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Deferiprone exerts a dose dependent reduction of liver iron in adults with iron overload

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Short running title: Deferiprone dose effect on liver iron

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Abstract

Objective: While doses of deferiprone up to 75 mg/kg/day have been demonstrated to be effective in cardiac iron removal, their efficacy in the reduction of liver iron have been equivocal. The aim of this study was to evaluate the effect of deferiprone dose on liver iron concentrations in adult iron overload patients.

Methods: A single-centered, retrospective, cohort observational study was conducted involving 71 patients exposed to deferiprone doses up to 113 mg/kg/day between January 2009 and June 2015 for a median of 33 months.

Results: At the end of the study period, liver iron measured by R2 MRI was reduced by a mean 1.7 mg/g dw. A dose effect was observed, with incremental reductions of 2.8 mg/g dw in end of study LIC for every 10 mg/kg/day higher dose of deferiprone ($p < 0.001$). A dose effect was also observed in end of study ferritin and cardiac iron concentration measured by T2* MRI ($p < 0.0001$ and $p = 0.048$ respectively). No associations between adverse effects and deferiprone dose were observed, but there was a trend toward higher rates of agranulocytosis at higher doses and two of three hereditary hemochromatosis patients developed this complication.

Conclusion: The present study failed to demonstrate that the use of deferiprone at >90 mg/kg/day was associated with increased risk of agranulocytosis or neutropenia, but did demonstrate more effective liver iron control in iron overload patients.

Keywords: deferiprone, liver, iron overload, thalassemia, chelation

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Introduction

Beta thalassemia major is a genetic disorder of reduced or absent production of functional beta-globin chains leading to severe anemia, excess intramedullary and extramedullary hematopoiesis and hemolysis [1]. Recent estimates suggest that clinically significant thalassemia syndromes affect over fifty-nine thousand births per year globally [2]. Life sustaining chronic transfusion programs are only available to a small percentage of these patients. However, those transfused are at risk of complications of iron overload. The goal of iron chelation therapy is to reduce iron overload and to prevent end-organ damage such as heart failure, liver cirrhosis and endocrinopathies, which are morbidities known to reduce survival in this population [1]. Retrospective cohort studies have shown that treatment with iron chelators in thalassemia major patients is associated with improvements in left ventricular ejection fraction (LVEF), a 25.5% to 46.4% reduced risk in the development of heart failure and reversal of endocrine complications such as abnormal glucose metabolism, hypothyroidism and hypogonadotropic hypogonadism [3,4]. Reversal or stabilization of liver fibrosis has also been shown in 83% of treated patients [5].

Traditionally, the trend in serum ferritin, in conjunction with liver biopsy results, have been used to guide iron chelation therapy. Because of this, chelation efficacy was originally measured by these metrics. Over the past decade, magnetic resonance imaging (MRI) techniques have been introduced and validated as less invasive, new gold standards to assess myocardial and hepatic iron overload [6,7]. Deferiprone is a bidentate oral iron chelator with a half-life of approximately two hours and time to peak of 1 to 2 hours which is excreted primarily in the urine [8]. It was first approved in the European Union in 1999, subsequently by the United States Food and Drug Administration (FDA) more than a decade later in 2011

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with dosing up to 99 mg/kg/d, and most recently by Health Canada in 2015 "for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate" [9]. Deferiprone is not currently approved for treatment of other iron overload syndromes by the FDA or Health Canada, however, these were not excluded from Health Canada's Special Access Program.

Deferiprone has been shown to be effective at improving myocardial iron overload as measured by T2* MRI when compared to deferoxamine treatment [10,11]. Randomized trials comparing the two have consistently shown equivalent or better improvement in cardiac T2* levels for deferiprone, as monotherapy or in combination with deferoxamine [12-14]. Liver iron concentration (LIC) was reported in 4 randomized monotherapy trials comparing the same drugs, and no significant difference was found by meta-analysis [15-19]. Finally, three studies compared combination therapy deferiprone-deferoxamine with either deferiprone or deferoxamine monotherapies with change in LIC reported [15,20,21]. With two of the three using deferoxamine as the control, the overall effect was non-significant in favour of combination therapy (-1.2, 95% CI -4.9, 2.6, $p = 0.54$) [19].

