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Original Research Article

LONG-TERM SAFETY AND EFFICACY OF DEFERASIROX IN PEDIATRIC B-THALASSEMIA MAJOR- AN OBSERVATIONAL STUDY.

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Abstract

Background: B-thalassemia is the most common single-gene disorder in India with nearly 36 million people carrying the responsible gene. Thalassemia major is the severe form of β thalassemia characterized by severe anemia, hepatosplenomegaly, facial and skeletal changes due to increased hemolysis of defective red blood cells (RBCs). Blood transfusion (BT) remains the first-line treatment in these patients. One unit of blood contains approximately 200–250 mg of elemental iron, and it can cause iron overload when transfused repeatedly. Transfusion-related iron overload has been associated with various complications,
for example, growth retardation, endocrinal abnormalities, and cardiac failure. To prevent complications iron chelators are used which remove excess of iron from the body by forming non-toxic stable, and water-soluble complexes. Deferasirox is a new iron chelator, that requires once-a-day oral administration. However, there is limited data regarding long-term efficacy and safety of this drug in the Indian population

Objectives: The present study will evaluate the long-term efficacy, safety, and tolerability of deferasirox in pediatric patients with transfusion-dependent β thalassemia major. The information obtained from the study could prove useful to recommend modifications, if any, in the management of iron overload in cases of thalassemia on long- term chelation therapy.

Material & methods: 64 B-thalassemia major regularly transfused children on deferasirox for a minimum of 5 years were enrolled and observed prospectively for reduction of serum Ferritin levels at the dose range of 20-30 mg/kg. Adverse drug reactions were recorded from monthly follow-ups. Reactions were classified by the Edwards and Aronsons system and severity by modified Hartwig and Siegel's method for judging the long-term safety.

Results: The mean age was 8.75(±2.6) years with 38 (59.4%) males and 26 (40.6%) Female. The mean duration and dose of deferasirox treatment received by children was 6.3 (2.24) years and 21.56 (7.5) mg/kg respectively. Mean ferritin levels at o month was 1956 ng/ml, at 6 months was1554ng/ml and at 1 year of study was 1232ng/ml. deferasirox was found to be efficacious at dose ranges between 20-30 mg/kg for various serum ferritin levels at 6 months and it was statistically significant (p-value 0.00). most of the adverse drug reactions were

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gastrointestinal like abdominal pain, diarrhea, and vomiting. They were mild. Some other reactions like transaminitis and raised creatinine were moderate in severity and responded to temporarily withholding the drug for 3 weeks. Two patients had macular pigmentation and mild raised curve for sensory neural hearing.
Keywords: β thalassemia, Deferasirox

INTRODUCTION

Thalassemia, a heterogeneous group of autosomal recessive disorders of hemoglobin synthesis, is the world's most common monogenic disease [1]. An estimated 80–90 million people in the world carry the beta thalassemia trait.[2] The disease is also common in India with approximately 10,000–12,000 children born every year with β thalassemia major.[3] India contributes to approximately 10% of the global disease burden.[4] Defective production of β globin chains in β thalassemia leads to an increased production of α globin chains. These globin chains get precipitated in RBCs, leading to extensive hemolysis and anemia. Resultant hypoxia and increased erythropoietin production cause the expansion of ineffective erythroid mass. Definitive treatment of thalassemia includes bone marrow transplantation and gene therapy, both of which are expensive. In resource-limited settings, repeated blood transfusion (BT)remains the mainstay of management. However, repeated BT's lead to iron overload and deposition of iron in various tissues of the body.

[5] Iron overload is associated with a variety of complications affecting skeletal, cardiovascular, hepatobiliary, and endocrine systems. Hepatotoxicity due to iron overload is one of the leading causes of death in patients suffering from thalassemia.[6] To prevent these complications, iron chelation therapy is now recommended and routinely prescribed to transfusion-dependent thalassemic patients.[7] Conventional iron chelators, i.e. desferioxamine and deferiprone, are effective in reducing iron overload. However, these drugs, owing to a shorter half-life, require frequent administration. Furthermore, desferioxamine administered by intravenous or subcutaneous route causes discomfort and affects patient compliance. Deferasirox is a newer iron chelator, effective orally. The drug requires once-daily administration. Efficacy and safety of deferasirox in children have been reported to be similar to that in adults.[8,9] However, data regarding the long-term efficacy and safety of this drug in the Indian population is yet lacking. Hence, this study was conducted to evaluate the utilization pattern, efficacy, safety, and tolerability of deferasirox in transfusion-dependent pediatric patients of B-thalassemia.

