Deferasirox effectively decreases iron burden in patients with double heterozygous HbS/β-thalassemia

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Abstract: Iron overload is present in several cases of double heterozygous HbS/beta-thalassemia (HbS/beta-thal). Deferasirox is an orally administered iron chelator which is effective on iron overloaded patients with transfusion-dependent anemia. The aim of this study was to investigate the efficacy and safety of deferasirox in HbS/beta-thal patients with iron overload. We evaluated 31 adult patients with HbS/beta-thal (14M/17F; median age 41 years) who had serum ferritin levels >1000 ng/mL and who were sporadically transfused. Total iron burden was monitored by measuring serum ferritin levels before and monthly after starting deferasirox, while liver iron concentration and cardiac iron burden were measured by magnetic resonance imaging (MRI) T2 and T2* parameters at baseline and 12 months after deferasirox treatment. Deferasirox managed to reduce the mean serum ferritin levels after 12 months of treatment from 1989±923 to 1008±776 ng/mL (P<0.001). This reduction was accompanied by a significant improvement on MRI T2* of the liver (from 3.9±3.2 to 5.8±3.1 ms; P<0.01) and by a comparable improvement of biochemical parameters of liver function. Mild nausea and diarrhoea of grade 1/2 were reported in 25% of patients within the first month of treatment, but did not re-occur. These data indicate that deferasirox provided effective control of iron levels (mainly of the liver) in minimally transfused patients with HbS/beta-thal, without significant adverse events, at similar doses to those studied widely for the treatment of patients with thalassemia syndromes.

Response to Reviewers: I would like to thank the reviewer for the valuable comments about our paper entitled "Deferasirox effectively decreases iron burden in patients with double heterozygous HbS/beta-thalassemia". Please find below our answers to these comments. All changes have been bolded into the text.

Reviewer #1:
Comment 1. The manuscript was thoroughly revised and has remarkably improved. However, concerning two of the previous comments were incompletely answered. A more detailed answer will increase the comprehensibility of the corresponding parts of the paper. Certainly, it will be very easy for authors to add the missing information: As stated in the previous comment 5, for liver MRI, it would be helpful for the reader to know how the T2star values correspond to liver iron concentration given as mg/g or micromole/g dry or wet weight since at present the majority of institutions and colleagues

are using these values and related cut-offs for the assessment of liver siderosis." In answering this comment the authors changed the text and included a reference explaining the use of R2 and R2* values. Actually the cited paper by J. Wood et al. accurately gives information on the hepatic iron concentration (HIC) in [mg/g d.w.] in relation to the corresponding R2 or R2* values. Such information on HIC corresponding to liver T2 and T2* values which were used in the present study would be desirable. What HIC corresponds e.g. to the inclusion criterion of T2* of 19ms?
Answer: We have included the respective HIC in the inclusion criteria (page 4, lines 5-6) as well as in the Table 1 (4th line), according to reviewer suggestions.

Comment 2. (see previous comment 6): In "Methods" it is stated that: "The starting deferasirox dose was 10 or 20 mg/kg/day depending on baseline iron burden..." In "Results", it is written that "patients were treated with deferasirox at 10 and 20mg/kg/day? based on the number of transfusions?")? How was the "baseline iron burden defined" (according to "Results" by the number of transfusions) and what was the cut-off number of blood transfusions to decide for 20mg/kg/d?
Answer: We thank the reviewer for this comment and sorry that we had not realized it in our previous revision. We have clarified now in the "study design" section that "The starting deferasirox dose was 10 or 20 mg/kg/day depending on previous transfusion requirements: if the patient had received 20-30 red blood cell (RBC) units the dose of 10 mg/kg/day was used; if the patients had received more than 30 RBC units the dose of 20 mg/kg/day was used." [page 4, lines 15-17].

Dear Professor Kulozik

We would like to thank you and the reviewers for the re-evaluation of our paper entitled “Deferasirox effectively decreases iron burden in patients with double heterozygous HbS/β-thalassemia”. Please find enclosed the second revised edition of this paper based on the reviewer’s comments. All changes have been bolded into the text.

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We think that we have addressed the reviewer comments adequately and that now our paper will be accepted for publication in Annals of Hematology.

We look forward to receiving your final decision on our paper.