The major limitations to these studies are a relatively low number of recruited participants and short follow up duration. Clinical outcomes directly related to patient morbidity were not assessed due to these limitations, and some of the outcome measurements used, such as liver biopsy and SQUID, are no longer in routine use. Analyses of cardiac T2* without logarithmic transformation magnifies clinically insignificant absolute changes in cardiac iron concentration (CIC) [22]. Although they were not found to be statistically significant, comparisons between deferiprone and deferoxamine monotherapies display trends in favour of deferoxamine using either change in ferritin or LIC as outcomes [15-18,23]. It is notable, however, that deferiprone doses used in these trials ranged from 71 to 92 mg/kg/day, and only one trial exceeded 75 mg/kg/day. Furthermore, these represent

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prescribed doses that do not take into account medication compliance, which is variable in the thalassemia population [24]. A proportional dose response in urinary iron excretion was shown in early safety studies with deferiprone, but dose escalation data has not been presented in larger cohorts since [8,25]. Owing to known toxicity and unfamiliarity with prescribing, it remains unclear if a significant clinical benefit can be gained by treating patients with doses of deferiprone higher than 92 mg/kg/day.

Several factors influence response to deferiprone, including baseline ferritin and LIC [26]. However, evidence regarding the influence of transfusion requirements on deferiprone is lacking [11,19,27]. From 2009 to 2015 deferiprone has been available and utilized at our institution, North America's largest adult thalassemia program, through the manufacturer's compassionate use program and Health Canada's Special Access Program. Early in 2015 it was approved by Health Canada for treatment of iron overload in thalassemia. Due to anecdotal concerns regarding the efficacy of deferiprone at standard dose (approved by FDA up to 99 mg/kg/day), the Red Blood Cell Disorders (RBCD) Program has safely exceeded this in a number of patients, as high as 113 mg/kg/day with patient reported compliance up to 100%. We hypothesize that deferiprone influences LIC and is dependent on prescribed dose and compliance, independent of other variables such as age, sex, transfusion dose or other chelation agent use.

Materials and Methods

Design

This is a retrospective cohort study designed to assess the effect of deferiprone dose on LIC and other clinical parameters. It was completed by the investigators without the influence of a commercial sponsor, and in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by the local research ethics board.

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Patients

Patients 18 years-old and over followed at our institution that were prescribed deferiprone between January 2009 and June 2015 were eligible for inclusion. These were identified by reviewing records of the Compassionate Use Program, Health Canada Special Access Program and the electronic medical record. Both patients receiving monotherapy and combination chelation therapy (with deferoxamine or deferasirox) were included. The study population also included several underlying diagnoses including thalassemia major, transfusion-dependent thalassemia intermedia, transfused sickle cell disease, hereditary hemochromatosis and transfusion dependent pyruvate kinase deficiency. Thalassemia major was defined as laboratory identification of a β^+ or β^0 genotype and transfusion-dependence starting in infancy. Patients were excluded if there was no clinical assessment documented within the time period of the study. Indications for treatment with deferiprone were severe cardiac iron overload (all hereditary hemochromatosis patients included), failure or non-acceptance of alternative chelators and combination use.

Efficacy assessments

Clinical data were collected retrospectively by individual chart review. Prescribed deferiprone dose and received dose were recorded, including any interruptions, dose or weight changes. Self-reported compliance to chelation was assessed systematically at every patient's quarterly clinic visits. Compliance was documented in electronic patient record as either number of missed doses over a period of time (missing 1 dose out of 3 over the past 30 days) or average compliance rate over a specified period of time (e.g. 6 out of 7 days). The

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same information was collected for any combination regimens, which included deferasirox, intravenous and subcutaneous deferoxamine. Transfusion volume and schedule were also recorded. Outcome metrics were LIC measured by MRI R2, T2* cardiac MRI and corresponding CIC, LVEF measured by MRI, and serum ferritin level. For each of these metrics a baseline value was recorded as the most recent result prior to exposure to deferiprone. Final measurements were those taken at completion of therapy, or at the end of the study period if patients were still on the medication. All results for each investigation recorded in the patient chart during the study period were also included. CIC was chosen as a metric in addition to T2* values for purposes of analysis because it is measured according to a linear scale.

