to microorganisms leads to an increased risk of infection.\(^16\) In HSCT, elevated NTBI is a key indicator of adverse outcome.\(^17\)

The implications of iron overload during HSCT have been examined. Prior to HSCT, excess iron may increase transplant-related mortality and worsen overall survival,\(^18\) as well as increase the risk of complications such as infection.\(^19,20\) In the post-HSCT setting, iron overload has been associated with reduced survival up to 5 years posttransplant,\(^3\) as well as complications such as hepatic fibrosis.\(^21\) The removal of iron to prevent associated negative outcomes after curative HSCT for \(\beta\)-thalassemia major is therefore warranted.

Studies in pediatric and adult patients have confirmed the safety and efficacy of phlebotomy in the post-HSCT setting, with and without the use of erythrocyte-stimulating agents.\(^8,22–24\) However, phlebotomy may not be well tolerated and patient adherence can vary;\(^25,26\) such that oral iron chelation may be preferable for some patients. The efficacy and safety of iron chelation therapy in \(\beta\)-thalassemia major is well established,\(^27–32\) and the survival benefit of iron chelation prior to HSCT has also been documented.\(^33\) However, data are limited in the post-HSCT setting in pediatric patients.\(^34–36\) Additionally, there is a lack of prospective data comparing the efficacy, safety, and patient satisfaction with iron chelation therapy or phlebotomy to in help in informed treatment decision-making.

We initiated a prospective, randomized, 1-year clinical trial that compares the efficacy and safety of the once-daily oral iron chelator deferasirox with phlebotomy for the treatment of iron overload in children with \(\beta\)-thalassemia major following HSCT. A secondary objective was to assess the perceived convenience of deferasirox compared with phlebotomy and patient adherence to the treatment.

## Methods

### Inclusion criteria

\(\beta\)-Thalassemia major patients aged 2 to less than 18 years who had undergone HSCT and had iron overload as shown by a serum ferritin level of at least 500 ng/ml on two consecutive readings at least 1 month apart and a liver iron concentration (LIC) higher than 3 mg Fe/g dry weight (dw) were included. Patients were negative for hepatitis B and C, as well as for graft-versus-host disease (GVHD). All patients fitting the inclusion criteria between June 2009 and April 2010 were included in the study and then randomized to either groups.

### Study design

The study was conducted at two sites in Lebanon. Enrolled patients were assigned a number, which was sent to a blinded person who entered it into a pre-prepared randomization table. Patients were randomized to phlebotomy (6 ml/kg blood every 2 weeks) or deferasirox (10 mg/kg/day). Deferasirox dose adjustments of 5-mg increments up to a maximum of 20 mg/kg/day were permitted every 3 months, if serum ferritin levels were unchanged or increased by 20% or more from baseline value and if the patient had not experienced any adverse event (AE). Treatment was interrupted if serum ferritin levels decreased to less than 300 ng/ml or if AEs occurred.

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by institutional ethics committees at the participating sites. All patients/parents provided written informed consent.

### Assessments

The primary endpoint was change in LIC as determined by spin-density projection-assisted R2 magnetic resonance imaging (MRI; FerriScan\(^8\)). Other measures of efficacy included change in serum ferritin levels, hemoglobin, total iron-binding capacity (TIBC), NTBI, and labile plasma iron (LPI). TIBC was calculated as the sum of serum iron and unsaturated iron-binding capacity (UIBC). Serum NTBI content was assayed by high-performance liquid chromatography according to the method of Porter et al.,\(^37\) with minor modifications. The LPI assay was performed as previously described,\(^38\) but using standards prepared in plasma-like medium containing 20 mg/ml human serum albumin. Transferrin was measured using the BN ProSpec System (Siemens Health Care Diagnostics).