MATERIALS AND METHODS:

This was a single-center hospital-based, prospective cohort study carried out at the thalassemia clinic and pediatric wards of our tertiary care hospital. All Thalassemia major children coming for regular blood transfusion and who were prescribed deferasirox for at least the last five years, were enrolled and followed over 12 months after getting consent from parents. Their serum ferritin levels were done three times i.e. at enrollment, at six months and after one year of enrollment. The dose of deferasirox was kept between 20-30 mg per kg to maintain the serum ferritin below 1000 ng/ml and to avoid hepatotoxicity or renal failure. Their relevant demographic and physical examination characteristics were entered in a sheet from records. Blood was collected for complete blood count, liver function test, renal functions test, and Serum [1,10,11]Ferritin in ethylenediaminetetraacetic acid and plain vacutainers respectively under all aseptic precautions. Haemoglobin was done on Sysmex XN 1000 automated blood analysis

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machine and serum ferritin was estimated with the electro-chemiluminescence method. A fully automated ortho diagnostics VITROS F1 S machine was used as per the manufacturer's instructions to do the renal function and liver function tests. After the transfusion was done according to the Thalassemia International Federation guidelines, Parents were given the monthly doses of deferasirox and were also given a diary for recording if they noticed any adverse reactions. They were also counseled about reporting back to the hospital in case of any severe reactions. The types of reactions were classified by Edwards and Aronson's system [1,12] and severity by modified Hartwig and Siegel's method for judging long-term safety.

Exclusion criteria:
Patients with non-transfusion hemosiderosis and those whose parents/ guardians did not consent to participate were excluded from the study.

Statistical methods:
Paired Student's t-test, unpaired Student's t-test, Pearson's R-test, and one-way ANOVA test will be used for statistical analysis. P-value<0.5 will be considered significant.
IBM SPSS Statistics (version 20, IBM Corp., NY) and GraphPad InStat (version 3.10, San Diego, U.S.A.) will be used for statistical analysis.

Results:
The mean age was 8.75(±2.6) years with 38 (59.4%) males and 26 (40.6%) Female. The mean pre-transfusion hemoglobin was 6.34(1.8) gm/dl with the average of 14 transfusions per year. The mean duration and dose of deferasirox treatment received by children was 6.3 (2.24) years and 21.56 (7.5) mg/kg respectively**.**

Table:1 Age

AGE CATEGORY	Frequency	Percent
6-8	44	68.8
9-11	6	9.4
12-14	14	21.9
Total	64	100.0

