ORIGINAL ARTICLE

EFFICACY OF INTERRUPTED AND MODIFIED DEFERASIROX DOSE AMONG PAEDIATRIC PATIENTS WITH B- THALASSEMIA MAJOR AND HIGH ALANINE AMINOTRANSFERASE LEVEL

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Background: Abnormal liver function tests lead to interruptions of Deferasirox therapy. The aim of this study is to assess the efficacy of deferasirox dose 30 mg /kg /day in maintaining cardiac protective level of serum ferritin of <2500 ng/ml among patients who received interrupted and modified doses. **Methods:** A retrospective cohort study was conducted in Ibn Al Atheer paediatric hospital in Mosul city, Iraq, utilizing the monthly reading of serum ferritin level during the period started in February 2013 to march 2014 using documented patients' records. Group A, patients included thirty-five patients with β- thalassemia major whose Deferasirox dose of 30 mg/kg/day was interrupted and modified due to ≥ 5-fold raise in alanine aminotransferase during any month of the study period. Compared group B patients included 40 children who received constant median deferasirox dose 30 mg/kg/day throughout one year of study period. Serum ferritin and alanine aminotransferase levels were routinely analysed every month among those patients. **Results:** Interrupted and modified Deferasirox dose of 30 mg/kg/day significantly (p=0.000) increase the frequency of having mean serum ferritin >2500 ng/ml, and was associated with 55 times relative risk of having mean serum ferritin >2500 ng/ml compared to group B with steady median deferasirox dose. **Conclusions:** Interrupted and modified deferasirox dose of 30 mg/kg/day has a significant adverse effect on cardiac protective level of serum ferritin.

Keywords: Deferasirox dose; β- thalassemia major; Alanine aminotransferase; Serum ferritin

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INTRODUCTION

Deferasirox is an oral iron chelator approved for the treatment of iron overload in patients with transfusion-dependent anaemia.[1–3] Deferasirox treatment should be interrupted following increases in serum transaminases, to be restarted at a lower dose followed by dose escalation.[4–6] A Deferasirox dose-dependent effect on serum ferritin has been revealed in several studies.[7] Serum ferritin levels ≤2500 ng/mL is regarded as a threshold associated with a decreased risk of cardiac failure and death.[2,8]

This is a retrospective cohort study aimed to assess efficacy of interrupted and modified deferasirox dose of 30 mg/kg/day in maintaining cardiac protective level of serum ferritin, among patients with hepatic adverse events in comparison to constant deferasirox dose of 30 mg/kg/day.

MATERIAL AND METHODS

This study is depended on medical records of registered patients with β- thalassemia major who were on Deferasirox monotherapy in a dose of 30 mg/kg /day during the period started from February 2013 till March 2014, in Ibn Al Atheer centre of thalassemia in Mosul city, Iraq. Serum ferritin and alanine aminotransferase (ALT) were routinely measured every month, serology for Hepatitis B and C was assessed every 6 months.

The first group named (group A) involved thirty-five patients whose Deferasirox dose of 30 mg /kg /day was interrupted and modified due to ≥ 5-fold raise in alanine aminotransferase level during any month of the study period. The last 3 enrolled patients in group A had ≥ 5-fold raise in ALT in the ninth month of the study period. The compared group B, included 40 patients who received constant median deferasirox dose 30 mg/kg/day throughout the study period without any interruption or modification of deferasirox dose.

The documented investigations performed one month prior to beginning of the intended study were regarded as baseline investigations. All selected Group A and Group B patients should have baseline serum ferritin of <2500 ng/ml and baseline ALT values <5 × upper normal level and should be seronegative for Hepatitis B and C at the start and the end of study period.

In line with drug manufacturer, Deferasirox dose had been discontinued when there was ≥ 5-fold raise in ALT and reinstalled again at a lower dose of 20 mg/kg/day upon decline of transaminase level below 5 folds during subsequent monthly interval assessment. A dose of 30 mg/kg/day was resumed when ALT level of <5 UNL was maintained for

another one month. Liver transaminase levels were measured by ChemWell-T automated chemistry analyser device (USA) and utilizing Pointe Scientific kit (USA). Serum ferritin was studied by minividas 69280 (Biomeriux, Italy) using VIDAS ® Ferritin kit (Biomeriux, France).

This study was approved by local research authority. The author declares that he had no competing interests. Chi-square test was used to compare the categorical variables, independent sample t-test was used to evaluate differences between means of continuous variables, *p*-value <0.05 was considered to be statistically significant. Data analysis was executed using version 17 SPSS program.

RESULTS

There were no significant differences in age groups and gender between Group A and Group B group (Table-1). Among group A, the calculated median deferasirox dose was 24 mg/kg/day. Alanine aminotransferase (ALT) returned to below fivefold level in the succeeding one month in 29 patients (82.9%) of analysed group A whereas ALT returned to below fivefold level after 2 months in the remaining 6 (17.1) of group A category.