Cardiovascular magnetic resonance (CMR) assessment of T2* was conducted and results were assessed at a central laboratory. Compliance with study treatment was also assessed. For phlebotomy, the ratio of performed and planned sessions was calculated and a tablet count of deferasirox was taken. Convenience of treatment was evaluated using parents’ responses to pre-prepared questions.

### Statistical analysis

General linear models (changes in LIC or serum ferritin as dependent variables) were performed, accounting for multiple potential influential factors simultaneously as follows: \(\text{delta} = f(x)\), where \(x\) is age at HSCT, mutation, gender, transfusions, risk class, LIC at HSCT, or serum ferritin level at HSCT. In this model, both transfusions and risk classes were varied. Differences between two measurements were tested with a paired \(t\)-test (two-sided, \(\alpha\) level of 0.05). The pooled standard
3 | RESULTS

3.1 | Patient demographics

All patients underwent HSCT using bone marrow from a human leukocyte antigen-identical family member, except for one case where an unrelated donor was used. Following the HSCT procedure, no patient had received any red blood cell transfusions, or iron chelation therapy prior to study initiation. In total, 27 patients with a median age of 3.4 years and a range of 1.25–5.4 years post-HSCT were randomized to either deferasirox (n = 12) or phlebotomy (n = 14). One patient randomized to deferasirox refused treatment and was not included in further analyses. As shown in Table 1, baseline patient characteristics were comparable between treatment groups. Baseline iron burden was considerably high in over half of patients. Patients were grouped according to their baseline iron burden for further analysis; 58.3% of deferasirox patients and 50.0% of phlebotomy patients had LIC higher than 7 mg Fe/g dw.

3.2 | Deferasirox dosing and phlebotomy volumes

Two and five patients had deferasirox dose increased to 15 and 20 mg/kg/day, respectively. The mean ± SD deferasirox dose at the last visit was 11.0 ± 2.2 mg/kg/day in the LIC less than or equal to 7 mg Fe/g dw and 18.1 ± 3.4 mg/kg/day in the LIC higher than 7 mg Fe/g dw

3.3 | Efficacy of iron removal

The mean duration of follow-up was 11.4 ± 1.1 months in patients receiving deferasirox and 11.6 ± 0.9 months in those undergoing phlebotomy. In total, five patients receiving deferasirox reached the stopping target of serum ferritin level below 300 ng/ml (all patients received 10 mg/kg/day), and six phlebotomy patients achieved this target. Of these patients, all apart from two phlebotomy patients had baseline serum ferritin levels less than 1,000 ng/ml; two other patients receiving either deferasirox or phlebotomy had LIC higher than 7 mg Fe/g dw at baseline.

Iron parameters before and after 1 year of treatment with deferasirox or phlebotomy are shown in Table 2. After 1 year of treatment, 20 patients had evaluable LIC measurements. LIC was significantly reduced from baseline with deferasirox (−5.8 ± 3.0 mg Fe/g dw; P = 0.0005 vs. baseline) and phlebotomy (−3.3 ± 4.9 mg Fe/g dw; P = 0.05; Fig. 1A). In patients with baseline serum ferritin levels 1,000 ng/ml or higher, deferasirox resulted in a significantly greater decrease in mean LIC when compared with phlebotomy (−8.1 ± 1.5 vs. −3.5 ± 5.7 mg Fe/g dw; P = 0.048) (Fig. 1A).

The median (range) serum ferritin level was significantly reduced from baseline over 1 year with deferasirox (−498 [−1,884 to −142] ng/ml; P = 0.0014 vs. baseline). Phlebotomy also led to a reduction in serum ferritin levels at end of study (−902 [−1,777 to −280] ng/ml; P < 0.0001 vs. baseline; Fig. 1B). There was no significant difference between treatment groups overall (P = 0.368), nor among iron overload categories.