With best regards

Evangelos Terpos, MD, PhD
Assistant Professor of Hematology &
Ersi Voskaridou, MD, PhD
Chairman of Thalassemia Unit

Original Report

Deferasirox effectively decreases iron burden in patients with double heterozygous HbS/β-thalassemia

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Running title: Deferasirox in HbS/β-thalassemia

Key words: double heterozygous HbS/β-thalassemia, sickle cell syndromes, deferasirox, iron overload, liver, heart

Abstract

Iron overload is present in several cases of double heterozygous sickle-cell/beta-thalassemia (HbS/β−thal). Deferasirox is an orally administered iron chelator which is effective on iron overloaded patients with transfusion-dependent anemia. The aim of this study was to investigate the efficacy and safety of deferasirox on HbS/β−thal patients with iron overload. We evaluated 31 adult patients with HbS/β−thal (14M/17F; median age 41 years) who had serum ferritin levels >1000 ng/mL and who were sporadically transfused. Total iron burden was monitored by measuring serum ferritin levels before and monthly after starting deferasirox, while liver iron concentration and cardiac iron burden were measured by magnetic resonance imaging (MRI) T2 and T2* parameters at baseline and 12 months after deferasirox treatment. Deferasirox managed to reduce the mean serum ferritin levels after 12 months of treatment from 1989±923 to 1008±776 ng/mL (P<0.001). This reduction was accompanied by a significant improvement on MRI T2* of the liver (from 3.9±3.2 to 5.8±3.1 ms; P<0.01) and by a comparable improvement of biochemical parameters of liver function. Mild nausea and diarrhoea of grade 1/2 were reported in 25% of patients within the first month of treatment, but did not re-occur. These data indicate that deferasirox provided effective control of iron levels (mainly of the liver) in minimally transfused patients with HbS/β−thal, without significant adverse events, at similar doses to those studied widely for the treatment of patients with thalassemia syndromes.

Introduction

The clinical severity of sickle-cell disease (SCD) varies from a very mild disorder to severe organ failure with increased mortality. Similarly, the double heterozygosity of SCD and beta-thalassemia (HbS/β−thal) produces a variety of clinical pictures with those of SCD to be dominant [1-3]. Despite adequate therapy, the majority of patients with HbS/β−thal have received repeated blood transfusions by adulthood [4, 5]. An imbalance between chronic inflammation which increases hepcidin expression, chronic hemolysis, accumulation of transfusional iron and increased iron absorption due to ineffective erythropoiesis leads to disruption of iron metabolism and possibly to iron overload in several HbS/β−thal patients. The increase in longevity during the recent years [2, 6] has revealed clinical evidence of iron overload in several patients with SCD and HbS/β−thal, especially in the liver; thus iron chelation has a definite indication in these cases.

Deferasirox (Exjade) is a novel iron chelator that has been licensed for the management of transfusional iron overload. There are several reports for the efficacy of deferasirox in thalassemia, SCD and other transfusion-dependent anemias [7-10] but there are very limited data for its role in HbS/β−thal. The aim of this study was to investigate the efficacy and safety of deferasirox on iron-overloaded patients with HbS/β−thal.

Patients and methods

Inclusion and exclusion criteria: Adult patients (≥18 years of age) with HbS/β−thal , who had received sporadic red blood cell transfusions (≤20 units of RBCs in their lifetime) and had confirmed liver or cardiac iron overload (serum ferritin levels of ≥1000 ng/mL and one of the following: liver MRI T2* of <19 ms, **which corresponds to a liver iron concentration (LIC) of 1.5 mg/g dry weight** or cardiac T2* of <28 ms) were eligible for entrance into this study. Patients were excluded if they were pregnant, showed signs of hepatic failure (transaminase levels of >500 U/L) or renal failure (creatinine clearance <60 mL/min) or had a left ventricular ejection fraction (LVEF) of <50%. Regarding the cut-off value of MRI T2* of the heart for inclusion in the study, we used the level of 28 ms instead of 20 ms which is used in the majority of the studies, as in another study of our group none of the patients with SCD had a heart T2* MRI value of <28 ms [11].

Study design: This was an open-label, prospective, single-centre, phase II study on the role of deferasirox in iron overload of HbS/β−thal, conducted over 1-year. The starting deferasirox dose was 10 or 20 mg/kg/day depending **on previous transfusion requirements: if the patient had received 20-30 red blood cell (RBC) units the dose of 10 mg/kg/day was used; if the patients had received more than 30 RBC units the dose of 20 mg/kg/day was used**. Dose adjustments were permitted after 3 months (in increments of 5 mg/kg/day every 3 months as required) based on serum ferritin trends (levels of ≥1000 ng/mL on 2 sequential visits or levels of >2500 ng/mL without decreasing trend). Deferasirox dosage was reduced if there were elevated levels of creatinine, urinary protein:creatinine ratio and transaminases, and in response to adverse events.