Liver MRI R2 studies were performed on a 1.5-T imager. Imaging was then sent to Resonance Health for interpretation using the Ferriscan protocol where LIC can be calculated according to the following formula: $[\mathrm{Fe}]_{\mathrm{R2\text{-}SP}} = (29.75 - \sqrt{900.7 - 2.283 \times R2})^{1.424}$ [28]. All LIC exceeding 43 mg/g dry weight (dw) was reported as 43 mg/g dw as this is the upper limit of LIC measurement using this method. Cardiac MR studies were performed with a 1.5-T imager (Magnetom Avanto fit; Siemens Healthcare, Erlangen, Germany) by using phased-array surface coils. T2* imaging was performed by using a cardiac-gated segmented multiecho gradient-echo sequence for assessment of myocardial iron. Imaging parameters included flip angle of 20°, field of view of 380 mm, matrix of 256 × 128, pixel size of 1.5 × 2.0 mm^2, section thickness of 10 mm, repetition time (ms)/echo time (ms) of 19/2.3–16.8 (eight echoes), bandwidth of 814 Hz per pixel, and generalized autocalibrating partially parallel acquisition factor of two. Three cardiac short-axis sections (basal, mid, and apical) were acquired by using a single end-expiratory breath hold per section. An inline T2* map was generated for each section with pixelwise T2* estimation and fitting to a monoexponential decay curve. Evaluation of T2* maps was performed offline by using an in-

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house–developed segmentation program (MatLab; MathWorks, Natick, Mass) on a remote workstation. Endocardial and epicardial borders were manually contoured on each T2* map. A mid-septal T2* value was reported for each participant. CIC was calculated with the following formula: $45(T2^*)^{-1.22}$ [22].

Safety assessments

Clinical and laboratory monitoring was performed for all patients on deferiprone according to previously published standards [29-31]. Complete blood counts (CBC) were performed weekly for the first six months on treatment, then monthly to monitor for neutropenia and agranulocytosis. This practice was adopted based on previously published data demonstrating that 61% of agranulocytosis cases occur during the first 6 months of treatment with deferiprone [32]. Clinical assessments for signs and symptoms of infection or arthralgia were regularly performed. In response to a significant adverse event such as neutropenia or transaminitis, deferiprone was held, appropriate acute care provided, and chelation treatment protocol reevaluated. Elevation in liver enzymes was defined as alanine aminotransferase (ALT) > 5 times upper limit of normal. Episodes of neutropenia were defined as absolute neutrophil count (ANC) < 1.5, and agranulocytosis as ANC < 0.5. Neutropenia and agranulocytosis were managed by discontinuation of deferiprone until counts recovered to normal range, as well as with admission to hospital, IV antibiotics and G-CSF if infectious symptoms were present. Deferiprone was reintroduced at a lower dose for cases of neutropenia, while it was discontinued in each case of agranulocytosis.

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Statistical methods

The null hypothesis was that deferiprone dose has no effect on change in LIC over time. In a linear regression model, with a type I error rate of 5%, a sample size of 63 patients is sufficient to give 80% power to detect a slope corresponding to a change of 1.4 mg/g dw in LIC per 10 mg/kg/day deferiprone. This assumes a standard deviation of 11 mg/kg/day for deferiprone dose and a residual standard deviation in LIC of 4.2 mg/kg/day. Equivalently, the sample size has 80% power to detect a correlation of 0.34 between LIC and deferiprone dose. Limited by a paucity of published data on the effect of deferiprone dose on LIC, this slope was chosen based on anecdotal experience and unpublished data showing that this reflected a 20% difference in a prior cohort [9]. However, in order to account for potential limitations such as incomplete records or early discontinuation we aimed to include 75 subjects, which was the estimated number of patients treated with deferiprone prior to data collection. Changes in outcome from baseline to final assessment were calculated such that positive numbers represented an increase and yearly rates of change were calculated by dividing each subject's change by the time interval between measurements.