With the exception of one patient, who had myocardial T2* 19.9 ms, all patients with cardiac siderosis had substantial body iron burden with LIC higher than 7 mg Fe/g dw and serum ferritin at least 1,000 ng/ml.
TABLE 2  Iron parameters before and after 1-year treatment with deferasirox or phlebotomy in pediatric β-thalassemia major patients following allogeneic HSCT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Deferasirox (n = 12)</th>
<th>Phlebotomy (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of study</td>
</tr>
<tr>
<td></td>
<td>LIC, mg Fe/g dw</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.5 ± 10.1</td>
<td>8.5 ± 9.3</td>
</tr>
<tr>
<td>P = 0.00045</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum ferritin, ng/ml</td>
<td>999 (503 to 5,884)</td>
<td>515 (139 to 4,000)</td>
</tr>
<tr>
<td>TIBC, μM</td>
<td>45.2 ± 5.9</td>
<td>61.5 ± 16.8</td>
</tr>
<tr>
<td>P = 0.0012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTBI, μmol/l</td>
<td>2.0 ± 2.0</td>
<td>0.2 ± 0.9</td>
</tr>
<tr>
<td>P = 0.014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPI, μmol/l</td>
<td>0.13 ± 0.25</td>
<td>0.15 ± 0.42</td>
</tr>
<tr>
<td>P = NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transferrin saturation, %</td>
<td>57.8 ± 26.7</td>
<td>42.0 ± 14.0</td>
</tr>
<tr>
<td>P = 0.026</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD, with the exception of serum ferritin, which is shown as median (range).

FIGURE 1  Absolute change in iron parameters during 1-year treatment with deferasirox or phlebotomy in pediatric β-thalassemia major patients following allogeneic HSCT: (A) LIC, (B) serum ferritin levels, (C) NTBI, and (D) LPI

1,000 ng/ml. Overall, two patients had severe cardiac siderosis, indicated by myocardial T2* less than 10 ms at study entry. Myocardial T2* improved from 8.9 ms at baseline to 10.6 ms at the end of the study in the patient randomized to phlebotomy and from 8.5 to 11.4 ms in the patient randomized to deferasirox. Notably, in the phlebotomy patient with improved cardiac T2*, substantial decreases from elevated baseline levels of LIC (21.0 mg Fe/g dw at baseline to 13.1 mg Fe/g dw at last follow-up), transferrin saturation (99.7 to 50.3%), LPI (1.4 to −0.2 μmol/l), and NTBI (6.1 to −0.4 μmol/l) were also observed. Improvements in iron parameters in the deferasirox patient were also evident, although baseline elevations were less severe: LIC (from 15.7 to 9.4 mg Fe/g dw), transferrin saturation (from 43.1 to 34.9), LPI (from 0.1 to 0.0 μmol/l), and NTBI (from 1.2 to 0.1 μmol/l). Three other patients had evidence of cardiac siderosis (myocardial T2* 19.2, 18.6, 26.7 ms at baseline).
3.4 | Relationship between iron parameters

There was a strong positive correlation between serum ferritin levels and LIC, both at baseline and after 1 year of treatment (Table 3). Of note, NTBI and LIC were also positively correlated at baseline (R = 0.565; P = 0.0026), with a stronger correlation after 1 year of treatment (R = 0.881; P < 0.0001). NTBI was also correlated with serum ferritin levels. Low levels of LPI correlated only with LIC at baseline (R = 0.574; P = 0.0027).

3.5 | Safety of iron removal therapy

3.5.1 | Adverse events

Two (16.7%) deferasirox patients experienced one or more AEs. These included skin rash (n = 1) and increased liver function tests (n = 1), both of which resolved after treatment interruption. One episode of gastrointestinal upset also resolved after adequate hydration. Four (28.6%) phlebotomy patients experienced difficulty with venous access (reported as an AE). In addition, one patient showed extreme distress during the phlebotomy procedure. Overall, there was no difference in the frequency of AEs between groups (P = 0.473).

