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Deferasirox Effect on Serum Ferritin in Iraq Patients with Hemoglobinopathies: A Single Center Experience

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Abstract

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Keywords: Iron overload; Chelating agents; Thalassemia; Deferasirox

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BACKGROUND: The introduction of deferasirox as an oral iron chelator for hemoglobinopathies has been hailed by many as an important milestone in the management of iron overload in the latter disorders.

AIM: The objectives of the study were to evaluate the effectiveness of deferasirox in patients with hemoglobinopathies and to assess predictors of response.

METHODS: In this cross-sectional study, 160 patients diagnosed with hemoglobinopathies were included retrospectively from Jin hematology and oncology center in Duhok city, Iraqi Kurdistan. The Jin center offers patients with hemoglobinopathies clinical advice, examination, follow-up, treatment, and blood transfusions.

RESULTS: The median age of enrolled patients was 12 years (range 3–34 years), and included 86 females and 74 males. All patients were on deferasirox with a compliance rate of 77.5%. Furthermore, 32.3% were on concomitant deferoxamine at their last follow-up. After a median follow-up of 2.1 years (range 1–4 years), there was a mean reduction of serum ferritin level of –478.7 overall and –821.1 ng/ml in complaint patients (both being significant at p of 0.042 and 0.001, respectively). Univariate analysis revealed that older age at enrollment, and older age at starting therapy, and initial serum ferritin (>3000 ng/ml) were all significantly associated with more mean reduction in serum ferritin; while only the latter remained so by multivariate analysis (p = 0.04).

CONCLUSIONS: Deferasirox was found to be effective in reducing the level of serum ferritin among this cohort of hemoglobinopathy patients, to a degree comparable to that reported in other studies worldwide. Furthermore, there were significant associations between the reduction of serum ferritin level and age, age at starting treatment, drug compliance, and the initial serum ferritin levels.

Introduction

Blood transfusion constitutes the cornerstone of the management of symptomatic hemoglobinopathies [1]. Each blood unit adds 200–250 mg of iron to body stores and since there is no physiological mechanism to remove the excess iron from the human body, iron overload would be inevitable [2]. As the iron storage capacity of macrophages and hepatocytes is exceeded, and the excess iron released to the plasma becomes beyond the capacity of transferrin, Non-Transferrin Bound Iron (NTBI) starts appearing. Thereafter, NTBI will be deposited in various tissues and reactive oxygen species are produced by its metabolism causing damage to these tissues, including: Cardiac muscles, hepatocytes, pancreatic, thyroid, parathyroid, and pituitary cells [3]. Hence, to counter iron overload several iron chelators were introduced over the past few decades including subcutaneous deferoxamine, oral defriprone, and more recently the oral Deferasirox [4]. Several studies over the past decade have revealed the relative safety and

convenience of deferasirox, and its efficacy in reducing iron overload across a variety of anemias, as shown by reductions in serum ferritin, liver iron content, and cardiac iron [5], [6].

There is paucity of studies evaluating the efficacy of deferasirox in reducing serum ferritin in hemoglobinopathy Iraqi patients, [7], [8] despite the fact that it has been in regular use for several years in the country and provided freely to these patients by government. Thus, the current study was initiated to assess the efficacy of this iron chelator in reducing serum ferritin among patients with hemoglobinopathies registered at the thalassemia center in Northern Iraq.

Patients and Methods

A total of 160 patients diagnosed as hemoglobinopathies and receiving deferasirox were included retrospectively from Jin hematology and oncology center in Duhok city, Iraqi Kurdistan. The

eligibility criteria included age in excess of 2 years and a treatment duration of at least 1 year. The patients with incomplete data were excluded from the study.

Patients had their medical records reviewed, and a detailed history and clinical examination performed at the time of enrollment. The data collected comprised age, gender, the number of blood units received per year, drug history including: dose, duration, compliance with the drug, history of the using other chelating agents, history of other drugs intake, as well as other associated illnesses. The following investigations were scrutinized: Serum ferritin, serum alanine transferase (ALT), and aspartate transaminase (AST) and creatinine at baseline level at the initiation of the drug therapy and at last follow-up.