We used single sample t-tests of the hypotheses that the mean change and mean yearly change were zero and also calculated 95% confidence intervals (CIs) for the mean changes. Effective received mean dose was computed as the sum of all doses received divided by the product of number of days of treatment and then body weight. The slopes for duration of treatment were compared across three groups according to received mean dose: < 75 mg/kg/d; 75 to 90 mg/kg/day; > 90 mg/kg/day. These boundaries were chosen first to represent similar numbers of participants in each group, and also to reflect limits of common doses in previously reported cohorts. Robust linear regression models in the R package robustbase were used to (a) examine the univariate relationship between yearly change in

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outcome by mean effective dose; (b) examine the relationship between final outcome and dose, adjusting for baseline value and duration of treatment; and (c) examine the effects of a pre-specified set of demographic and clinical variables: baseline value, sex, age, combination therapy, transfusion volume and dose [33]. The robust regression models reduce the influence of outlying values but keep the outcomes on an untransformed scale for easier interpretation than analyses of logarithmic values, for example.

Counts and proportions of patients with adverse events were calculated and compared across dose groups using chi squared tests or Fisher's exact test for more infrequent outcomes. These relationships were also assessed by logistic regression on the continuous dose variable. All analyses were done in R version 3.3.2 [34].

Results

Baseline demographics and clinical characteristics

A total of 71 patients treated with deferiprone were identified, of which 52 had a diagnosis of thalassemia major. Median age at end-of-study was 34 (range 18 to 61) years. Male to female ratio was 29:42. The median transfusion burden was 119 (interquartile range 94.2 to 141.5) mL/kg/year, and 61% of patients had undergone a splenectomy. Table 1 outlines the baseline clinical characteristics. Sixty-six (93%) patients had baseline and follow-up ferritin measurements, 58 (82%) had measurements of CMR, CIC and T2*, and 57 (80%) had measurements of LIC.

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Treatment and compliance

The median duration of exposure to deferiprone in this cohort was 33 (range 1.7 to 90.8) months for a total of 215.4 patient years. The median prescribed dose of deferiprone was 93.5 (55.7 to 115.2) mg/kg/day, while the median received dose was 79.4 (0 to 113.1) mg/kg/day after adjusting for compliance (median 84%). The total number of patients receiving combination therapy at some point during the study period was 39 while 32 received only monotherapy.

Effect of deferiprone on liver iron

Mean baseline and end-of-treatment LIC were 15.6 ± 14.6 and 13.9 ± 12.9 mg/g dw (95% CI for change: -5.7 mg/g dw to 2.3 mg/g dw, p = 0.39). Accounting for different treatment durations, this equated to a mean decrease in LIC of -0.17 (95% confidence interval -2.6, 2.2) mg/g dw per year (Table 2). Overall, 47% of patients had a net decrease in LIC over the treatment period, while 5% were unchanged and 47% increased.

In univariate regression, the yearly change in LIC decreased by 0.53 mg/g dw/year for every 10 mg/kg/day higher dose of deferiprone (p = 0.054, Figure 1). Subgroup analysis including only thalassemia phenotypes (N =57) revealed the yearly change in LIC decreased by 0.73 mg/g dw/year for every 10 mg/kg/day deferiprone (p = 0.013). In a model adjusting for baseline LIC and years of treatment, final LIC was lowered by 2.8 mg/g dw for every 10 mg/kg/day higher dose of deferiprone, and this was essentially unchanged in the thalassemia only subgroup analysis (p < 0.001, Table 3). In this model, final LIC was on average 0.32 mg/g dw higher per 1 mg/g dw of initial LIC (p = 0.0012) but duration of exposure to deferiprone had a negligible effect (p = 0.86). Splenectomy status was not found to influence

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changes in LIC on univariate analysis (P = 0.78). No other covariates, including combination therapy, were independent predictors of change in LIC.