TABLE 2: GENDER

Gender	**Frequency**	**Percent**
Female	26	40.6
Male	38	59.4
Total	64	100.0

TABLE 3: DURATION OF DEFERASIROX

yrs of deferasirox	Frequency	Percent
>10	2	3.1
5-10	62	96.9
Total	64	100.0

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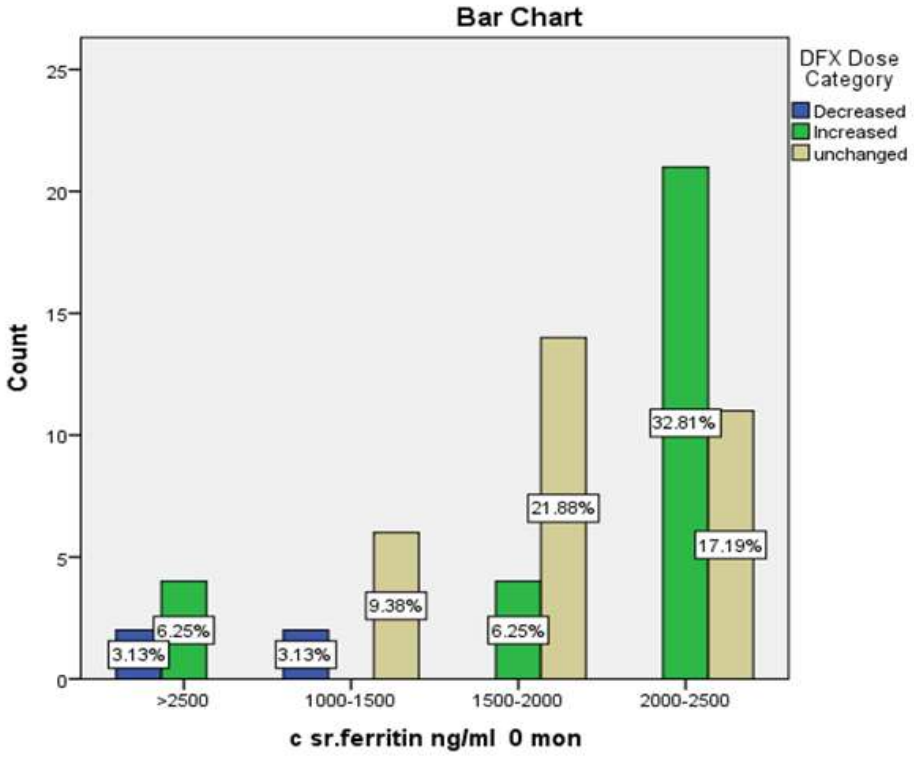
Mean ferritin levels at o month was 1956 ng/ml, at 6 months was1554ng/ml and 1 year of study was 1232ng/ml. deferasirox was found to be efficacious at dose ranges between 20-30 mg/kg for various serum ferritin levels at 6 months and it was statistically significant (p-value 0.00). At 12 months also we could see a decrease in serum ferritin levels and no child had levels above 2000 ng/ml but this decrease was not seen to be statistically significant. (p-value0.06)



GRAPH 1

TABLE 4: SERUM FERRITIN AT 0 MONTH

Serum ferritin ng/ml			DFX Dose Category			Chi-square value	P-value
			Decreased	Increased	Unchanged		
0 month	>2500	number	2	**4**	**0**	32.504	**0.000**
		% within sr. ferritin ng/ml	33.3%	66.7%	0.0%		
	1000-1500	number	2	0	6		
		% within. sr. ferritin ng/ml	25.0%	0.0%	75.0%		
	1500-2000	number	0	4	14		
		% within sr. ferritin ng/ml	0.0%	22.2%	77.8%		
	2000-2500	number	0	21	11		
		% within sr. ferritin ng/ml	0.0%	65.6%	34.4%		
Total		Count	4	29	31		
		% within sr. ferritin ng/ml	6.2%	45.3%	48.4%		

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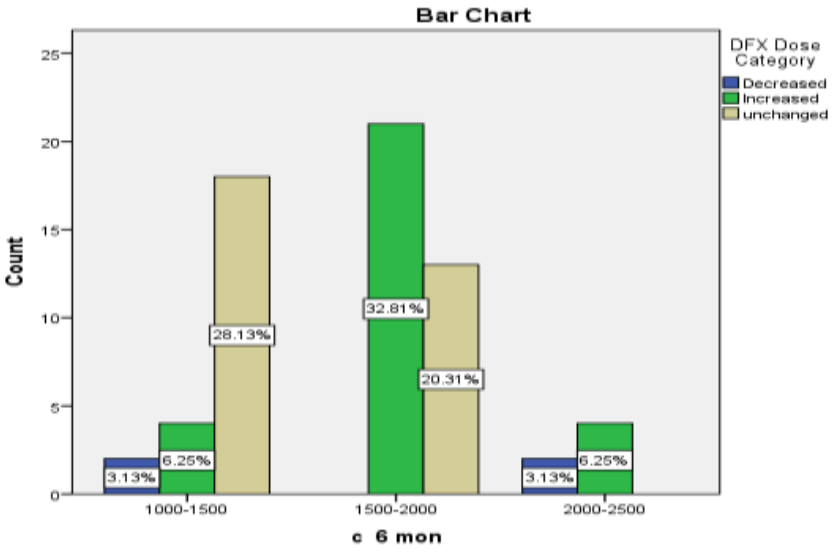
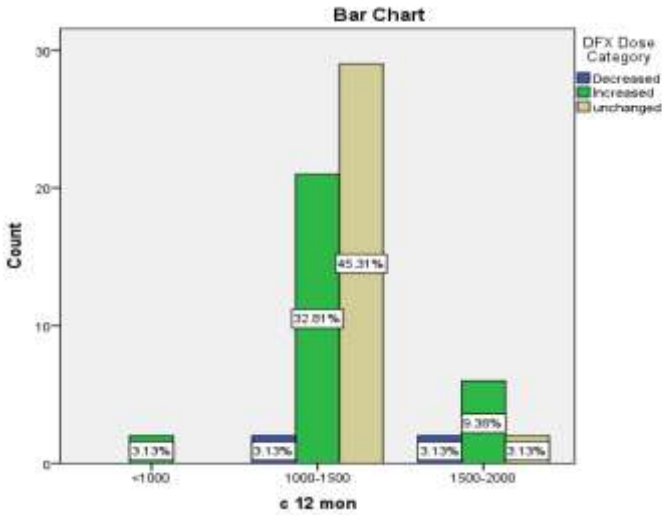