The study was approved by the scientific and ethics committee at the college of medicine, University of Duhok, Iraq. Informed consent was obtained from all enrolled patients.

Statistical analysis

The data were entered into SPSS version 22 statistical package (IBM Corp, 2013). Analytic statistics included testing paired differences by the paired t-test, and examining differences between two independent groups using the unpaired t-test and among more than two groups using one-way analysis of variance (ANOVA). Pearson’s correlation (r) was used to test the association between the change in serum ferritin and clinical and laboratory findings. Multivariable binary logistic regression was used to determine the independent factors predicting the change in ferritin level, with measurement of risk as the adjusted odds ratio (OR); the independent variables used were the significant ones, plus those with p-value up to 0.250 in the univariate analyses (except diagnostic category where p = 0.272); the dependent variable was decreased serum ferritin (coded zero) and increased serum ferritin (coded one). The significance level was set at p < 0.05.

Results

The median age of the 160 enrolled patients was 12 years (range 3–34 years) with 74 males and 86 females. The majority of enrolled patients were β-thalassemia major (129 patients [80.6%]), followed by sickle cell disease in 28 cases (17.6%) and thalassemia intermedia in 3 cases (1.9%). The median number of transfusion sessions received in the last year was 15 (range 0–27). The proportion of splenectomized patients was 42.5%. All received Deferasirox (DFX) with a mean dose of 34.2 mg/kg/day at their last follow-up. The median duration of therapy with DFX was 2.1 years (range 1–4), while the median age at initiating therapy

was 9 years (2–32 years). Full compliance with the drug was reported in 124 patients (77.5%). Forty patients (32.3%) were on concomitant Deferoxamine (DFO) with DFX at their last follow-up.

Table 1: A paired comparison of some laboratory findings before and after the administration of deferasirox (n = 160)

	Mean	SE	Mean difference (after – before)	95% CI of Difference	p*
Ferritin (ng/ml) [all patients]					
Before	5405.8	248.5	-478.7	17.8 – 939.5	0.042
After	4927.1	280.1			
Ferritin (ng/ml) [in complaint patients]					
Before	5346.4	281.3	-821.1	-1288.1–354.1	0.001
After	4525.3	286.4			
SGPT (u/l)					
Before	120.2	29.9	-34.5	-24.2–93.3	0.247
After	85.6	4.3			
SGOT (u/l)					
Before	64.2	4.7	3.0	-8.6–2.5	0.278
After	67.2	4.6			
Creatinine (mg/dl)					
Before	0.42	0.01	0.02	-0.06–0.02	0.316
After	0.44	0.02			

SE: Standard error, CI: Confidence interval. *Based on paired t-test. The bold number shows a significant difference

The study showed that the concentration of serum ferritin, and after a median follow-up of 2.1 years on therapy, was significantly decreased [Mean difference: -478.7 ng/ml (p = 0.042)]. The degree of reduction and significance was more noticeable when the evaluation was restricted to the 124 complaint patients (mean difference -821.1; p = 0.001; Figure 1). The study did not find any significant difference in the concentration of serum ALT, AST, or of serum creatinine (Table 1).

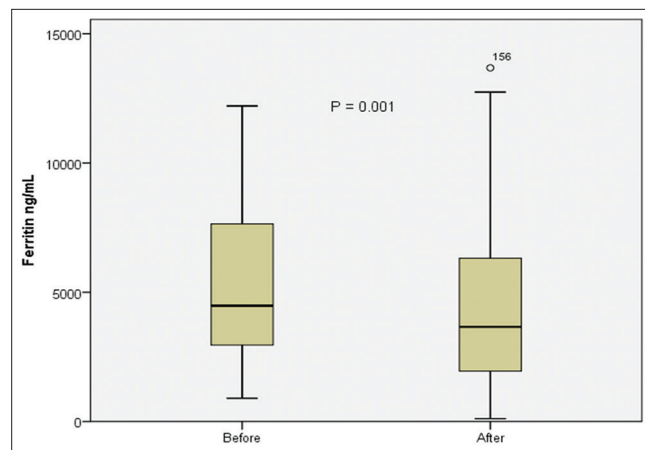


Figure 1: Changes in serum ferritin after a median follow-up of 2.1 years in complaint patients