3.4.2 | Laboratory parameters

Mean serum creatinine increased slightly overall in patients treated with deferasirox (0.45 ± 0.11 IU/ml at baseline to 0.62 ± 0.23 IU/ml at month 12), although levels remained within the normal range. The majority of deferasirox patients (10/12) did not show progressive increases from baseline to end of study (Fig. 2A). Among the four patients with observed increases from baseline, three patients had LIC higher than 7 mg Fe/g dw and serum ferritin 1,000 ng/ml or higher and iron burden decreased substantially after 1 year of treatment. Of these four patients, one remained on 10 mg/kg/day until treatment was stopped when reaching serum ferritin level less than 300 ng/ml, two patients had dose escalations to 15 mg/kg/day after the initial increase in serum creatinine had occurred, and one patient had dose escalations to 15 and then 20 mg/kg/day, which coincided with increases in serum creatinine but followed an early increase in treatment initiation. Levels returned to baseline levels after cessation of treatment for all patients. Serum creatinine remained stable in phlebotomy patients (0.45 ± 0.12 to 0.47 ± 0.11 IU/ml; Fig. 2B). Individual patient data of alanine aminotransferase (ALT) are shown in Figure 3 and demonstrate stable levels; transient increases were seen in some patients, but these had typically resolved by the next visit either without intervention or with treatment interruption.

3.5 | Patient adherence and treatment satisfaction

The majority (deferasirox: 91.7% [n = 11]; phlebotomy: 85.7% [n = 12]) of patients had excellent adherence to therapy and completed all their deferasirox doses or phlebotomy sessions as scheduled. One patient missed two doses of deferasirox and another had delayed phlebotomy sessions. One phlebotomy patient was poorly compliant and only underwent phlebotomy every 4 weeks. However, this patient discontinued treatment after approximately 7 months when the serum ferritin level dropped below 300 ng/ml, as specified.

When parents of children receiving phlebotomy were asked if they prefer to switch to deferasirox, 13 out of 14 indicated that they would. Their reasons included pain, risk of anemia, longer or more frequent hospital visits, and missing work days or their children missing school. One parent declined to switch from phlebotomy over concerns of possible AEs with deferasirox and indicated satisfaction with phlebotomy. All parents of children receiving deferasirox chose to continue treatment because of the following reasons: once daily oral tablet, fewer/shorter visits, and less needle pricks.

4 | DISCUSSION

Baseline characteristics in this study show that, in the absence of dedicated treatment, pediatric patients cured of β-thalassemia major continue to be iron overloaded for several years post-HSCT. Despite a median 3.4 years between HSCT and MRI measurement at study entry, mean baseline LIC for all patients was 11.3 mg Fe/g dw but ranged as high as 36.6 mg Fe/g dw and median serum ferritin was 1,255 ng/ml, with a maximum of 5,884 ng/ml. Additionally, 26.9% of patients had...
TABLE 3  Correlation of efficacy parameters at baseline and after 1-year treatment with deferasirox or phlebotomy in pediatric β-thalassemia major patients following allogeneic HSCT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LIC</th>
<th>Serum ferritin</th>
<th>NTBI</th>
<th>LPI</th>
<th>Transferrin saturation</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.000</td>
<td>0.825</td>
<td>0.565</td>
<td>0.574</td>
<td>0.658</td>
<td>-0.454</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.0001</td>
<td>= 0.0026</td>
<td>= 0.0027</td>
<td>= 0.0003</td>
<td>= 0.0198</td>
<td></td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>0.825</td>
<td>1.000</td>
<td>0.618</td>
<td>0.300</td>
<td>0.646</td>
<td>-0.525</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.0001</td>
<td>= 0.0008</td>
<td>= NS</td>
<td>= 0.0004</td>
<td>= 0.0059</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>1.000</td>
<td>0.859</td>
<td>0.881</td>
<td>-0.330</td>
<td>0.747</td>
<td>-0.501</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>= NS</td>
<td>= 0.0002</td>
<td>= 0.0244</td>
<td></td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>0.859</td>
<td>1.000</td>
<td>0.898</td>
<td>-0.096</td>
<td>0.635</td>
<td>0.096</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>= NS</td>
<td>= 0.0006</td>
<td>= 0.64</td>
<td></td>
</tr>
</tbody>
</table>

*At last follow-up. Significant correlations are in bold.