Effect of deferiprone on ferritin

Similar patterns of response were seen with serum ferritin. Mean baseline and end-of-treatment ferritin levels were 3390 ± 2824 mg/L and 2758 ± 2700, giving a mean change of -631 (95% CI: -1230, -31; p = 0.040). Mean yearly change was -467.9 (95% confidence interval -839.8, -96.0) mg/L per year. Overall, 65% of patients had a net reduction in ferritin over the study period. In univariate regression, yearly decrease in ferritin was higher with increasing dose (140 mg/L/year lower per 10 mg/kg/d of deferiprone; p = 0.014). In multiple regression (Table 3), final ferritin was 536 mg/L lower per 10 mg/kg/day higher dose of deferiprone (p < 0.001) and 50 mg/L higher per 100 mg/L of baseline ferritin (p < 0.001). Duration of treatment had no important effect (p = 0.89).

Effect of deferiprone on cardiac iron and function

Mean baseline and end-of-treatment mid-septal T2* were 16.2 ± 10.3 ms and 24.9 ± 12.5 ms, corresponding to a reduction in CIC from 2.3 to 1.3 mg/g dw of heart tissue (mean change -1.0; 95% CI: -1.3, -0.70; p < 0.001). For comparison, a normal CIC has been calculated as up to 0.34 mg/g dw in other studies [35]. The mean rate of change was 2.9 ms per year (95% CI: 1.8-4.0; p < 0.001) for T2* and -0.34 mg/g dw per year (95% CI: -0.48, -0.20; p < 0.001) for CIC. Overall, 86% of patients had a net reduction in CIC over the study period but there was large inter-individual variability.

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In the univariate model, yearly CIC was reduced by 0.040 mg/g dw for every 10 mg/kg/day higher dose of deferiprone ($p = 0.034$). In the multiple regression, mean end-of-treatment CIC was reduced by 0.17 mg/g dw for every additional year on deferiprone therapy, and 0.087 mg/g/dw per 10 mg/kg/day of deferiprone. Final CIC increased by 0.46 mg/g dw for each mg/g dw of baseline CIC ($p < 0.001$).

Mean baseline and end-of-treatment LVEF as assessed by cardiac MRI were 57.0 ± 6.9% and 59.7 ± 5.2% (mean change 2.7%; 95% CI: 0.38, 2.1; $p < 0.001$). The yearly increase in LVEF was 1.2% (95% CI: 0.42, 2.1; $p = 0.004$). Overall, 62% of patients had a net increase in LVEF over the study period. Only 6 patients (10%) had LVEF values < 50% at any point during the study period, and only 1 at the end of follow-up.

In univariate regression, yearly increase in LVEF was largely unrelated to dose (0.07% decrease in LVEF per 10 mg/kg/day higher dose of deferiprone, $p = 0.60$). In multiple regression (Table 3), final LVEF was significantly related only to initial LVEF, with duration ($p = 0.20$) and dose of deferiprone ($p = 0.32$) having only weak relationships.

Effects of demographic and clinical variables

Final cardiac T2* was 6.5 ms higher for males than for females ($p = 0.010$). Additionally, CIC was 0.41 mg/g/dw lower for males ($p = 0.008$) and increased by 0.12 per 100 mL of transfusion volume ($p = 0.011$), but no other clinical outcomes had a statistically significant relationship with age, sex, combination therapy or transfusion volume (all $p > 0.1$).

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Safety evaluation

Adverse events (AE) attributable to deferiprone occurred in 57% of patients overall, and 85% of these resolved while on treatment. The most common AE being arthralgia, followed by gastrointestinal upset, elevated liver enzymes, neutropenia and agranulocytosis (Table 4). Deferiprone was held or discontinued when an AE was encountered, with exception of some episodes of mild gastrointestinal upset. Deferiprone was discontinued permanently in 11% of the 40 patients who experienced an AE.