Correlation of serum ferritin change with various parameters among complaint enrollees: when the evaluation was restricted to 124 complaint patients, it was found that the change in the level of serum ferritin with the administration of DFX was significant in the age group (≥16 years) in comparison to the age group (< 16 years) [p = 0.019] (Table 2). Furthermore, age at starting therapy as a continuous variable correlated with change in serum ferritin (p = 0.01) (Figure 2). Other significant variables include age at starting DFX, and initial Ferritin prior chelation (p = 0.01 and 0.003, respectively). Other parameters shown in Table 2 were not significantly associated with changes in serum ferritin.

Table 2: Comparison between various parameters and degree of change in serum ferritin after a median of 2.1 year of DXT therapy in 124 complaint patients

Characteristic (n = 124)	n	Ferritin change		p*
		Mean	SE	
Current age (years)				
3–15 years	91	-490.7	258.9	0.019
16–34 years	33	-1732.1	498.8	
Deferasirox Starting age (year)				
2–12	88	-433.3	256.1	0.01
13–32	36	-1769.0	489.0	
Sex				
Male	56	-1071.9	318.8	0.337
Female	68	-614.6	340.9	
Diagnosis				
β-Thalassemia major	101	-605.0	279.1	0.244
β-Thalassemia intermediate	1	-3338.0	NA	
Sickle/β-Thalassemia	4	-2120.5	958.3	
Sickle cell anemia	18	-1604.9	270.1	
Splenectomy				
Yes	53	-1066.5	389.7	0.371
No	71	-637.9	292.4	
Chelation therapy				
Concomitant use of DFO	40	-213.5	355.1	0.075
DFX as a single agent	84	-1110.4	300.7	
DFX Dose (mg/kg)				
<30	19	-1160.4	484.3	0.736
30–39	71	-848.0	275.1	
≥40	34	-575.3	588.1	
Initial ferritin				
<3000	32	115.7	288.3	0.003
≥3000	92	-1146.9	295.0	
No. of transfusions per year				
0–6	11	-1796.2	360.2	0.480
7–12	23	-848.6	371.7	
13–18	69	-829.1	359.9	
>18	21	-254.0	576.6	

*Based on unpaired t-test for two groups, and one-way ANOVA for more than two groups. NA: Not applicable, because there is only one case of Thalassemia – intermedia who had extreme value.

When a multivariate analysis in a model including age group, age at starting DFX, diagnostic category, concurrent chelation, and initial ferritin was performed, it was found that none was significant except initial ferritin in excess of 3000 ng/ml ($p = 0.04$).

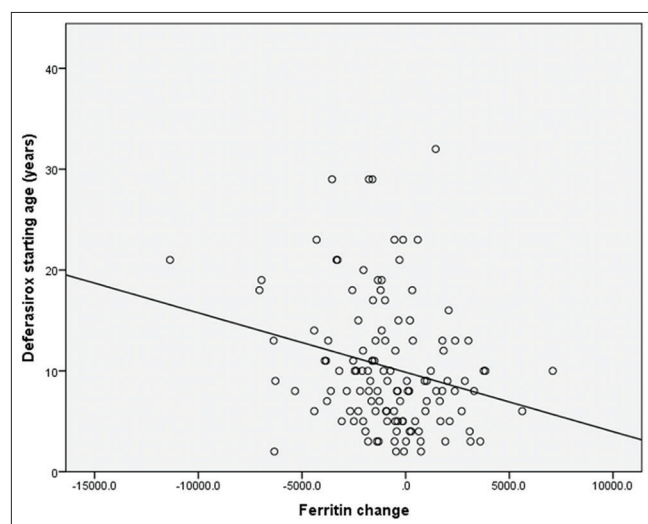


Figure 2: Correlation between age at starting Deferasirox and changes in serum ferritin in 124 complaint patients

