Original Article

موضوع أصيل

EFFICACY AND SAFETY OF DEFERASIROX THERAPY IN A GROUP OF BETA THALASSEMIA PATIENTS DURING THREE YEARS FOLLOW UP IN BABYLON THALASSEMIC CENTER IN BABYLON PROVINCE IN IRAQ

سلامة وفعالية المعالجة بعقار Deferasirox عند مجموعة من مرضى البيتا تلاسيميا خلال ثلاث سنوات من المتابعة في مركز بابل للتلاسيميا في محافظة بابل–العراق

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ملخص البحث

هدف البحث: تقييم فعالية وسلامة تطبيق المعالجة بدواء Deferasirox لمدة 3 سنوات عند مجموعة من مرضى التلاسيميا بيتا.

طرق البحث: شملت الدراسة 132 من مرضى التلاسيميا بيتا الكبرى أعمارهم بين 2–16 سنة، تم البدء بمعالجتهم بدواء Deferasirox في مركز بابل لأمراض الدم الوراثية في العراق. تمت متابعة المرضى بشكل مستقبلي من شهر آذار 2012 وحتى الشهر نفسه من عام 2015. تم تعديل جرعة Deferasirox المعطاة حسب استجابة المريض حتى جرعة 40 ملغ/كغ. تم قياس مستويات الفيريتين في المصل، خمائر الكبد، والألبومين في البول بشكل دوري.

النتائج: لوحظ تراجع في مستويات الفيريتين في المصل عند 105 مرضى من أصل 132 مريضاً (بنسبة 71%) لتصبح ما دون 1000 نانوغرام/مل ($p<0.05$). بلغت المستويات الوسطية للفيريتين في المصل في الحالة القاعدية، وبعد 12، 24 و36 شهراً من المعالجة القيم التالية على الترتيب: 3120، 2077، 1402 و1075 ($p<0.05$). كانت الجرعة الأكثر فعالية من Deferasirox هي إعطاء 30- 30.79 ملغ/كغ خلال الفترة من 6-12 شهراً من الدراسة، و25.68 - 30.42 ملغ/كغ بعد مدة 12 شهراً من الدراسة. كانت مستويات خمائر الكبد ووظائف الكلية طبيعية عند جميع المرضى باستثناء 3 سجل لديهم ارتفاع في مستويات خمائر الكبد ومريض واحد تطور لديه خلل بسيط في مستوى الكرياتينين في المصل.

الاستنتاجات: يساعد عقار Deferasirox على خفض مستويات الفيريتين في المصل بشكل هام عند معظم مرضى التلاسيميا بيتا الكبرى. يجب استخدام جرعة ≤30 ملغ/كغ للوصول لتوازن سلبي لمستويات الحديد في الدم. يعتبر هذا العقار آمن وجيد التحمل عند الأطفال، كما أنه فعال عند مرضى المستويات المرتفعة جداً من الحديد في الدم.

ABSTRACT

Objective: *To assess the efficacy and safety of 3 years deferasirox therapy in group of patients with β thalassemia.*

Methods: *One hundred and thirty two patients with beta-thalassemia major, (2-16 years old), had been started treatment with deferasirox in Babylon Center of Hereditary Blood disorders in Babylon governorate-Iraq. They were followed prospectively from March 2012 till March 2015. The dose of deferasirox was adjusted up to 40 mg/kg according to the response.*

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Serum ferritin, liver enzymes, urine for albumin and renal function tests were regularly checked.

Results: *Out of 132 patients, 105 patients (71%) had decreased level of serum ferritin (less than 1000 ng/dl), (p-value<0.05). The mean serum ferritin at basal, 12, 24 and 36 months were 3120, 2077, 1402 and 1075 respectively, (p-value<0.05). The most effective deferasirox dose which was used to reduce ferritin level was between 30-30.79 mg/kg from 6-12 month of treatment, while 25.68-30.42 mg/kg after 12 month of therapy. All patients had normal liver enzymes and renal function tests except three patients who experienced mild elevation of liver enzymes and one patient had mild disturbance in creatinine level.*

Conclusions: *Deferasirox significantly reduces serum ferritin in the majority of patients with beta-thalassemia major. A dose of ≥30 mg/kg is required to achieve a negative iron balance. It appears to be safe, well tolerated in pediatric patients and efficacious even in patients with very high iron load.*