GRAPH 2

TABLE 5: SERUM FERRITIN CHANGE AT 6 MONTHS

Serum ferritin ng/ml			DFX Dose Category			Chi-square Value	P-value
			Decreased	Increased	Unchanged		
6 months	1000-1500	number	2	4	18	23.447	**0.000**
		% within 6 months	8.3%	16.7%	75.0%		
	1500-2000	number	0	21	13		
		% within 6 months	0.0%	61.8%	38.2%		
	2000-2500	number	2	4	0		
		% within 6 months	33.3%	66.7%	0.0%		
Total		Count	4	29	31		
		% within 6 months	6.2%	45.3%	48.4%		



GRAPH 3

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TABLE 6: SERUM FERRITIN CHANGE AT 12 MONTHS

Serum ferritin ng/ml			DFX Dose Category			Chi-square Value	P-value
			Decreased	Increased	unchanged		
12 Mon	<1000	number	0	2	0	8.921	**0.063**
		% within 12 months	0.0%	100.0%	0.0%		
	1000-1500	Count	2	21	29		
		% within 12 months	3.8%	40.4%	55.8%		
	1500-2000	Count	2	6	2		
		% within 12 months	20.0%	60.0%	20.0%		
Total		Count	4	29	31		
		% within 12 months	6.2%	45.3%	48.4%		

The safety of deferasirox was seen from the adverse drug reactions (ADR) that occurred during the study. A total of 118 ADR'S were noted. Out of which 82 were augmented (A),36 were chronic (C) according to Edwards and Aronson's classification system. The severity of the ADR'S was judged according to the modified Hartwig and Siegel's classification. 80 ADR'S were level 2 (mild) and 38 ADR'S were level 4 (moderate). In the Level 2 ADR'S 38 were abdominal pain,24 were diarrhoea, 10 were vomiting,4 were transaminitis and 4 were raised creatinine levels. In level 4 ADR'S 6 were diarrhoea,4 were vomiting, 16 were transaminitis ,8 had raised creatinine levels 2 had macular pigmentation and 2 had raised sensorineural hearing pattern. for severe transaminitis, jaundice, and elevated creatinine cases admission was required and deferasirox was deferred for 3 weeks. no severe reactions were seen. Most of the ADR'S were gastrointestinal constituting abdominal pain, vomiting, and diarrhoea as mentioned in the table below. In 6 cases of diarrhoea and 4 cases of vomiting the parents had skipped the doses of deferasirox for a couple of days. In such instances, deferasirox was restarted in two divided doses instead of one.

ADR	Mild		Moderate		Severe		Augmented		Chronic	
	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
Abdominal pain										
Abdominal pain (h)	38	100								
Abdominal pain (a)							38	100		
Diarrhoea										
diarrhoea (h)	24	100								
diarrhoea (a)							24	100		
vomiting										
vomiting (h)	10	100								
vomiting (a)							10	100		
jaundice										

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jaundice (h)			6	100						
jaundice (a)							6	100		
thrombocytopenia										
thrombocytopenia (h)			4	100						
thrombocytopenia (a)							4	100		
transaminitis										
transaminitis (h)	4	20	16	80						
transaminitis (a)									20	100
elev. creatinine										
elev. creatinine (h)	4	33.3	8	66.7						
elev. creatinine (a)									12	100
ophthalmic										
ophthalmic (h)			2	100						
ophthalmic (a)									2	100
auditory										
auditory (h)			2	100						
auditory (a)									2	100