Discussion

Oral iron chelators including Deferasirox had changed the prospects of iron chelation in

hemoglobinopathies. In the current cohort nearly four-fifth of the enrolled patients were compliant with the DFX therapy, such a high rate of compliance is not unexpected and has been attributed by previous researchers to greater convenience (37%) compared to deferoxamine, absence of injection-site soreness (25%), and minor disruption of their daily activity (23%) [9]. Furthermore, it is associated with longer half-life and more limited side effects when compared to the other oral iron chelator Defriprone [4]. Furthermore, it was documented that once-daily appropriate dosing with deferasirox provides a sustained reduction in labile pool iron levels in heavily iron-overloaded patients, and thus may reduce unregulated tissue iron loading and prevents further end-organ damage [10], [11], [12].

The study showed a significant reduction in serum ferritin level with the administration of DFX with a mean difference: -821.1 ng/ml, after a median of 2.1 years in complaint patients. In the ESCALATOR study, which is a prospective, open-label multicenter trial conducted at seven sites in the Middle East, including 237 patients aged 2–42 years with β -thalassemia and transfusional iron overload, documented a median reduction in ferritin of -341 ng/ml and -929 ng/ml after 1 and 2 years, respectively [13], [14]. The latter figure was to a great extent comparable to our results. Another prospective multicenter study “The EPIC study” including 1744 patients from 23 countries, most of whom being hemoglobinopathies reported a significant reduction in serum ferritin from baseline (-264 ng/mL) after 1 year of follow-up [5]. Abdul-Hassan *et al.* (2019) in their study on 93 chelation naive hemoglobinopathy patients aged 2–5 years from Basra in Southern Iraq, reported a reduction in the mean serum ferritin of -596.75 ng/ml, after a 2 year follow-up [7]. Other studies, with longer follow-up period on deferasirox in patients with hemoglobinopathy, reported even higher reductions of their serum ferritin [15, 16].

On dividing the compliant patients according to their initial serum ferritin level into two groups; ≥ 3000 ($n = 92$) and < 3000 ng/ml ($n = 32$), we found that the reduction was significant more among patients whose serum ferritin level is ≥ 3000 ng/ml, by both univariate and multivariate analysis. This result may be due to more aggressive treatment at a higher level of serum ferritin. As 30.4% of patients of the former group received a dose of 40 mg/kg/day of DFX versus 12.5% of patients of the latter group; also 29.4% of the former group and 9.4% of the latter group were on combined treatment with DFX and DFO. This result is also shared by Porter *et al.* who showed a more pronounced response among those with greater iron overload [17].

There was a significant reduction in serum ferritin levels among patients with age groups between >16 years old, as compared to younger ones. The result was the obtained overall and among compliant patients. A similar finding was reported in the ESCALATOR study [13]. The patients in the latter study were classified

as pediatrics aged (<16 year) and adults as aged (≥16 year), and it was documented that the reduction was more among adults than it was in children.

A greater reduction in serum ferritin level was found in the current study among splenectomized (mean reduction -750.8 ng/ml) compared to non-splenectomized (mean reduction -277.5 ng/ml), but the reduction was not significant. This is similar to the observations of Cohen *et al.* who found that splenectomized patients on chelation therapy had lower transfusional iron intake and greater reduction in iron stores than patients with intact spleens [18].

The current study also included following *S. creatinine* and ALT prior therapy and at last follow-up. The absence of significant change in *S. creatinine* after a median of 2 years of therapy is contrary to that reported by others where an increase was documented after therapy [7], [19]. Likewise, our study did not document any significant change in ALT, which is consistent with some studies but is contrary to others [7], [20], [21].

Conclusions

Deferasirox was effective in reducing the level of serum ferritin among this cohort of hemoglobinopathy patients, to a degree comparable to that reported in other studies worldwide. Furthermore, there was a significant association between the reduction of serum ferritin level and the age, timing of treatment, drug compliance, and the initial serum ferritin level.

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