INTRODUCTION

Thalassemia refers to spectrum of hereditary anemias characterized by reduced or absent production of one or more globin chain.[1] Regular blood transfusions from an early age are essential therapy for child with beta-thalassemia major in order to achieve optimal growth and adequate organ function as well as improve survival.[2] Every unit of packed blood cell contain 200-250 mg of iron. This rate of transfusion leads to iron deposition in the body, of about 15-20 mg/day, with aiming of good chelation therapy to remove more than 15-20 mg/day to achieve negative iron balance.[3] Iron overloaded is a main cause of morbidity and mortality in transfusion-dependent thalassemic patients.[4]

The introduction of iron-chelation therapy has led to a significant improvement in the survival patients with thalassemia. Desferioxamine (Desferal) is hexadenate has been the established chelation therapy for iron-overloadedpatients (introduced at 1970) and was safe and effective, excreted in stool and urine with short half-life (20-30 minutes), so that it needs infusion regimen with eventual poor compliance.[2,5]

Deferiprone (Ferriprox) is bidenate has been introduced since 1987, oral chelation therapy used as second line therapy when desferrioxamine is contraindicated. It is effective in removing cardiac iron but associated with other side effect like hepatic fibrosis, erosive arthritis and granulocytosis, so this needs close monitoring.[6,7]

Deferasirox (Exjade) is a tridenate once-daily oral chelation therapy approved by FDA in 2005 used effectively and safely in transfusion-dependent thalassemia in pediatric and adult with half-life 8-16 hours, it is excreted in stool.[8,9] Deferasirox once-daily dosing permits circulating drug at all tissue scavenge non-transferrin bound (labile plasma iron), the chemical species responsible for tissue damage in iron-overloaded patient.[10]

The effectiveness of deferasirox was monitored and followed by monthly assessment of serum ferritin levels which is non-expensive, easily reproductive and to some extent convenient. A serum ferritin levels can be affected by factor such as inflammation so the level should be interpreted with caution, however serial measurement of serum ferritin are more reliable indicator of body-iron burden.[11] Several recent reports suggest that deferasirox therapy is more cost effective than traditional therapy.[12] It has a positive effect on lowering liver iron and producing high patient compliance.[13,14]

Side effect of deferasirox may associated commonly with gastrointestinal symptoms (like nausea, vomiting, abdominal pain and diarrhea), skin rash, increased alanine aminotransferase and serum creatinine which are mild to moderate in severity and resolved without treatment, thrombocytopenia, deafness and cataract were rarely reported.[15] Deferasirox doses were initially based on Liver Iron Concentration (LIC) and were adjusted according to trends in serum ferritin levels. Efficacy was monitored by monthly serum ferritin values, safety was assessed by incidence and type of adverse reactions and laboratory indices.[8] The efficacy and safety of deferasirox has been demonstrated widely in variety of underlying anemias needing recurrent blood transfusions.[16]

METHODS

The 132 patients known cases of beta-thalassemia major, aged from 2-16 years old, to start with deferasirox, in Babylon Center of Hereditary Blood disorders in Babylon governorate were included prospectively from march 2012 till March 2015. All patients aged older than 2 years (the deferasirox was not licensed to be used in age less than 2 years) with history of blood transfusion of 1-2 units every 3-6 weeks, serum ferritin of more than 1000 ng/ml were included in the study, Those patients with age younger than 2 years, baseline serum creatinine above the upper normal limit and those with rising liver enzyme (ALT, AST) more than 10 time the upper normal, systemic disease like heart problems, platelet disorder and using anti convulsant were excluded from the study.

The starting dose of deferasirox was 20 mg/kg/day and increased in 5-10 mg/kg every 3-6 months depending on the patient response which was reflected by serum ferritin and laboratory finding, while if patient with initial level of serum ferritin of more than 2500 ng/ml, we start with 30-35 mg/kg and increased to the maximum dose 40 mg/kg/day. The therapy was stopped when serum ferritin of less than 500 ng/ml.