FIGURE 2  Serum creatinine during 1-year treatment with (A) deferasirox or (B) phlebotomy in pediatric β-thalassemia major patients following allogeneic HSCT

FIGURE 3  ALT during 1-year treatment with (A) deferasirox or (B) phlebotomy in pediatric β-thalassemia major patients following allogeneic HSCT

LIC higher than 15 mg Fe/g dw, a level known to be associated with increased risk of progressive organ dysfunction and death. Other studies have also demonstrated that iron overload can remain significant for many years after HSCT for hematologic malignancies, which is to be expected since humans have no physiologic pathway for iron excretion. Collectively, these results highlight the need for ongoing assessment of iron burden post-HSCT and the use of appropriate therapeutic intervention to prevent iron-associated organ damage.

Our results demonstrate that 1-year of therapeutic intervention in these patients with either deferasirox or phlebotomy led to a reduction in iron burden, as demonstrated by decreases in LIC, serum ferritin, and NTBI. In two patients with severe cardiac siderosis (myocardial T2* < 10 ms), a clinically relevant improvement in myocardial T2* to a lower risk status for heart failure (T2* > 10 ms) after treatment with either phlebotomy or deferasirox was observed. While improvement in cardiac T2* has been widely reported in clinical studies with deferasirox, improvement in cardiac T2* following removal of liver iron without chelation has not been reported. This is mechanistically important because it suggests that removal of heart iron can occur as a consequence of removing iron from the body, initially
from the liver. It is noteworthy that transferrin saturation decreased during phlebotomy, and most substantially from 99.1 to 50.3% in the patient with improved cardiac T2* providing a potential mechanism for increased iron egress from the heart. This study shows that residual cardiac iron can be decreased with either phlebotomy or deferasirox. Importantly, neither of the patients with high cardiac iron normalized their levels in 1 year with either phlebotomy or deferasirox, so that continued follow-up and treatment is recommended.

Other studies evaluating the efficacy and safety profile of iron chelation therapy in the post-HSCT setting have also reported a reduction in iron burden,

\[^{34,36}\] although effects on cardiac iron have not been reported. Furthermore, among 30 thalassemia patients whose treatment was initiated approximately 3 months postransplant — although the degree of iron reduction was similar — deferoxamine treatment resulted in more rapid reduction in serum ferritin levels than phlebotomy.\[^{47}\] Deferasirox had a clinically manageable safety profile, which is particularly important in these patients who were no longer transfused and thus had no active source of iron loading. AEs were similar to those previously reported in \(\beta\)-thalassemia major\[^{28,30,31,48}\] and in the post-HSCT setting.\[^{28,30,31}\] One episode of gastrointestinal upset resolved without treatment interruption or dose adjustment. The low incidence of gastrointestinal disturbance is noteworthy, since HSCT conditioning regimens and GVHD themselves can sensitize patients. Nevertheless, a lower rate of gastrointestinal disturbance related to deferasirox treatment has been reported in pediatric patients compared with adult patients.\[^{27}\] Dose reduction is likely to be appropriate when serum ferritin levels and LIC approach low near-normal levels; this study did not systematically address the optimal dose adjustment under these circumstances.