Patients provided written, informed consent before entering the study. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Efficacy and safety assessments: The primary efficacy endpoint was the improvement in magnetic resonance imaging (MRI) T2* values of the liver and the heart from baseline to 12-month values post-deferasirox therapy. The secondary efficacy endpoints included evaluation of changes in serum ferritin and liver function, and assessment of incidence, type and severity of adverse events relating to biochemical changes and patient disposition. We have used liver MRI T2* change as a primary efficacy end-point because it reflects accurately the LIC. Indeed a combination of the relaxation rates R2 (1/T2) and R2* (1/T2*) measured by MRI can accurately measure hepatic iron concentration throughout the clinically relevant range of LIC with appropriate MRI acquisition techniques [12].

Hemoglobin (Hb) levels, serum creatinine, alanine (ALT) and aspartate aminotransferase (AST) and 24-hour proteinurea (Prot 24h) were measured before and every month during deferasirox treatment, using standard methodology. Serum cystatin C was also measured at the same time-points on a Behring Nephelometer-II analyser using a latex particle-enhanced nephelometric immunoassay (Dade Behring, Liederbach, Germany), as previously described [13].

MRI evaluation: All patients were examined using the same 1.5 Tesla apparatus (Philips 1.5 T Gyroscan Intera; the Netherlands). Morphological evaluation and gross pathological assessment of liver was based on high resolution, T2-weighted, turbo spin echo images (TR/TE/matrix: 1600ms/100ms/400). For spin-spin relaxation time (T2) measurements, images of the liver were obtained using a 2D, 16-echo, Carr-Purcell-Meiboom-Gill spin echo sequence (TR/TE/matrix : 1000ms/5ms/256) T2-maps, so that images in which pixel signal intensity is related to the T2 of the corresponding voxel, can be automatically derived by the

imager's software. These maps were used for hepatic parenchyma T2 determination within selected regions of interest. For the T2 measurements of the heart, a short axis mid-ventricular slice was acquired. Respiratory and cardiac triggering were used for the heart measurements. T2* MRI of the heart and the liver were performed as previously described [11]. LVEF measurements were also performed using a phased array cardiac coil and a multi-slice, multi-phase ECG, gated bFFE sequence. Normal ranges for the T values of liver and heart were established in 10 age-matched volunteers (4 males and 6 females).

***Statistical analysis*:** The Wilcoxon signed rank test was used to evaluate differences between baseline and values of the studied parameters at the various time points. The correlation between changes of various biochemical parameters and BMD was evaluated with the Spearman's (r_s) correlation coefficient. All p values are two sided, the level of significance is <0.05 and confidence intervals refer to 95% boundaries.

Results

Thirty-one adult patients with HbS/β−thal (14M/17F) who are regularly followed-up in the Thalassemia Center of Laikon Hospital (Athens, Greece) were entered into this study. The median age of all patients was 41 years (range: 27-55 years). Twenty-four patients had HbS/β^0−thal, while 7 patients had HbS/β^+−thal. Twenty-three and 8 patients were initially treated with deferasirox at 10 and 20 mg/kg/day, respectively.

Deferasirox produced a significant reduction of mean serum ferritin levels after 6 and 12 months of treatment, while the mean baseline liver T2 and T2* significantly increased following 12 months of therapy (Table 1 & Figure 1). Mean cardiac T2* and LVEF were normal at baseline and did not change after 12 months of treatment (normal values of T2* were >28 ms and of LVEF >65%). A strong correlation was observed at baseline between liver MRI T2* and serum ferritin (r=0.61, P<0.01), but there was only weak correlation between percentage changes of serum ferritin and liver MRI T2* after 12 months of therapy (r=0.233, P=0.09). The reduction of ferritin levels after 12 months of deferasirox administration (approximately 50% of the mean values) was accompanied by a comparable reduction in the mean levels of ALT and AST (40% and 30%, respectively; Table 1). There were no significant correlations between serum ferritin and heart MRI T2* or between MRI T2* of heart and liver at baseline or after the 12-month duration of the study.

Regarding renal function, there were no significant changes in mean serum creatinine; all observed increases were within the normal range of our laboratory. On the contrary, cystatin-C significantly increased after 6 months of treatment and remained increased post-12 month of deferasirox. Hb or Prot 24h levels did not change after 6 and 12 months of treatment.