Taken history regarding side effect of deferasirox like nausea, vomiting, abdominal pain, and development of skin rash. Basal serum creatinine urine for albumin, Aspartate transaminase (AST), Alanine Aminotransferase (ALT), CBC, were done monthly while serum ferritin every 3 months. Compliance of patient can be assessed by counting the number of tablets returned in bottles at each visit. The drug was stopped transiently if there was disturbed renal function (Baseline serum creatinine above the upper normal limit), rising liver enzyme, (AST) and (ALT) more than 10 time the upper normal and severe skin rash developed. Audiometry and ophthalmological tests were performed annually. All patients and parents provided oral informed consent before being allowed to participate in our study.

Normal level of AST (10-48 IU/L, ALT (7-56 IU/L, platelet count (150.000-450.000 platelets in each micro-liter of blood), blood urea nitrogen (2.5 to 7.1 mmol/L), serum creatinine (50-110 μmol/L).

Statistical analysis: Data was collected, tabulated and subjected to statistical analysis by using SPSS 18 software. Appropriate statistical tests (ANOVA test, T.Test) were applied to various variables.

The aim of this study was to assess the efficacy and safety of 3 years of deferasirox therapy in group of patients with β thalassemia major

RESULTS

Total number of patients enrolled in the study were 132 patients: males 76 (57.5%), with median age of 9±2.72 years, and females 56 (42.5%) with median age of 10±3.07 years.

The commonest basal level of serum ferritin between 1000-5000 ng/dl seen in 94.6%, Table 1.

Serum ferritin (ng/ml)	No.	Percentage
1000-2500 ng/ml	50	37.8%
2500-5000 ng/ml	75	56.8%
>5000 ng/ml	7	5.4%
Total	132	100%

Table 1. Distribution of patients with basal level of mean serum ferritin at beginning of study.

The ferritin level began to decrease at 9 month of therapy and its reduction was increased with increased duration of therapy to reach 1075 ng/dl at 36 month (base level was 3120 ng/dl), and was statistically significant at 9 month of therapy and became very highly significant 0.0000 after 12 month of treatment. Also shown in Figure 1 and Table 2.

The commonest level of serum ferritin at the end of the study between 501-1000 ng/dl in 70 patients 53%, while only 9 patients 6.9% was above 2500 ng/dl. We stop deferasirox therapy in 25 patients (SF less than 500 ng/ml), majority of them achieved this level after 24-36 months of therapy, Table 3, Figure 2.

Time	Mean serum ferritin (ng/ml)	p-value
Initial	3120	
3 Months	3139	0.95
6 Months	2910	0.27
9 Months	2252	0.05
12 Months	2077	0.000
24 Months	1402	0.000
36 Months	1075	0.0000

Table 2. The mean serum ferritin during the duration of deferasirox therapy (36 months).

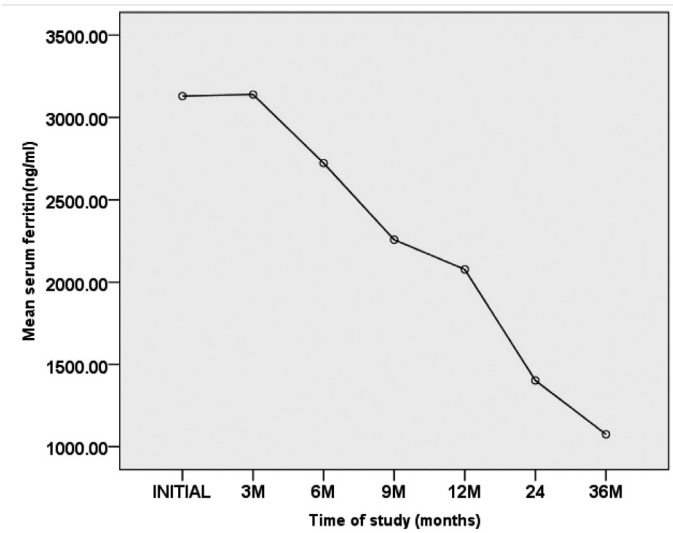

Figure 1. Mean serum ferritin along with 36 months duration of deferasirox therapy.

Level of serum ferritin (ng/ml)	Number	Percentage (%)
<500	25	18.9
501-1000	70	53
1001-1500	18	13.6
1501-2000	7	5.3
2001-2500	3	2.3
>2500	9	6.9
Total	132	%100

Table 3. Distribution of patients with mean serum ferritin levels at the end of study.

