RESEARCH ARTICLE

Efficacy of Deferasirox Median Dose of 30 mg/kg/day in Pediatric Patients with β-Thalassemia Major during One Year Follows-up Therapy

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ABSTRACT

Objective: To assess the efficacy of deferasirox median dose of 30 mg /kg /day in pediatric patients with β- thalassemia major during one year of follow up

Patients and methods: This study was conducted at Ibn Al Atheer center of thalassemia, Mosul city, Iraq, during the period from 3rd of February 2013 to 2nd of February 2014. Serum ferritin was measured at baseline and four weekly intervals thereafter among 49 transfusion-dependent children with β-thalassemia major, who were treated with a median deferasirox dose of 30 mg /kg /day.

Results: No statistically significant difference was detected between the mean serum ferritin level at baseline (2189.39 ± 85.7) ng/mL and its mean value at four-weekly intervals during forty-eight weeks of deferasirox therapy. There was significant (p = 0.027) improvement of serum ferritin at 52 weeks reading (1750.6 ± 202.8 ng/mL) compared to baseline reading. The percentage of patients with baseline serum ferritin levels of >2,500 ng/ml was 32.7% (16/49), which increased significantly (p=0.000) to 65% at four weeks of therapy, and ranged between 32.1% - 46.2 % in the remaining readings.

Conclusions: There was no significant reduction of serum ferritin during the initial forty-eight weeks of deferasirox median dose of 30 mg /kg /day among patients with baseline mean serum ferritin above 2000 ng /ml.

Keywords: Deferasirox, Iron overloaded, β- thalassemia.

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INTRODUCTION

Thalassemia is a global public health challenge.[1,2] In Iraq, B-thalassemia is a frequent hematological disorder, with a prevalence of carriers of about 4% and an estimated 15,000-registered thalassemia major/intermediate patients[3] The point prevalence of B-thalassemia in Nineveh province is 10.3 per 10000 of those less than 15 years aged children.[4]

Transfusion therapy in patients with B-thalassemia leads to iron overload and consequent tissue damage if patients are not chelated efficiently.[5,6] Chelation aims to decrease iron stores or manage iron imbalance, and it represents a cornerstone therapy for patients with thalassemia major.[6,7]

Deferasirox, an iron chelator, has been used in clinical practice for the treatment of transfusion iron overload in pediatric patients at least 2-year of age.[8,9] The efficacy of deferasirox is evaluated by the measurement of serum ferritin, which remains the commonly used practice for assessing body iron burden.[10]

This study was performed to evaluate the efficacy of a median dose of 30 mg/kg/day of deferasirox therapy among pediatric patients aged > 2 years with β-thalassemia major and iron overload during follow-up treatment for one year.

PATIENTS AND METHODS

This is a hospital-based prospective study conducted at Ibn -Al Atheer pediatric thalassemia center in Nineveh governorate in Iraq, from the 03 February 2013 to 02 February 2014.

Since December 2012, upon the availability of the oral chelator drug Deferasirox (Exjade, Novartis) in Nineveh governorate, patients aged ≥ 2 years with serum ferritin of ≥ 1000 ng/mL, were selected to start Deferasirox monotherapy, regardless of presence or absence of previous administration of chelator therapy.

In agreement with deferasirox drug manufacturer prescribing information, all enrolled patients started Deferasirox treatment at an initial dose of 20 mg/kg/day, increasing after 3 months to 30 mg/kg/day. The studied forty-seven patients were maintained on a median dose of 30 mg/kg/day of Deferasirox therapy throughout the whole one-year follow-up study. Since doses were calculated to the nearest whole tablet, the calculated actual received deferasirox dose

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(mean ± standard deviation) was 30 ± 2.9 mg/kg/day. The patient was excluded from the study of the drug was suspended, or a dose was modified for any reason.

A serum ferritin level of each patient was measured by minividas 69280 (Biomeriux, Italy) using VIDAS ® Ferritin kit (Biomeriux, France). Serum ferritin level was measured for the enrolled patients just before the first Deferasirox dose of 30 mg/kg/dose, which was considered as the baseline reading, serum ferritin level was reassessed every 4 weeks thereafter.

