EFFICACY AND SAFETY OF DEFERASIROX THERAPY ON B-THALASSEMIA MAJOR PATIENTS IN BABYLON THALASSEMIA CENTER

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ABSTRACT

Background

Chronic iron overload from frequent blood transfusion leads to significant morbidity and mortality. Iron chelation therapy is an important part of management of those patients. Deferasirox is once daily oral iron chelator that is now widely used for treatment of transfusion hemosiderosis and represents a significant advance in treatment.

Objectives

The aim of this study is to assess the efficacy and safety of deferasirox therapy in a group of patients with β-thalassemia major.

Patients and Methods

A prospective study of 160 patients with β-thalassemia major for one year duration in Babylon thalassemia center, whose age ranged from 2—15 years with mean age of 6.7 ± 2.3years, have their serum ferritin level ranged from 1000—4000 ng/ml. The initial usage of Deferasirox dose depended on serum ferritin level ranged from 20 - 40 mg/kg/day, the patients classified into 2 groups based on serum ferritin either higher or lower than 3000ng/ml (137 patients with level of < 3000ng/ml, 18 patients>3000ng/ml and only 5 patients stopped treatment due to poor Compliance), the initial dose for first group is ≥20-<30mg/kg/day and the dose adjustment was performed in steps of 5-10 mg/kg/day every 3 months based on serum ferritin and safety marker of the drug, while the initial dose for the second group is 40mg/kg/day.

Results

The median base serum ferritin level was 2836.456±1244 ng/ml decreased to 2000.56±531.1 ng/ml after 12 months of deferasirox therapy (p value<.001). The optimum dose in reducing serum ferritin in the first group is ≥30-<40mg/kg/day in 65.69%. While, for the second group is 40mg/kg/day in 62.5% and 23 patients discontinued treatment. The commonest adverse effect is gastro-intestinal upset in 38.7%.

Conclusion

Deferasirox is effective and tolerable chelation in treatment of β-thalassemia major with iron overload.

Keywords: *Deferasirox, β thalassemia major, Babylon thalassemia center*.

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INTRODUCTION

Chronic iron overload is a serious complication of the repeated blood transfusions that are necessary for the treatment of the patients with blood disorder such as thalassemia, sickle cell anemia and various other rare anemias including aplastic anemia [1], if left untreated, chronic iron overload causes significant damage to the heart, liver and endocrine gland leading to premature death [2], and without adequate iron chelation therapy, patients with iron overload experience greater morbidity and mortality as well as higher hospitalization rates and medical care cost, than patients who are adequately chelated [2]. The extensive clinical management of iron overload by effective iron chelation therapy was found to have significant improvement on survival [1].

Desferioxamine is current reference standard of care in iron chelation, it requires subcutaneous infusion lasting 8-12 hr per day, 5-7 days a week for as long as the patient continues to receive blood transfusion and this regimen is problematic for most patients, interfering significantly with their daily life and subsequently, often resulting in poor patient compliance [2].

The introduction of the first oral chelator (deferiprone), three times daily promising a step forward for the treatment of the iron overload, however, its use has been limited due to the occurrence of the serious adverse events such as neutropenia and agranulocytosis [2].

Deferasirox (Exjade) is a once daily oral chelator provided 24 hr chelation coverage, has potential compliance advantage, is administered as an oral suspension, its demonstrated dose dependant efficacy, reducing iron overload or maintaining iron balance with dose of 20-30 mg/ kg/ day with an acceptable and clinically management safety profile [3].

Adverse events may be associated commonly with gastrointestinal symptoms like (nausea, vomiting, diarrhea and abdominal pain), skin rash increased alanine aminotransferase and serum creatinine which are mild to moderate in severity and resolved without treatment needing to be discontinued, while peptic ulcer, thrombo-cytopenia, deafness, hearing impairment or hypoacusis and cataract were rarely reported [1].

The starting dose of deferasirox based on baseline liver iron concentration [4] rather than serum ferritin (S. F) as (S.F. is effected by many factors like infection, inflammation, liver damage and vitamin C deficiency), with subsequent individual dose titration every 3 month according to S. F. trends and safety marker [4]. However, the efficacy of deferasirox has been shown to be dependent on the dose and transfusional iron intake [5] with doses up to 30 mg/kg/day that decreased body iron store in many patients and if more than 30mg/kg/day is achieving therapeutic goal [5].

Liver iron concentration (LIC) is assessed by either liver biopsy or super conductive quantum interference device (SQUID) or magnatic resonance imaging (MRI) [1, 6]. Liver biopsies are uncomfortable and may lead to hemostatic impairment and the results obtained from measuring LIC by SQUID is generally poor [1], measurement of LIC by R2MRI require special software, expertise and relatively expensive [1].

The aim of this study was to assess efficacy, tolerability and safety of deferasirox therapy in a groups of pediatric β-thalassemia major enrolled in the study over one year of treatment as indicated by changes in S.F. level.