There was no significant difference of baseline mean serum ferritin level between group A and group B group. Mean serum ferritin levels were significantly higher in group A compared to group B patients in six out of twelve monthly assessments (Table-2). There were significant differences (*p*-value =0.000) in cardiac protective level of serum ferritin (≤2500 ng/ml) between group A and group B patients, and there was relative risk of 55 times failure to protect the heart in patient who have interrupted and modified Deferasirox dose. On the other hand, a steady median dose of 30 mg/kg/ day-maintained serum ferritin level below 2500 ng/ml in 91.7% of the analysed monthly readings (Table-3).

Table-1: Characteristics of 75 paediatric patients with β. thalassemia on deferasirox therapy.

		Group A (n= 35) n (%)	Group B (n= 40) n (%)	*p*-value
Age	<5 years	20 (43.5)	26 (56.5)	0.486
	>5 years	15 (51.7)	14(48.3)	
Gender	Male	20 (45.5)	24 (54.5)	0.802
	Female	15 (48.4)	16 (51.6)	

Table-2: Independent sample t test comparing means of serum ferritin levels at monthly assessments comparing group A and group B paediatric patients with β. thalassaemia during one-year follow –up.

Time of serum ferritin level assessment	Group A (n=35) and Group B (n= 40)	Means of serum ferritin levels	Std. Error Mean	*p*-value	95% Confidence Interval of the Difference	
					Lower	Upper
Basal serum ferritin	Group A	2392.77	107.782	0.139	71.617	502.160
	Group B	2177.50	95.533			
First month	Group A	2556.51	134.381	0.029*	41.235	753.849
	Group B	2158.97	118.093			
Second month	Group A	2883.77	175.122	0.012*	132.766	1035.499
	Group B	2299.64	144.172			
Third month	Group A	3317.29	215.745	0.023*	98.710	1279.750
	Group B	2628.06	202.960			
Fourth month	Group A	3139.31	255.637	0.006*	228.884	1339.634
	Group B	2355.06	116.613			
Fifth month	Group A	2597.00	176.148	0.276	193.102	666.047
	Group B	2360.53	125.528			
Sixth month	Group A	2680.77	176.128	0.115	89.569	810.334
	Group B	2320.39	141.916			
Seventh month	Group A	2752.35	198.723	0.031*	49.918	993.121
	Group B	2230.83	132.450			
Eighth month	Group A	2646.43	179.915	0.130	101.386	776.688
	Group B	2308.78	128.442			
Ninth month	Group A	2615.97	125.456	0.114	71.795	653.903
	Group B	2324.92	131.098			
Tenth month	Group A	2682.73	117.621	0.028*	43.840	735.670
	Group B	2292.97	126.104			
Eleventh month	Group A	2450.76	131.195	0.173	117.630	639.276
	Group B	2189.94	135.549			
Twelfth month	Group A	2401.46	133.039	0.070	30.987	751.070
	Group B	2041.42	141.557			

* *p*- value: value less than 0.05 is considered significant.

Table 3: Comparison of twelve readings of serum ferritin among compared group A and group B groups

	Monthly Serum ferritin level (ng /ml) n= 12 readings		*p* -value	Odd ratio	95% Confidence Interval	
	>2500	< 2500	0.000	55	Lower	Upper
Group B patients	1 (8.3)	11 (91.7)			4.30	703.4
Group A patients	10 (83.3)	2 (16.7)				

DISCUSSION

During recent years, Deferasirox has been widely used as efficacious iron chelation treatment.[9] the most common adverse event that led to Deferasirox discontinuation was increased alanine aminotransferase.[2] Although ALT returned to below fivefold level in the succeeding one month in majority (82.9%) of analysed Group A group which is similar to the finding of other studies.[8] interrupted and modified deferasirox dose resulted in calculated actual received deferasirox dose (Mean±Standard deviation) of 23.5±0.36 mg /kg /day which led to significant higher mean serum ferritin in half of monthly readings during the study period in comparison to Group B group. Response to deferasirox was shown to be dose dependent,[4] and the 20 to <30 mg/kg/day deferasirox dose had a non-significant reduction in serum ferritin over one-year course,[3] which are findings in harmony to this study outcome.

Heart failure is the most common cause of death in β-thalassemia major and principally results from cardiac iron accumulation.[10,11] It is important for an iron chelator to prevent myocardial iron accumulation while reducing total body iron burden.[12] The most striking observation in this study was the finding of 55 times relative risk of having serum ferritin above 2500 ng/ml among Group A group compared to Group B group.

In the view of the findings of this study ,given that prevention is always better than treatment ,and in order to achieve a balance between providing an effective iron chelating agent that decrease the cardiac complication which is greatly related to mortality,[13–15] and at the same time to insure hepatic safety, it may be advisable to recommend a future study of an alternative approach in place of deferasirox dose interruption like halving deferasirox dose or using deferoxamine during the deferasirox-hepatic critical period.

CONCLUSION

Interrupted and modified Deferasirox dose of 30 mg/kg/day significantly failed to maintain cardiac protective level of serum ferritin

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