Serious adverse events occurred in 5 patients (7.0%), corresponding to 4 cases of agranulocytosis (1.86 cases per 100 patient-years; 95% confidence interval 0.5 to 4.7 cases per patient-years) and 2 deaths. One death was classified as secondary to agranulocytosis in a patient being treated for hereditary hemochromatosis with deferiprone monotherapy at a dose of 50.5 mg/kg/day for a total 6.9 weeks. The other was classified as febrile death in a patient being treated for transfusion-dependent thalassemia intermedia with a combination of deferasirox (10.8 mg/kg/day) and deferiprone (89.7 mg/kg/day) for a total 50.2 weeks. However, leukocyte count was not confirmed in the second case due to incomplete records from an out-of-country hospitalization and neither patient was treated for their agranulocytosis and febrile illness according to manufacturer or Canadian sepsis guidelines [9,36]. Neither individual AE or the risk of AE as a whole were significantly associated with the deferiprone dose taken (Table 4).

Discussion

Deferiprone, in combination with deferoxamine, is currently the recommended option in the removal of cardiac iron and stabilization of ventricular function [37,38]. This recommendation is supported by numerous randomized controlled trials and controlled

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studies showing that deferiprone, at a dose of 75 mg/kg/day or lower, is able to effectively remove cardiac iron [19]. However, deferoxamine and deferasirox are still the recommended therapies for removal of liver iron overload, primarily because studies on the ability of deferiprone to remove liver iron have been equivocal, particularly at high iron burden [15-18]. The present study demonstrated that liver iron can be maintained with deferiprone in a population of patients with high hepatic iron overload, and that the effect is dose-dependent, up to 113 mg/kg/day. The dose effect demonstrated in univariate regression (0.53 mg/g dw/year for every 10 mg/kg/day deferiprone – $p = 0.054$) is clinically significant. Adjusting for baseline LIC and years of treatment further strengthened the effect.

Studies that suggest reduced efficacy at removing liver iron with deferiprone compared to other chelators were based on a restricted dose range below 92 mg/kg/day, with only one trial exceeded 75 mg/kg/day [15-18,23]. Furthermore, these studies reported the prescribed dose, without accounting for compliance. This is an important factor since compliance is known to be poor in this population [24]. In contrast, studies that examined the patient reported dose of deferiprone taken by factoring in compliance, such as the GPO-L-ONE A001 study, were able to show an improvement in liver iron overload [26]. Although patient reported compliance was used in some studies assessing adherence to iron chelation therapy, it is not always representative of actual dose received, and represents a limitation of this study [39,40]. The follow-up period for most studies were between 12 and 36 months, with only 2 studies of durations up to 60 months [12,41]. The use of combination therapy with deferiprone over monotherapy was not associated with improved liver iron removal in the present study. This finding is in line with previous meta-analyses of controlled trials that examined this very question [11,19]. Although combination therapy was not shown to be an independent predictor of change in LIC on multivariable analysis, the small sample size

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precluded subgroup analyses on this and other variables, highlighting an important limitation of the present study.

A dose-dependent effect of deferiprone taken on reduction in ferritin was observed in the present study. This is a novel finding, although reduction of ferritin irrespective of dose is consistent with findings from previous studies [12,15,16,18,20,21,23,29,42-44]. While duration of therapy had no effect on improving liver iron removal, both duration and dose of deferiprone taken were important predictors in improving cardiac iron removal. The observed difference may be due to the cardio-selective nature of deferiprone, and thus the duration of the study may not have provided sufficient time to observe the effect of therapy duration on liver iron removal. A functional improvement in LVEF was also observed in this study, consistent with prior reports showing increases in EF of 2.5 to 3.1% after deferiprone treatment [18,45]. Improvement in LVEF was weakly associated with dose and duration of deferiprone treatment, and differences in the final LVEF was only associated with initial LVEF. It is possible that the study was not sufficiently powered to detect modest changes in LVEF.