As for serum ferritin, the value may be altered by the presence of hepatitis, infection, and inflammation.[11] The studied patients were evaluated at the initiation of a dose of 30 mg/kg/day of deferasirox therapy, and then every four weeks after that by assessing alanine aminotransferase and C-reactive protein (CRP) values. Hepatitis B surface antigen and hepatitis C antibody were analyzed every 12-week. Patients with positive hepatitis B or positive hepatitis C tests, abnormal alanine aminotransferase or abnormal CRP were excluded from this study.

The ethical review board approved this study. Data analysis was executed using the version 17 SPSS program. A paired t-test was used to study the changes in serum ferritin levels every 4 weeks after initiation of chelation therapy. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Forty-nine children with P Thalassemia major were included. Their median age was 5 years with age range 3–8 years. There were 25 (51%) male.

The mean serum ferritin value at baseline time was (2189.39 ± 85.7 ng/mL), ranged from 1044 to 3336 ng/mL. In comparison to the baseline mean serum ferritin value, the mean serum ferritin value did not decrease significantly at each of four weekly readings during the forty-eight weeks of deferasirox therapy. In the contrary; there was a significant (p = 0.005) increase in serum ferritin level at the twelfth week measurement, and on the other hand mean serum ferritin value was significantly (p = 0.045) improved at fifty – two weeks reading (1949.37 ± 88.81 ng/mL) compared to baseline reading (Table 1) .

Table 2 showed that there was no significant reduction of serum ferritin level to below 2500 ng/ml along with the whole fifty–two weeks of the study period.

The patient group with serum ferritin levels >2,500 ng/mL at baseline constitute 16 out of 49 (32.7%) of all studied patients, this percentage increased significantly (p=0.000) to 81.25% at four weeks of therapy, and ranged between 31.3 – 62.5% in the remaining readings (Table 2).

There was no significant difference between genders in relation to mean serum ferritin values among deferasirox-analyzed children.

DISCUSSION

Deferasirox is used as oral monotherapy; however, its efficacy in decreasing high iron overload is unpredictable.[12]

During the first forty-eight weeks of therapy, there was no significant effect of a median dose of 30 mg/kg/day of Deferasirox treatment on serum ferritin level in studied patients. A similar conclusion was reached by other researchers, which showed that, after 12 months of deferasirox 30 mg/kg/day, serum ferritin values decreased from a mean of 3859.2 to 3417.4 ng/mL.[13] There was no significant effect on serum ferritin in patients who received deferasirox therapy with deferasirox, 20-40 mg/kg/day for less than 36 months,[12] which is also comparable to our finding.

An initial increase in serum ferritin levels during Deferasirox therapy was similarly observed in other studies.[14] There was significant (p = 0.045) improvement at fifty–two

Table 1: Paired samples t-test comparing the means of serum ferritin levels at 4-weekly intervals compared to baseline values of 49 pediatric patients with β. Thalassemia during one-year follow – up of median dose of 30 mg /kg /day of deferasirox therapy

			Paired Differences from baseline value				
					95% Confidence Interval of the Difference		
Time of serum ferritin measurement	*Mean of serum ferritin*	*Std. Error Mean*	*Mean*	*Std. Error Mean*	*Lower*	*Upper*	*P value*
Baseline	2189.39	85.723					
Fourth week	2261.71	112.571	72.327	109.851	148.543	293.196	0.513
Eighth week	2367.59	119.290	178.204	147.208	117.778	474.186	0.232
Twelfth week	2687.51	159.860	498.122	167.757	160.825	835.420	0.005
Sixteenth week	2360.27	114.816	170.878	115.525	61.402	403.157	0.146
Twentieth week	2380.57	120.251	191.184	130.040	-70.279-	452.646	0.148
Twenty fourth week	2478.80	143.146	289.408	146.707	5.567	584.383	0.054
Twenty eighth week	2316.18	122.182	126.796	135.285	145.213	398.805	0.353
Thirty second week	2362.96	120.391	173.571	135.245	98.357	445.500	0.206
Thirty-sixth week	2410.69	117.538	221.306	128.058	36.171	478.784	0.090
Forty week	2334.00	106.299	144.612	130.290	117.354	406.579	0.273
Forty-four	2124.06	98.856	65.327	126.679	320.032	189.379	0.608
Forty-eight	2051.61	94.027	137.776	120.539	380.136	104.585	0.259
Fifty-second week	1949.37	88.807	240.020	116.491	474.241	5.800	0.045

Table 2: Serum ferritin level groups, above and below 2500 ng/ml at four-weekly intervals compared to baseline values of 49 pediatric patients with β thalassemia during one-year follow–up of median dose of 30 mg/kg /day of deferasirox therapy