Table 7: ADR= adverse drug reactions, h=modified Hartwig & Siegel scale of severity & a= Edwards & Aronson's

Discussion

Deferasirox is an effective oral chelator for reducing iron overload in multi-transfused β-thalassemia patients. Iron overload in β-thalassemia major patients is associated with high morbidity and mortality due to complications associated with tissue hemosiderosis. These patients therefore require continuous iron chelation with good compliance and safety. In recent years multiple iron chelation regimens were used including monotherapy, combined, and alternative sequential regimens.[10,11]. deferasirox is used as oral monotherapy due to its prolonged half-life and selective role in reducing tissue iron of the heart and liver, however, its efficacy in decreasing high iron overload is unpredictable.[12,13,14]

In the present study also serum ferritin was reduced with one oral dose of deferasirox but changes in high values were statistically not significant. On the other hand, the duration of chelation plays an important role in the decline of serum ferritin levels. In earlier studies it was shown that prolonged treatment for more than twelve to thirty-six months with high doses up to 40mg/kg decreases serum ferritin levels significantly,[15,16] In our study there was no significant correlation between duration of chelation and serum ferritin as below thirty-six months 56.9% had ferritin levels above 2500ng /ml and 43% less than 2500ng. In contrast, after sixty months of optimal therapy, 41.8% had serum ferritin between 1000-2500ng/ml and 58% showed value above 2500ng/ml, probably due to higher serum ferritin levels at the beginning of chelation, inadequate dose being administered, or inadequate compliance with the drug. This highlights the importance of more frequent monitoring of the doses and compliance. In our study, we noted most of the parents even after instructing about increasing the dose were not following it at the beginning of the study during enrollment. It is also reported that changes in iron burden due to high transfusion

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requirement and variable gastrointestinal absorption of the drug may contribute to variable patient response and require dose adjustments. In the present study mean serum ferritin decreased from 1956 ng/ml to 1232 ng/ml approving the efficacy of once-a-day oral deferasirox. Another observation was 20-30 mg/kg dose was effective and higher doses like 40 mg/kg were not required for reducing serum ferritin which was higher than 2500 ng/ml. Most of the adverse effects were mild and augmented type as seen in other studies[1,12,17]. Gastrointestinal adverse drug reactions like abdominal pain, vomiting, and diarrhea were commonly seen in this study group. Only some cases of diarrhea or vomiting needed two divided doses instead of one. These tablets were dissolved in water or juice.

[12,16,17] serum creatinine in various studies was reported to be elevated with prolonged duration of deferasirox therapy, however in this study also it was raised above normal levels in 18.75% of children.

Another significant finding in our study was an improvement in gastrointestinal symptoms after thirty-six months which has not been reported previously however one of the earlier studies have shown improvement in liver enzymes at twenty-four to thirty-six months of treatment. Most of the other studies have been done with children on 5 years of deferasirox treatment but in this study, 96% of the children were on it for 5-10 years Most of the adverse effects reported in the present study were mild and did not require dose adjustment or cessation of therapy except in a few with elevated liver enzymes and raised creatinine. In such cases, temporary withdrawal of chelation dropped enzyme levels to normal values, other clinical trials have also reported dose adjustment and interruption of therapy in a few patients only[19].

Two cases had mild macular pigmentation and a raised pattern of curve for sensorineural hearing loss. These changes have been seen in other studies also, and were documented to be reversible after dose reduction [20,21,22]. These cases had been taking deferasirox for more than 10 years. However limitation of this study was being a single-center observational study.

More evidence would be required to confirm these findings.

Conclusion

Deferasirox is an effective oral chelation agent for β-thalassemia major patients with few adverse effects. The study results show that deferasirox reduces serum ferritin levels After long-term therapy, changes in serum ferritin values were statistically significant. The most common adverse effects of the drug were gastrointestinal symptoms. Elevation of liver enzymes and raised creatinine are reversible after withholding for two to three weeks. Quarterly Ophthalmic and audiological screening is recommended for patients on long-term deferasirox therapy. Patients receiving deferasirox should be monitored regularly for timely management of side effects that may occur with long-term treatment to improve compliance and efficacy.

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