Safety data on the administration of deferiprone above 92 mg/kg/day have not been published previously. The present study did not observe a relationship between deferiprone dosage and frequency of adverse events, up to 113 mg/kg/day. Incidence of neutropenia, arthralgia, elevated liver enzymes and gastrointestinal irritation were in keeping with previous reports [12,30,31,46]. We observed a higher incidence of agranulocytosis in this cohort. This may be attributable to small sample size in this study as demonstrated by the wide 95% confidence interval estimate of the rate of agranulocytosis (0.5 to 4.7 cases per 100 patient-years). It is notable that two of three hereditary hemochromatosis patients treated for severe cardiac iron overload with deferiprone in this cohort were complicated by agranulocytosis, and the third by neutropenia. The underlying pathophysiology contributing

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to this finding is not clear, and the very small sample size limits further interpretation of the data, but it does necessitate caution and vigilance in educating both patients and health care practitioners around agranulocytosis risk in patient populations less commonly treated with deferiprone. It also highlights the limitation that non-thalassemia phenotypes were analyzed together with thalassemia cases in this study, although the same analyses repeated in thalassemia patients only demonstrated the same outcome. One confirmed case of agranulocytosis in our cohort proved to be fatal, highlighting the importance of close observation of hematologic parameters while on this medication.

The present study failed to demonstrate the use of deferiprone at >90 mg/kg/day was associated with increased risk of agranulocytosis or neutropenia, and was associated with more effective liver iron control in iron overload patients. As such, deferiprone monotherapy at doses higher than 90 mg/kg/day may be considered as a treatment option for liver iron overload in thalassemia patients that cannot tolerate deferasirox and deferoxamine, or when concomitant cardiac iron overload is present. Extrapolation of the findings presented here are limited by their representation of a single institution. Further controlled trials with larger sample sizes of similar study duration should be undertaken to confirm these observations, and to specifically evaluate rates of agranulocytosis at doses greater than 90 mg/kg/day. Further studies are also required to determine safety and efficacy of deferiprone for treatment of severe cardiac iron overload in patients with hereditary hemochromatosis.

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Table 1. Baseline Characteristics and Deferiprone Treatment

Findings	N = 71
Median age (Range)	34 (18-61)
Female	29 (41%)
Genotype	
Thalassemia major	52 (73%)
Thalassemia intermedia	11 (15%)
Sickle cell disease	4 (5.6%)
Other	4 (5.6%)
Median transfusion requirement - mL/kg/year (Range)	120.5 (0-197.1)
Prior splenectomy	43 (61%)
Deferiprone treatment	
Monotherapy	32 (45%)
Combination therapy	39 (55%)
Median exposure duration - months (Range)	33 (1.7-90.8)
Median prescribed dose - mg/kg/day (Range)	93.5 (55.7-115.2)
Median compliance (Range)	84% (0-100)
Median received dose - mg/kg/day (Range)	79.4 (0-113.1)
Interruptions in treatment	18 (25%)

Table 2. Summary of Clinical Outcomes at Start and End of Study

Metric	Start of study (SD[a])	End of study (SD)	p Value	Mean change per year (95% CI[b])
LIC[c] - mg/g dry weight	15.6 (14.6)	13.9 (12.9)	0.39	-0.17 (-2.6, 2.2)
Ferritin - ug/L	3390 (2824)	2758 (2700)	0.04	-467.9 (-839.8, -96.0)
Cardiac T2* - ms	16.2 (10.3)	24.9 (12.5)	<0.001	2.9 (1.8, 4.0)
CIC[d] - mg/g dry weight	2.3 (1.5)	1.3 (1.1)	<0.001	-0.34 (-0.48, -0.20)
Cardiac MR ejection fraction - %	57.0 (6.9)	59.7 (5.2)	<0.001	1.2 (0.42, 2.1)

[a] SD: Standard Deviation

[b] CI: Confidence Interval

[c] LIC: Liver Iron Concentration

[d] CIC: Cardiac Iron Concentration

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Table 3. Regression Results for Clinical Outcomes at End of Study Period with the Predictors: Baseline Value, Duration of Treatment and Deferiprone Dose

Predictor	Outcome - Cells contain parameter estimate[a] (95% CI) p-value.				
	LIC[c] (mg/g dw)	Ferritin (ml/L)	Cardiac T2* (ms)	CIC[d] (mg/g dw)	Ejection fraction (%)
Baseline[b]	0.32 (0.13, 0.50) 0.0012	0.5 (0.33, 0.67) <0.0001	0.83 (0.60, 1.1) <0.0001	0.46 (0.34, 0.59) <0.0001	0.37 (0.22, 0.52) <0.0001
Years of treatment	0.13 (-1.3, 1.6) 0.86	-16 (-247, 216) 0.89	2.00 (0.79, 3.3) 0.0018	-0.17 (-0.26, -0.08) 0.0004	0.34 (-0.19, 0.86) 0.21
Dose (per 10 mg/kg/d)	-2.8 (-4.0, -1.5) <0.0001	-536 (-759, -313) <0.0001	1.1 (0.1, 2.2) 0.04	-0.087 (-0.20, 0.0) 0.048	-0.24 (-0.70, 0.20) 0.32

