Original article:

Changes of liver transaminases levels during one year follow up of Deferasirox treatment in children with β-thalassemia major

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Abstract:

Objectives: Abnormal liver function tests lead to interruptions of Deferasirox therapy. The aim of this study is to determine the changes in liver transaminases levels in pediatric patients with β -thalassemia major during one year follow up of Deferasirox treatment. ***Material and methods:*** This study was conducted at Ibn Al Atheer center of thalassemia, Mosul city, Iraq during the period from 3rd of February 2013 till 2nd of February 2014. Seventy one pediatric patients with β -thalassemia major were included in the study. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured every 4 weeks after starting Deferasirox therapy dose of 30 mg /kg/day for one year. ***Results:*** In comparison to mean baseline ALT values, there were significant elevations of mean ALT values in each of the subsequent 4-weekly interval readingsafter Deferasirox therapy. There was nearly eleven times relative risk of having ALT ≥ 5 upper normal level (UNL) in patient with abnormal baseline ALT (Odd ratio 10.96,95% Confidence Interval: lower 2.05, upper 58.58). During a year of study, Deferasirox therapy was associated withALT readings of ≥ 5UNL in 22(31%) of pediatric β-thalassemia patients and that elevation lasted for 4 weeks in 95.5% of patients. ***Conclusions:*** Elevated ALT of ≥ 5UNL after Deferasirox therapy was short- lived, and lasted for 4 weeks in 95.5% of patients. It is advisable to start Deferasirox therapy at a dose of 30 mg /kg / day when baseline ALT level is normal.

Keywords: Thalassemia, Deferasirox, liver transaminases, pediatrics.

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Introduction

Patients with β-thalassemia demand permanent iron chelation therapy to prevent complications relatedtotransfusional iron overload[1,3].During recent years, Deferasiroxhas been widely used as efficaciousiron chelation treatmentfor patients at least 2 years of age.[4,5].

Thalassemia patients frequently have abnormal liver function tests due either to iron overload or concomitant viral hepatitis, moreover among the most common side effects of Deferasirox was increased liver enzyme [6-15]. Adverse events that led to discontinuations of Deferasirox included abnormal liver function tests and drug-induced hepatitis [9, 16].

The aims of the present one year, follow- up study is to determine the changes in Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in Deferasirox treated children with β -thalassemia major, also to identify the effects of age, sex and baseline level of transaminase on subsequent measured transaminase levels.

Material and methods

This follow up study was conducted in Nineveh governorate, located in north of Iraq. It included registered patients in Ibn Al Atheer center of thalassemia in Mosul city, which is the only center

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in the governorate that provide medical care and management of patients with thalassemia.

Since 2/11/2012 upon availability of the oral chelator drug Deferasirox (Exjade, Novartis) in Nineveh governorate and regardless of presence or absence of previous administration ofchelator therapy, patients aged ≥ 2 years with serum ferritin of 1000- 2000 ng/ml were selected to start Deferasirox (Exjade ®) monotherapy. Inagreement with Deferasiroxdrug manufacture prescribing information, all patients should start Deferasiroxtreatment at initial dose of 20 mg/kg/day, increasing after 3 months to 30 mg /kg/day.

All enrolled patients for this study should have their ALT and AST baseline values ≤ 2 × upper normal level (UNL) just prior to administration of Deferasirox dose of 30 mg /kg/day.In order to eliminate other causes of elevated liver transaminase, all patients were tested initially and every 6 months of study for Hepatitis B and C; any seropositive patients were excluded from the study.A total of 71 patients, 39 (54.9%) males and 32 (45.1%) females with mean age of 4.8 years and age range between 2-9 years, were eligible to be analyzed in this one year follow upresearch. The study started after a first dose of 30 mg /kg/day of Deferasirox is administered to each patient and it is dated from 3rd of February 2013 till 2ndof February 2014. Each patient was investigated thirteen times in the study year, at 4–weekly intervals for measurements of ALT and AST and serum ferritin. Deferasirox dose of 30 mg /kg/day is discontinued if patient displayed elevated transaminases levels ≥ 5 × UNL and reinstalled at a lower dose of 20 mg/kg/day upon decline of transaminase level below 5 folds duringsubsequent 4 weekly interval transaminase level assessment. A dose of 30 mg /kg /day is resumed when ALT level of < 5 UNL was maintained for another 4 weeks.

Liver transaminase levels were measured using ChemWell-T automated chemistry analyzer device (USA) and utilizingPointe Scientific kit (USA) which had upper normal value of 34U/L for ALT and AST. Serum ferritin was analyzed by minividas 69280 (Biomeriux, Italy) using VIDAS ® Ferritin kit (Biomeriux, France).