		Serum ferritin measurement at baseline reading		
Time of serum ferritin measurement	*Serum ferritin groups*	*< 2500 (No. of patients 33) No. (%)*	*> 2500 (No. of patients 16) No. (%)*	*p. value*
Fourth week	< 2500	26 (78.8)	3 (18.75)	0.000
	> 2500	7(21.2)	13(81.25)	
Eighth week	< 2500	19(57.6)	8(50.0)	0.617
	> 2500	14(42.2)	8(50.0)	
Twelfth week	< 2500	17(51.5)	6(37.5)	0.357
	> 2500	16(48.5)	10(62.5)	
Sixteenth week	< 2500	19(57.6)	8(50.0)	0.617
	> 2500	14(42.4)	8(50.0)	
Twentieth week	< 2500	21(63.6)	10(62.5)	0.938
	> 2500	12(36.4)	6(37.5)	
Twenty fourth week	< 2500	22(66.7)	9(56.3)	0.478
	> 2500	11(33.3)	7(43.8)	
Twenty-eighth week	< 2500	21(63.6)	10(37.5)	0.938
	> 2500	12(36.4)	6(62.5)	
Thirty- two week	< 2500	19(57.6)	9(56.3)	0.930
	> 2500	14(42.4)	7(43.8)	
Thirty-six week	< 2500	21(63.6)	6(37.5)	0.085
	> 2500	12(36.4)	10(62.5)	
Forty week	< 2500	20(60.6)	9(56.3)	0.771
	> 2500	13(39.4)	7(43.8)	
forty-four	< 2500	22(66.7)	10(62.5)	0.774
	> 2500	11(33.8)	6(37.5)	
forty-eight	< 2500	26(78.8)	10(62.5)	0.226
	> 2500	7(21.2)	6(37.5)	
Fifty-two	< 2500	27(81.8)	11(68.8)	0.304
	> 2500	6(18.2)	5(31.3)	

weeks reading (1949.37± 88.81 ng/mL) compared to baseline analyzed reading indicating a delayed in the achievement of significant serum ferritin level dropping effect.

Serum ferritin levels persistently greater than 2500 µg/L rise the risk of cardiac and endocrine complications in transfusion-dependent thalassemia.[15,16] Patient group with serum ferritin levels >2,500 ng/ml at the start of this study constitute 16 out of 49 (32.7%) of all studied patients, and reached to the lowest percentage of 31.3% after one year of deferasirox therapy, however, that was non-significant dropping in percentage between the compared two serum ferritin groups. It is comparable to the findings of research conducted in Pakistan, which revealed that at 36 months, 56.9% still had ferritin levels exceeding 2500 ng/ml in patients who received deferasirox 20–40 mg/kg,/day.12 Also, in accordance with our results, serum ferritin maintained above 2500 ng/mL at 1 year of Deferisirox therapy in all patients in Taiwan who had baseline serum ferritin levels of 2500–5000, and mean deferasirox dose during that study was 29.5 ± 4.1.[17] Patients who received deferasirox dose of 30 mg/kg/day, serum ferritin did not drop below 2500 during 12 months period deferasirox, and their mean baseline serum ferritin was 3859.2 ng/mL.12 A decrease in serum ferritin levels compared with initial value was observed in only 26.6% of patients who received a median deferasirox dose of 28.8 mg/kg/day, at a follow-up of 24 months, : and mean serum ferritin level at the start of therapy was 2657.7 ± 1414.6 (mean±SD).14

Response to deferasirox exhibits a dose-dependent pattern.[10,17] Patients who required escalation to doses of >30 mg/kg per day had high serum ferritin levels at baseline; this highlights the need to modify deferasirox dose based on the goal of therapy, iron burden.[10,18,19]

Limitation of the present study was a small number of enrolled patients, which was unavoidable because of the exclusion of patients in whom the drug was suspended, or a dose was modified or had hepatitis or abnormal CRP.

In conclusion, a median dose of 30 mg/kg/day of deferasirox among patients with mean serum ferritin value at baseline time over 2000 ng/mL was unable to have a significant drop of serum ferritin below 2500 ng/mL, and it was associated

delayed achievement of significant effect on serum ferritin level

We do not recommend using a dose of 30 mg/kg/day of deferasirox if serum ferritin value at baseline time is over 2000 ng/mL

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