Time	Mean deferasirox (mg/kg)	p-value
Initial	23.37	
3 months	28.31	0.14
6 months	31.50	0.01
9 months	31.79	0.05
12 months	30.42	0.000
24 months	27.68	0.000
36 months	25.68	0.000

Table 4. Mean doses of deferasirox through deferent time of our study.

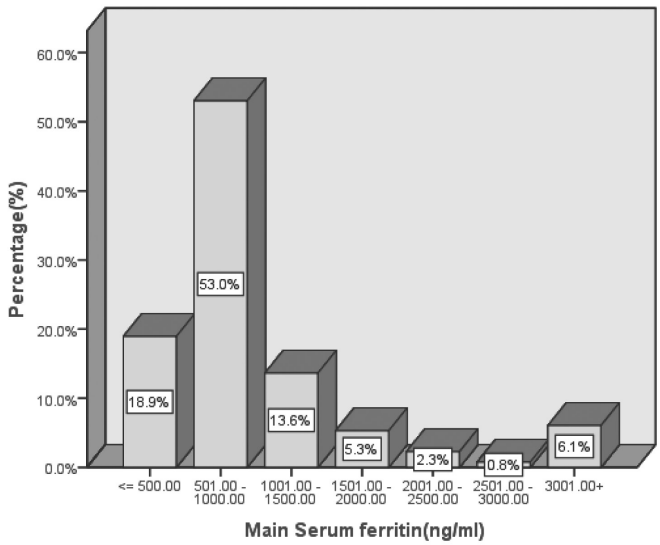

Figure 2. Percentage and mean level of serum ferritin at 36 month of deferasirox therapy.

The most effective deferasirox dose used to reduce ferritin level was between 30-30.79 mg/kg from 6-12 month of treatment, while 25.68-30.42 mg/kg after 12 month of therapy, Table 4 and Figure 3.

The most common side effect was gastrointestinal disturbance in 43 patients 32.5%, and compliance to treatment seen in 113 patients 86.3%, Table 5.

The main serum level of liver enzymes (ALT, AST), were normal initially and at the end of 36 months of deferasirox therapy, and also with renal function tests, Table 6.

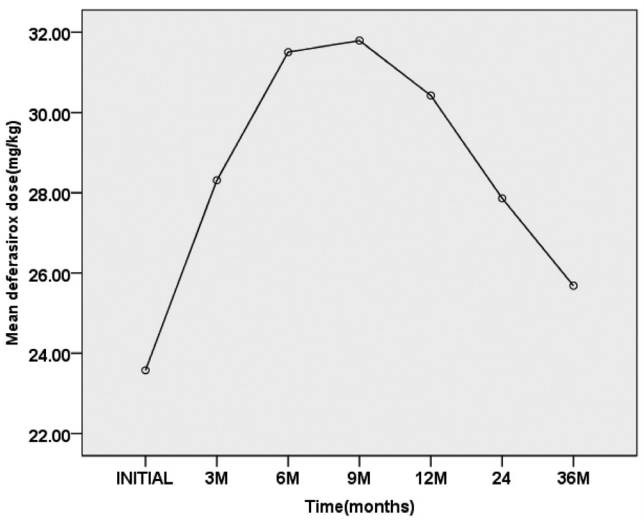

Figure 3. Shows distribution of deferasirox doses in deferent time of study.

Complication	Frequency	Percentage
Nausea	20	15.1%
Vomiting	14	10.6%
Thrombocytopenia	2	1.5%
Abdominal pain	9	6.8%
Diarrhea	0	0%
Skin rash	2	1.5%
Rising liver enzyme (>300 IU/L)	3	1.7%
Rising serum creatinine (>%33 of basal line)	1	0.75%
Good compliance	113	86.3%
Poor compliance	18	13.7%

Table 5. Frequency of drug-related complications and compliance with 3 years of deferasirox therapy.