This study was approved by local research authority in Ninevah College of medicine, Ninevah University. Chi-square test was used to compare the categorical variables, Paired 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

Throughout a year of follow up, ALT levels were not increased in all of thirteen readings in 17(23.9%) patients, whereas 22(31%) of studied patients had one or more than one readings out of the 13 assessments of each patient displayed ≥ 5UNL ALT level. Elevation of >1-<5 folds ALT level were displayed in the remaining 32 (45.1%) of patients.

In comparison to mean baseline ALT values, there was significant elevation of mean ALT value in each of 4-weekly readings afterDeferasirox therapy in all compared pairs, nevertheless the differences between assessed mean ALT values compared to mean baseline ALT value ranged between 6.18 ± 2.31 - 30.41 ± 4.63 U/L (Table 1). Single time ALT elevation of ≥ 5 UNL among the thirteen readings throughout a year of follow upensued in 15 (21.1 %) of 71 patients

Table 1: Paired T test of mean Alanine aminotransferase (ALT) values measured at 4 weekly interval in comparison to mean of baseline ALT values among 71 Deferasirox treated β .thalassemia patients.

Compared mean ALT values in relation to time of measurement	Paired Differences			P - value
	Mean ± SE** (U/L)	95% Confidence Interval of the Difference		
		Upper	Lower	
Fourth week ALT -Baseline ALT	6.310 ± 3.090	12.472	0.147	0.045*
Eighth week - Baseline ALT	13.662 ± 3.753	21.147	6.177	0.001*
Twelfth week ALT - Baseline ALT	21.028 ± 4.161	29.327	12.730	0.000*
Sixteenth weekALT - Baseline ALT	9.141± 3.481	16.083	2.199	0.011*
Twentieth weekALT – Baseline ALT	6.183 ± 2.311	10.793	1.574	0.009*
Twenty fourth week ALT- BaselineALT	11.380 ± 3.552	18.465	4.296	0002*
Twenty eighth weekALT – Baseline ALT	7.169 ± 2.494	12.144	2.194	0.005*
Thirty second weekALT– Baseline ALT	8.042 ± 2.769	13.565	2.519	0.005*
Thirty sixth weekALT -Baseline ALT	6.324 ± 3.352	23.009	9.638	0.000*
Fortieth weekALT - BaselineALT	15.197± 3.029	21.238	9.156	0.000*
Forty forthweekALT - Baseline ALT	9.192 ± 2.605	14.387	3.996	0.001*
Forty eighth week ALT -Baseline ALT	30.408 ± 4.634	39.650	21.167	0.000*
Fifty second week ALT -Baseline ALT	9.201± 4.039	15.655	4.368	0.001*

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

** SE: standard error of mean.

Table 2 shows a significant (*P= 0.011*) increase in frequency of patients having equal or more than five folds raise in ALT level in those with their baseline ALT > 1- 2UNL compared to those with normal baseline ALT, moreover there is nearly eleven times relative risk of having ALT ≥ 5 UNL in patient with abnormal baseline ALT (Odd ratio 10.967, 95% confidence interval: lower 2.053, upper 58.579). Seven out of nine patients (77.8%) who had baseline ALT levels >1-2UNL had post baseline reading of ALT ≥ 5 UNL. Levels of AST were equivalent to those of ALT in 51 (71.8 %) of analyzed 71 patients. There was no significant frequency difference in level between ALT and AST timely matched readings at each 4 weeks (Table 1). There was elevation of AST of ≥ 5 UNL at same time of ≥ 5 UNL ALT increment in 18 (35.5 %) of patients. AST of ≥ 5 UNL values had sensitivity of 81.8 and specificity of 32.7% in relation to ALT ≥ 5 UNL values.

Table 2: Characteristics of 71 Deferasirox treated β.thalassemia patients in relation to occurrence of ALT level of above versus below 5 upper normal level (UNL).

Variables		ALT < 5UNL	ALT ≥ 5 UNL	P -value	Odd ratio	95% Confidence Interval	
						lower	upper
Age	**<5 year**	**30 (68.2)**	**14 (31.8)**	**0.846**	**0.902**	**0.318**	**2.557**
	>5 year	**19 (70.4)**	**8 (29.6)**				
Sex	Male	25 (64.1)	14 (35.9)	0.323	0.595	0.212	1.673
	Female	24 (75.0)	8 (25.0)				
Baseline ALT	Normal	47 (75.8)	15 (24.2)	0.001*	10.967	2.053	58.579
	>I -2UNL	2 (22.2)	7 (77.8)				
Timely matched ALT and AST level	Not equivalent level	16 (80)	4(20)	0.210	2.182	0.633	7.517
	Equivalent level	33(64.7)	18 (35.3)				

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

Among 22 patients with ALT ≥ 5 UNL; Majority 21 (95.5 %) of patient's ALT decline to a lower level after 4 weeks. About two third (63.6 %) of them dropped to < 2 UNL of ALT. Only one (4.5 %) of patients had ALT ≥ 5 UNL at 2 consecutive post baseline visits. Timing of first ALT elevation is almost comparable in first and second half of follow up year (Table 3). Only one patient (4.5 %) had ALT of ≥ 10 UNL.