PATIENTS AND METHODS

The prospective study is done on 160 patients with β-thalassemia major, conducted in Babylon thalassemia center (Babylon Pediatric and Maternal Hospital) of Babylon governorate from March 2011 to September 2012, their age ranged 2-15 years with mean age of 6.7± 2.3 years, with transfusional iron overload (1-2 units every 3-6 weeks) as shown by elevation of SF of more than 1000 ng/ml (liver iron concentration is difficult to assess and R2 MRI is not available in our country), to asses long term safety, tolerability and efficacy of deferasirox therapy in patients who completed one year of therapy.

Exclusion criteria

1- Patients with level of alanine amino transferase (ALT) above 300U/L and serum creatinine of upper limit of normal.

2- Patients with systemic disease like cardiovascular, renal, hepatic, bleeding tendency or medical conditions that could affect the absorption of drug.

3- Levels of S.F more than 4000 ng/ml were excluded from the study.

The initial dose of deferasirox was individualized based on level of S.F measured monthly to the end of extension period of one year, its protocol specified adjustment of 5-10 mg/kg/day based on 3 months SF trend and safety marker which evaluated through physical examination and laboratory finding (change in serum creatinine, SGPT, cytopenia (white blood cell and platelets), skin rash and gastro intestinal upset (G.I.T).

We classified the patients into 2 groups depending on S.F either higher or lower than 3000ng/ml (first group are 137 patients with level of SF of ≤3000 ng/ml and the second group are 18 patients with SF of more than 3000 ng/ml and only 5 patients stopped treatments due to poor compliance).

The recommended initial dose of the first group was ≥ 20 – <30mg/ kg/day with increment dose 5-10 mg/kg/day every 3 months based on S.F level and safety marker to reach maximum dose of less than 40mg/kg/day.

The patients of the second group plus those patients in the first group who did not respond to previous dose with increased SF to more than 3000 ng/ml, were kept on a dose of 40 mg/kg/day (of those patients not received deferasirox previously, given initially 30mg/kg/day for 2 weeks to look for deferasirox tolerance and then increased dose immediately to 40 mg/kg/day if tolerated).

Therapy was stopped or suspended with severe adverse effect (severe G.I.T upset, severe skin rash, SGPT of more than 10 times of base level, serum creatinine of more than 33% of upper limit of normal), level of SF was increased to more than 4000 ng/ml or decreased to less than 500ng/ml.

Monthly aspirate of blood for serum ferritin, alanine amino transferase, blood urea, serum creatinine, white blood cell count, platelets count and urine examination for proteinuria were done.

All patients or parents provided verbal informed consent before being allowed to enter the extension therapy.

Statistical analysis

Reported P-value for the investigator were based on 2 sided significant test (student t- test) and considered significant if P-value of less than 0.05, highly significant of less than 0.01 and not significant if more than 0.05.

RESULTS

The mean age is 6.7± 2.3years, 95 males 59.37% and females 40.63% with transfusional iron overload. The median base level of S.F was 2836.5± 1244.9 ng/ml and patient's compliance was 96.88% and where only 5 patients stopped treatment.

Table 1 shows median SF level decreased significantly only after 9month of therapy with p-value of < 0.01 and become highly significant after 12 months of therapy (S.F decreased from base level to 12 months of therapy is -835.895 ng/ml) with p-value of <0.001 .

Table 2 shows 107 patients 78.1% from 137 patients enrolled in first group with SF of < 3000 ng/ml responded to more than 20- **<** 40 mg/kg/day, while 30 patients 62.5% of patients in second group 48 patients with level of SF of ≥ 3000 -< 4000 ng/ml responded to 40 mg/kg/day and only 18 (11.6 %) patients stopped treatment either because of S.F increased to more than 4000ng/ml in 17 patients and one patient because of adverse effect (high blood urea and serum creatinine).

Table 3 shows that G.I.T symptoms are the commonest adverse effect 38.7% which are mild to moderate in severity and resolve spontaneously without drug interruption (nausea is commonest in 20 patients 12.5%) and the least is proteinuria in 2 patients 1.25% and we have no patients developed thrombocytopenia.

Table 1. Median change of serum ferritin within one year of study.

Serum ferritin				
Base level	3 month later	6 month	9 month	12 month
2836.456±1244.9	2720.35±1200.51	2601.978±874.02	2328.8±777.104	2000.6±531.1
P-value	>**0.05**	>**0.05**	<**0. 01**	<**0.001**

Table 2. Distribution of patients according to level of s. ferritin & dose of Exjade with improvement.