[a] Estimate: Change in outcome measure according to predictor (eg. final LIC was lowered by 2.8 mg/g dw for every 10 mg/kg/day increase in dose of deferiprone).

[b] Baseline: Value of corresponding clinical outcome prior to initiation of deferiprone treatment.

[c] LIC: Liver Iron Concentration

[d] CIC: Cardiac Iron Concentration

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Table 4. Adverse Events by Deferiprone Dose Group

Adverse Event	All subjects (n = 71)	Dose < 75 mg/kg/d (n = 33)	Dose 75-90 mg/kg/d (n = 17)	Dose > 90 mg/kg/d (n = 21)	p Value
Any	40 (56%)	20 (61%)	10 (59%)	10 (48%)	0.37
Arthralgia	25 (35%)	12 (36%)	7 (39%)	6 (29%)	0.54
Gastrointestinal upset	12 (17%)	9 (27%)	2 (12%)	1 (4.8%)	0.063
ALT > 5x ULN[a]	7 (10%)	3 (9.1%)	1 (5.6%)	3 (14%)	0.68
Neutropenia	4 (5.6%)	1 (3.0%)	2 (11%)	1 (4.8%)	0.33
Agranulocytosis	4 (5.6%)	1 (3.0%)	0	3 (14%)	0.2

[a] ALT: Alanine Aminotransferase, ULN: Upper Limit of Normal

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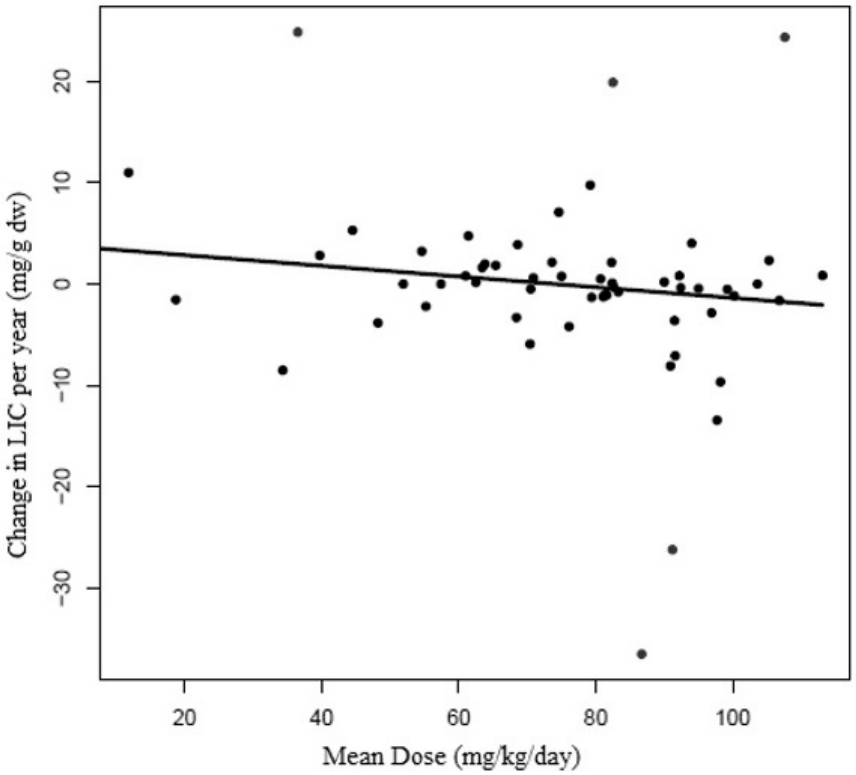

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