DISCUSSION

The majority of patients in our study (62.2%) had higher basal serum ferritin >2500 ng/ml as compared with other studies,[17,18] and this is possibly reflect suboptimal chelation therapy in the past. In our study, the mean basal SF was decreased over 36 months with deferasirox therapy, this is compatible with results obtained by Dhamija M et al,[20] and Ali Taher et al.[24,25] This is indicated that over period of 36 month of therapy, provided a dose dependent overall reduction

Time	ALT (IU/L)	AST (IU/L)	Blood urea (mmolLl)	Serum creatinine (Mg/L)
Base line	14.8	10.01	2.3	41.4
3 months	14.6	9.16	2.9	42.5
6 months	18.6	14.6	3.1	44.2
9 months	17.4	12.5	3.7	43.7
12 months	14.7	16.9	3.6	42.3
24 months	14.2	11.3	3.9	41.2
36 months	11.3	15.9	3.4	42.1
p-value	0.7	0.16	0.6	0.76

Table 6. The mean liver enzyme and renal function test through 36 months of deferasirox therapy.

in iron burden as measured by serum ferritin which reduced from 3120 ng/ml at beginning of study to 2077 ng/ml at 12 month of therapy, and reach ferritin level 1075 ng/ml at 36 month.

In the present study, the efficacy of deferasirox in lowering SF was appeared after 9 months duration of therapy with significant p-value (0.05), then SF decreased significantly in the subsequent months till the end of study with highly significant p-value (0.000), and this is perhaps due to redistribution of iron between reticular-endothelial system and hepatic iron in first 3-6 months of therapy making no significant statistical change.[22]

In our study, we found 95 patients (71.9%) with mean SF after 36 months with deferasirox therapy were <1000 ng/ml, and goes with results Dhamija M et al.[20]

The staring dose of deferasirox in our study was 23.3 mg/kg with effective dose (lowering SF) at 30-32 mg/kg/day after 9 months of study, Cappellini et al,[19] showed in their cohort that at increased doses of 5-10 mg/kg every 3-6 month. However, to achieve a negative iron balance, a minimum of 30 mg/kg was required. Taher et al[21] also documented this in the escalator study, however the mean dose of deferasirox at the end of our study was 25.68 mg/kg/day, while 34.6 mg/kg/day in Dhamija M et al[20] which may explained by sample size different and lab error.

The frequency of GIT disturbances in our study was 32%, and majority was mild to moderate in severity and necessitate no stopping of deferasirox (sometimes we need to divide the twice per a day or we use domperidone as antiemetic), and this percentage compatible with results were obtained by Tahir A and Cappellini E,[23] while 10% in Dhamija M et al.[20] Skin rash in present study manifested in 2 patients (1.5%) and was mild and not need dose modification, and was compatible to, some extent, with Tahir A and Cappellini E[23] and Porter J et al,[22] but lower than results were obtained by Cappellini E,[24] and Domenica et al,[25] and these variations could be related to large number of patients included in last studies.

In the present study, we found only 3 patients (1.7%) with rising liver transaminase (ALT, AST) more than 10 fold the upper normal values which near to some extent similar to that obtained by Domenica M et al,[25] while higher percentage (70%) in both Chaudhary,[26] and Muzami et al,[27] while 16% in Dhamija M et al.[20] In our study, mild, non-progressive increases in serum creatinine levels were recorded (>33% basal line) in only 1 patient (0.7%) needing dose modification then reintroduce the usual dose gradually, while 8.8% in Domenica M et al,[25] 8.5% in Dhamija M et al[20] and 2.5% in Al-Wataify.[28] The compliance of our patients to deferasirox in present study was 86.3% and this also to some extent was reported in Haghpanah S et al.[29]

CONCLUSIONS

The results obtained from this study confirm that deferasirox significantly reduces serum ferritin in the majority of patients with thalassemia major. A dose of ≥30 mg/kg is required to achieve a negative iron balance. It appears to be safe, well tolerated in pediatric patients and efficacious even in patients with very high iron load. But some patient does not get good response (negative iron balance) even with maximum dose of deferasirox 40 mg/kg/day, so those subset of patient need special flow up and alternative management.

RECOMMENDATIONS

To know the effective starting dose of deferasirox, we should know the liver iron concentration (LIC), so we need MRI R2* (soft wear and expertise hand).

We need further studies (multi-centric) to clarify the efficacy and safety profile of deferasirox therapy in thalassemic child patients.

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