	Level of S.F.	**Dose of Deferasirox**	**Improvement***		**Total improvement of same group**		**Total no. of patients**	**Total Improvement**	
			No.	**%**	**No.**	**%**			
1	<3000 ng/ml	20- < 30 mg/kg/day	17	12.4	107	78.10	137		
		≥ 30- < 40 mg/kg/day	90	65.69					
2	≥ 3000- < 4000 ng/ml	40 mg/kg/day	30	62.5	30	62.5	48		
								137	88.38
3	Discontinue treatment (≥ 4000 ng/ml)or adverse effect		18**	11.7	17	94.4	18		
					1	5.6			
	Total		**155**						

*** Mean reduced serum ferritin**

****18 patients discontinue treatment**

Table 3. Drug related adverse event during one year of therapy.

	Adverse effect	Mild–moderate		Severe	
		No.	%	No.	%
1	**Nausea**	20	12.5	0	
2	**Vomiting**	17	10.62	0	
3	**Diarrhea**	15	9.37	0	
4	**Abdominal pain**	10	6.25	0	
5	**Skin rash**	5	3.12	0	
6	**Blood urea ***	4	2.51	1	0.62
7	**S. creatinine ****	3	1.87	1	0.62
8	**SGPT**	3	1.87	0	
9	**Proteinuria**	1	0.62	1	0.62
10	**Thrombocytopenia**	0		0	

*** Blood urea (normal value: 20-40 mg/dl; mild to moderate elevation means level of 100 mg/dl; severe elevation in one patient 300mg/dl.**
**** Serum creatinine (normal value 62-64 mmol/L ; mild to moderate elevation means level of 125 mmol/L ; severe elevation level of 210 mmol/l .**

DISCUSSION

The results of this study confirms the efficacy of deferasirox in reducing S.F in a patients with B-thalassemia major from base line 2836.456 to 2000 ± 535.1 after one year of therapy (S.F from base line –835ng/ml with P- value <0.001).This gives information to monitor monthly S.F to asses patients response and dose be adjusted every 3-6 months. Our results became significant statistically only after 6 months of therapy which is explained by redistribution of iron between reticulo-endothelial system and hepatic iron in first 3 - 6 months of therapy making no significant statistical change [3].

The reduction of S.F in present study is higher than the result done by capellini [1, 7] which may be explained by higher iron intake from higher blood unit given to maintain Hb above 9 gm/dl which in contrary to our patients, it is difficult to maintain normal Hb due to poor compliance and poor social economic status to visit the center regularly, making less number of blood units given.

The observed reduction in the level of S.F reflects dosage adjustment and mean iron burden [1].

The starting dose by 20 mg/kg/day initially was insufficient to achieve significant reduction in iron burden or S. F. level (17 patients 12.4%). However, a significant reduction observed when the dose increased to ≥ 30-< 40 mg/kg/day in 90 patients 65.69% and statistically is significant p< 0.01.

Those patients (30 patient) who were not responding to previous dose (≥ 30-< 40 mg/kg/day) plus those with level of S.F initially of more than 3000 ng/ml (18 patients), 40 mg/kg/day is the starting dose and the response was shown in 62.5% after 6 months of therapy.

Only 18 patients (11.6%) from total 155 did not complete the study, 17 patients stopped treatment because of increased level of S.F of more than 4000 ng/ml and the other one patient stopped treatment due to the adverse effect which were severe elevation of serum creatinine 210 mmol/L and this result is compatible with the study done by capellini [7].

The most frequent reactions are G.I.T disturbances, occurred in 38.7% which are transient, mild to moderate in severity that resolve spontaneously with no interruption of therapy. This result is compatible with studies done by Ali Tahir and Cappellini [2].

Skin rash appeared in 5 patients (3.12%) was mild, did not need treatment, is compatible with study by Ali Tahir [2] and David Ress [3], but our result is lower than the results of cappellini [5], Al Jefri [8] and Al bashlawy [9] which is explained by large number of patients enrolled in their studies associated with decreased bias.

Elevation of serum creatinine in 4 patients 2.5%, SGPT in 3 patients 1.87%, which is nearly similar to the studies done by MS Elalfy and Cappellini [7] and DJ Pennel [10]. It is lower than that done by Al-Beshlawy and Akattamis [9] in which elevation of serum creatinine in 31.7%, and SGPT in 6.9%.

No thrombocytopenia appeared and it goes with study done by Cappellini [7], Dj Pennel [10] and Elliott [11]. Poor compliance occurs in 5 patients 3.12% resulting from consent withdrawal and follow up discontinuation which mostly due to worries about reported complications as new medication and this is compatible with the study done by P. Eshghi in Iran [12].

In conclusion Deferasirox is effective, safe and tolerable chelation therapy in treatment of β-thalassemia major with iron overload due to its ability to provide constant chelation coverage and potential to improve compliance,

Recommendation

Evaluation the efficacy and starting dose of deferasirox on liver iron concentration which is assessed by R2 MRI technique and larger sample is needed with multi-center presented in Iraq to support our clinical approach of using specified starting dosing of deferasirox based on transfusional requirement and liver iron concentration.

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