In patients with higher baseline iron burden, deferasirox decreased LIC to a greater extent than phlebotomy. This could reflect the flexibility of appropriate dosing with deferasirox treatment compared with phlebotomy volume. At study end, phlebotomy volume was similar in patients with low and high iron burden. However, deferasirox was highest in patients with LIC higher than 7 mg Fe/g dw, with deferasirox dose adjustments from 10 to 20 mg/kg/day required in some patients in order to achieve therapeutic goals, highlighting the need for appropriate and timely dose adjustments.\[^{48}\] Indeed, results from the 1-year Evaluation of Patient’s Iron Chelation with Exjade (EPIC) study and another report by Sivgin et al. (2011) showed that pediatric patients with \(\beta\)-thalassemia major may also require prompt dose escalation in order to optimize efficacy with a manageable safety profile.\[^{55}\] Rapid weight change in pediatric patients should be considered during deferasirox dose adjustments.

Strong correlation between LIC and serum ferritin levels was observed, as has been reported previously.\[^{28,49}\] With the increasing availability of noninvasive MRI techniques, and the altered pattern of iron distribution in the posttransplant period,\[^{50}\] the utilization of the more clinically robust method of direct LIC measurement becomes important.\[^{42}\] NTBI was significantly reduced with both treatments and correlated with LIC and serum ferritin levels both at baseline and even more strongly after 1 year of treatment. This contrasts with LPI levels, where the correlations with serum ferritin were weaker at baseline and absent for both LIC and serum ferritin at 1 year. Other studies have also demonstrated NTBI as a potential index of iron overload in \(\beta\)-thalassemia intermedia and sickle cell disease.\[^{51}\] The utility of NTBI as a biochemical marker for monitoring iron overload and response to iron reduction therapy warrants further investigation.

In our study, patient adherence was high for patients receiving either deferasirox or phlebotomy. However, patients were followed up for 1-year only, and patient adherence to phlebotomy regimens has been shown to decrease with increasing number of years on treatment.\[^{25}\] Treatment satisfaction with deferasirox in \(\beta\)-thalassemia major has been previously reported.\[^{41}\] When questioned about treatment satisfaction, it was notable that no parents of patients receiving deferasirox expressed a wish to switch to phlebotomy. In contrast, the majority of parents with children receiving phlebotomy stated a desire to switch to deferasirox, highlighting the possible preference for oral deferasirox in this pediatric population.

In conclusion, iron burden was reduced with deferasirox and phlebotomy over 1 year in pediatric patients with \(\beta\)-thalassemia major who have undergone curative HSCT. In patients with higher baseline iron burden, deferasirox decreased LIC to a greater extent than phlebotomy. The dose of deferasirox was higher in these patients, which underscores the need for appropriate and timely deferasirox dose adjustments, as has been recommended in \(\beta\)-thalassemia major patients with significant iron overload.\[^{48,52}\] Importantly, deferasirox demonstrated a clinically manageable safety profile in these patients who were not receiving transfusions. Since patients are no longer anemic and not requiring transfusions, iron removal in post-HSCT patients with \(\beta\)-thalassemia major is only needed for a finite period of time. These efficacy and safety data from the comparison of oral deferasirox and phlebotomy may help inform clinical decision-making when considering that an oral treatment may be advantageous in terms of quality of life benefits, such as patient satisfaction, particularly when treating young patients.

ACKNOWLEDGMENTS

This study was supported by funding by Novartis Pharma AG. We thank Dominik Pfluger, PhD, of Datametrix AG for statistical assistance and Debbi Gorman, PhD, of Mudskipper Business Ltd, for medical editorial assistance. Financial support for statistical and medical editorial assistance was provided by Novartis Pharmaceuticals. The authors thank Dr Lorena Duca for performing NTBI measurements.

CONFLICT OF INTEREST

A.I. reports participation in advisory boards for Novartis Pharmaceuticals. J.B.P. reports participation in advisory boards for Novartis Pharmaceuticals. M.D.C. reports participating in Novartis, Genzyme and Celgene Pharmaceuticals advisory boards. A.T.T. receives research funding and honoraria from Novartis Pharmaceuticals. K.M.M. received consulting fees and research support form Novartis Pharmaceuticals. All other authors do not report conflict of interest.
REFERENCES