The side-effects of deferasirox were minimal and easily manageable. Eight patients (25%) referred gastrointestinal disturbances: 5 had mild nausea and 4 had diarrhea (one had both). All were reported within the first month, they were of grade I or II, and they did not re-occur. In all patients the compliance was excellent.

There were no dose adjustments of deferasirox in this study.

Discussion

Iron overload may play an important role in increasing the morbidity and mortality of patients with HbS/β−thal and iron chelation has a definite indication in several cases. Chelation guidelines for sickle-cell syndromes are similar to those for other iron overload situations as thalassemia major and multi-transfused patients [14, 15]. Until recently, desferrioxamine and deferiprone were the only active iron-chelating agent approved for clinical use, mainly in the thalassemia setting [16,17]. Recent advances have led to the development of new oral iron chelators, such as deferasirox, which has changed the clinical practice in several transfusion-dependent anemias with iron overload. Vichinsky et al suggest that treatment adherence with deferasirox may be better than that of desferrioxamine and thus it should lead to improved long-term outcomes [18]. Deferasirox mobilizes iron stores by binding selectively to the ferric form of iron. It has been shown to be as effective as desferrioxamine with favorable safety profile in patients with different hemoglobinopathies [7-10]. However, there is very limited information in the literature for the effect of deferasirox on HbS/β−thal patients.

In our study deferasirox was proven very effective on reducing liver iron and serum ferritin in the vast majority of HbS/β−thal patients. Serum ferritin is a marker of iron overload but also an acute phase protein. Its reduction post-deferasirox may reflect a beneficial effect of deferasirox on reducing iron overload, a possible anti-inflammatory effect of deferasirox or both phenomena. Our group has recently presented that deferasirox reduces the levels of tumor necrosis-alpha (a major inflammatory cytokine) in patients with thalassemia major and HbS/β-thal [19].

Iron overload contributes to the severity of SCD aggravating the already compromised liver and increasing the probability of cardiac complications. Our group has previously shown that

deferiprone is able to reduce liver iron overload in sickle-cell syndromes [20]. In the present study, which according to our knowledge is the first where deferasirox has been given in patients with HbS/β−thal, we also showed that liver T2 and T2* significantly increased following 12 months of deferasirox therapy. Additionally, the reductions in liver enzymes (ALT and AST) post-deferasirox administration further support a possible beneficial effect of deferasirox on liver function. Liver disease does occur in patients with sickle-cell syndromes not only as a result of chronic obstruction by sickled red cells but also because of fibrosis and cirrhosis induced by iron deposition [21]. Thus, in these patients, liver is considered as the main target organ and deferasirox seems to improve its function by removing the excess iron. On the contrary, heart MRI T2* failed to display any differences between baseline and 12-month values. However, we have to mention that all baseline and post-therapy values were within normal values. Furthermore, heart MRI T2* showed no correlations with either the serum ferritin levels nor with liver MRI T2*. These results are in agreement with those of Inati et al who reported that no one of 23 evaluated SCD patients had evidence of cardiac iron overload although they had significant transfusion burden, systemic and hepatic iron overload. Moreover, the authors found no significant correlations between cardiac MRI T2* values and biochemical variables [22].

Preclinical studies of deferasirox indicated that the kidney is a potential target organ of toxicity. Patients with SCD have often normal serum creatinine values, although their renal function is abnormal. In this study, we evaluated a reliable and sensitive marker of glomerular filtration rate, named cystatine-C [23], which has been found to be increased in patients with sickle-cell syndromes, including HbS/β−thal [24]. Deferasirox increased serum cystatin-C at 6 and 12 months of therapy, but there was no further increase between the 6th and 12th month

of treatment. Such an increase was not observed in patients with thalassemia intermedia who were treated with deferasirox in a similar fashion in our center [8]. Vichinsky et al reported in a randomized study of 195 adult and pediatric patients with SCD that deferasirox produced mild non-progressive increases in serum creatinine of some patients [10]. In our study, we did not notice any increases in serum creatinine values or any changes in 24-hour proteinuria. However, our results on cystatin-C levels suggest that a very close monitor of renal function is needed when we use deferasirox in HbS/β−thal.

We conclude that our data indicate that over 12 months, deferasirox significantly reduced liver iron burden and serum ferritin levels in iron-overloaded patients with HbS/β−thal. Our study suggests that deferasirox provides effective iron chelation therapy of the liver in this cohort of HbS/β−thal patients with minimal toxicity.