Table 3: Characteristic of 22 Deferasirox treated β .thalassemia major patients having level of ALT ≥ 5UNL, during one year of follow up.

Variables	No (%)
Frequency of occurrence of ALT elevation of ≥ 5UNL during studied year	
Once	15(68.2)
Twice	4(18.2)
4 times	2(9.1)
6 times	1(4.5)
Timing of declining of ALT level to ≤ 5UNL	
After 4 week	21(95.5)
After 8 week (2 consecutive elevations)	1(4.5)
ALT levels	
>5-10 UNL	21(95.5)
>10 UNL	1(4.5)
Folds of ALT reduction following elevation	
Decrease to normal	6(27.3)
Decrease to > 1 – 2 UNL	8(36.4)
Decrease to ≥ 2 – 3 UNL	3(13.6)
Decrease to ≥ 3 -4 UNL	5(22.7)
Timing of first time ≥ 5UNL ALT elevation	
First 6 months	10(45.5)
Second 6 months	12(54.5)

Mean ± standard error(SE) of mean baseline serum ferritin value was 2392.8 ± 107.8 ng ⁄ ml. Paired samples T test showed that the mean of serum ferritin readings measured at time of first ALT elevation above 5 UNL was 2801.97±171.5 ng/ml which was not significantly different (p=0.818) when compared to the mean of serum ferritin values of 2832.59 ± 167.1 ng/ml, assessed when those ALT levels dropped below 5 UNL.

Discussion

Of the adverse events that led toDeferasirox discontinuation, the most common were increased

alanine aminotransferase[1]. Studied patients receiving Deferasirox chelation therapy for one year displayed deranged ALT in 54/71 (83%) of them. Almost one third (30.9 %) of studied patients had one or more than one readings displayed ≥ 5UNL increase in ALT level , nevertheless , that elevation occurred single time in 15 (68.1%) of those patients, it was short-lived and returning to below fivefold level in the succeeding 4 weeks in 95.5 % of analyzed patients. These finding supported that Deferasirox adverse events generally are mostly transient and there were no progressive increases liver transaminase levels [17, 18]. Albeit there were significant elevation of studied mean ALT values in comparison to mean baseline ALT values, however the assessed mean ALT paired differences ranged between 6.18 ± 2.31 -30.41 ± 4.63 U/L,a value of only about one fold ALT increment. Mean ALT levels were mildlyelevated during the first 2 years of Deferasiroxtreatment[11].

Only one (4.5 %) of studied patient had ALT levels >10 UNL which is comparable to other studies [4]. Only one (4.5 %) of investigated patients had ALT ≥ 5 UNL at 2 consecutive post baseline visits. Minority of patients experienced two consecutive increases in ALT[1, 4, 17]. In accordance with results of this research majority of patients who had ALT levels above UNL at baseline had higher ALT in their follow up[4, 17].

AST increased less frequently than ALT among investigated patients, similar finding was obtained by other study[2].Elevated serum ALT levels indicate a high specificity and a reasonable sensitivityof liverinjury [17]. Analyzed ≥ 5 UNL of AST values has sensitivity of 81.8 % in relation to ≥ 5 UNLof ALT values, implying that ALT was the determinant of Deferasirox dose interruptions and modification

The measurement of serum ferritin provides a relatively strong marker of iron burden [18]. There was no significant difference between means of analyzed serum ferritin during first time changes of ALT above versus those below 5 folds, denoting that iron overload was not the reason for the studied ALT elevations.

Conclusions

In the view of this study results, it is reasonable to start Deferasirox therapy at a dose of 30 mg /kg / day whenbaseline ALT level is normal, since there is nearly eleven times relative risk of having ALT ≥ 5 UNL in patient with abnormal baseline ALT. It is not necessary to test for AST taking into consideration that ALT was the determinant ofDeferasirox dose modification.

Authors' contribution:

Both authors designed the study and gathered the study data. Both authors wrote, edited and revised the manuscript. Nashwan M. Al-Hafidh submitted the manuscript. Both authors approved the final draft

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