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Table 1. All evaluated parameters at baseline, after 6 and 12 months of deferasirox treatment (mean±SD)

	Baseline	6 months	12 months
Serum ferritin, ng/mL	1989 ± 923	1620 ± 894 (*P*=0.05)	1008 ± 776 **(*P*<0.001)**
Liver T2, ms	20.4 ± 6.0	NM	28.2 ± 8.3 **(*P*=0.001)**
Liver T2*, ms	3.9 ± 3.2	NM	5.8 ± 3.1 **(*P*=0.01)**
HIC, mg/g dry weight	6.9 ± 8.7	NM	4.7 ± 8.8 **(*P*=0.01)**
Cardiac T2*, ms	35.4 ± 8.3	NM	37.8 ± 6.4 (*P*=0.481)
LVEF, %	64.5 ± 7.4	NM	66.0 ± 6.8 (*P*=0.376)
AST, U/L	57.7 ± 26.8	47.9 ± 29.4 (*P*=0.06)	40.5 ± 22.6 **(*P*<0.01**)
ALT, U/L	50.6 ± 23.9	37.2 ± 19.1 **(*P*<0.01)**	30.2 ± 19.6 **(*P*=0.004**)
Hemoglobin, g/dL	8.4 ± 1.4	8.6 ± 1.6 (*P*=0.568)	8.5 ± 1.8 (*P*=0.386)
Serum creatinine, mg/dL	0.7 ± 0.2	0.8 ± 0.3 (*P*=**0.09**)	0.8 ± 0.4 (*P*=0.124)
Cystatin-C, mg/L	0.9 ± 0.4	1.1 ± 0.4 **(*P*=0.001**)	1.2 ± 0.6 **(*P*<0.001**)
Prot 24h, mg/24h	440.4 ± 578.9	477.2 ± 450.11 (*P*=0.065)	469.6 ± 466.7 (*P*=0.073)

NM, value not measured

HIC, hepatic iron concentration

LVEF, left ventricular ejection fraction

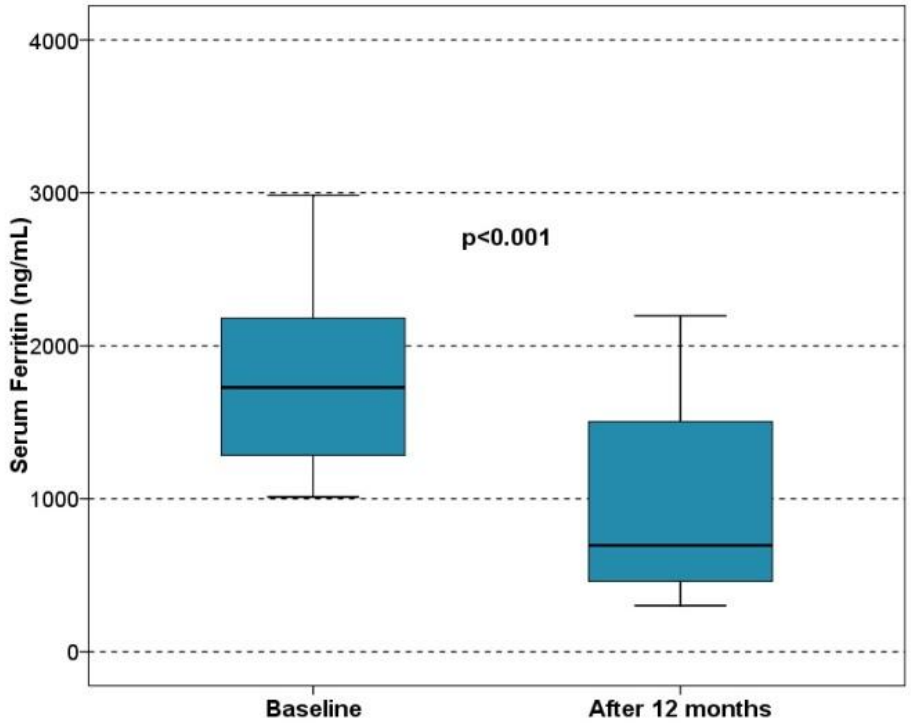
4000
3000
2000
1000
0
Serum Ferritin (ng/mL)
p<0.001
Baseline
After 12 months

Figure 1.

Legend to Figure

Deferasirox produced a dramatic reduction of serum ferritin levels after 12 months of treatment (see also Table 1)

***Conflict of interest**

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