

Original Research Article

Effect of deferasirox on serum ferritin level in children with thalassemia major: impact of transfusional iron load

Santosh K. Shukla*, Anubha Shrivastava, Prakash C. Mishra

Department of Pediatrics, Motilal Nehru Medical College, Prayagraj, Uttar Pradesh, India

Received: 29 May 2019

Revised: 30 June 2019

Accepted: 02 July 2019

*Correspondence:

Dr. Santosh Kumar Shukla,

E-mail: mukul.shukla10@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Ongoing transfusional iron load (TIL) is an important determinant while deciding starting and subsequent dose adjustment of deferasirox during course of chelation therapy. So present study aims to find out effect of different dosing of deferasirox over the serum ferritin level in children with thalassemia major with impact of rate of transfusional iron load.

Methods: This one year observational study was carried out in 35 transfusion dependent β -thalassemic patients aged 2-18 years. Patients with baseline serum ferritin 1000-1500ng/ml and/or receiving TIL 0.2-0.3mg/kg/day were started 20mg/kg/day deferasirox and patients with ferritin >1500ng/ml and/or having TIL > 0.3mg/kg/day were started 30mg/kg/day deferasirox. Serum ferritin was repeated in every three months. Dose adjustments were performed on serum ferritin trends in steps of 5-10mg/kg /day to maximum 40mg/kg/day. Evaluation of relationship between dose adjustment, percentage of reduction in serum ferritin and TIL was done.

Results: Group-1 patients(42.8%) had TIL 0.2 to 0.3mg/kg/day whereas Group-2(37.1%) and Group-3(20%) children had TIL >0.3-0.4mg/kg/day and >0.4 mg/kg/day respectively. Starting dose of deferasirox in 25.7% patients was 20mg/kg/day and in rest were 30mg/kg/day. Average dose of deferasirox in group-1 was significantly lower as compared to group-2 and group-3 patients ($p < 0.05$). Significant decline in mean serum ferritin was observed in all three groups ($p < 0.05$). There was a significant positive correlation between TIL and average drug dose prescribed ($r=0.5411$ and $p=0.0007$) but negative insignificant correlation was observed with percentage of reduction in serum ferritin($r=0.0027$ and $p=0.98$).

Conclusions: Deferasirox 30mg/kg/day significantly reduces serum ferritin and is well tolerated in majority of patients having TIL 0.3-0.4mg/kg/day where as 20mg/kg/day is required in patients having low transfusional iron intake.

Keywords: Deferasirox, Iron load, Serum ferritin, Thalassemia, Transfusional

INTRODUCTION

Primary goal of chelation therapy is to maintain safe levels of body iron at all times, in order to prevent accumulation of iron in vital organs such as liver and heart by balancing iron intake from blood transfusion with iron excretion. Deferasirox (DFX) was developed as a once-daily oral monotherapy for treatment of transfusional iron load (TIL). Dosing and treatment

regimen require adjustment by monitoring trends of iron load (Liver iron concentration and serum ferritin level) and rate of iron loading (transfusional iron load).^{1,2} Serum ferritin concentration remains a convenient, inexpensive and widely used method of assessing body iron and, when followed serially, is a suitable alternative marker of trends in body iron burden as significant correlations between changes in liver iron concentration (LIC) and serum ferritin have been identified in various studies.³

Dose dependent effect of deferasirox on serum ferritin level has been observed in several studies which showed initial dose of deferasirox was 20mg/kg/day for the patients receiving 2-4 packed red blood cell units/ month and 10 or 30mg/kg/day for patients receiving less or more frequent transfusion respectively. Patients with heavy iron overload may require high dose 35-40mg/kg/day in order to achieve negative iron balance.^{2,4-6,9,11} Metabolic balance studies showed, equilibrium or negative iron balance can achieve by DFX at daily doses of 20mg/kg/day and 30mg/kg/day respectively.^{4,5} However Cohen et al 2008 analysis showed that the blood transfusion rate influences the response to treatment.⁴ If chelation therapy has been delayed, it will be necessary to excrete iron at a rate which exceeds this ongoing transfusional iron load. Thalassaemia International Federation recommend a starting dose of DFX 20mg/kg/day in patients of thalassaemia major who have received 10-20 transfusion episodes and currently receiving standard transfusional iron load at rate of 0.3 to 0.5 mg/kg/day and in those patients rate of iron intake from transfusion is > 0.5mg/kg/day or with pre-existing high level of iron loading 30mg/kg/day is recommended. For patients with low rate of iron loading < 0.3mg/kg/day, a dose of 10-15mg/kg may be sufficient to control iron loading.² So present study aims to find out effect of different dosing of deferasirox over the serum ferritin level in children with thalassaemia major with impact of rate of transfusional iron load on the chelation therapy.

METHODS

This single centred retro-prospective observational study was carried out between September 2017 and December 2018 in tertiary care hospital in eastern Uttar Pradesh on 35 children with thalassaemia major. In initial two months, children 2 years and above up to 18 years of age with thalassaemia major having serum ferritin level 1000ng/ml or more were enrolled for the study. Data of patients was recorded in a pretested case record form including demographic profile, details of blood transfusions including number and volume of packed red blood cells transfused, baseline serum creatinine, SGOT, SGPT levels along with the mean value of last three serum ferritin levels. Children with less than 2 year of age, those with deranged baseline serum creatinine above the upper limit of normal (ULN-1.2mg/dl) or patients with elevated baseline liver enzymes (SGOT and SGPT) to more than 4 times the ULN (40 IU/L for both) were excluded from the study. Baseline serum ferritin was taken as the average of the available last three serum ferritin values prior to start of treatment. Patients with baseline serum ferritin level of 1000-1500ng/ml and/or receiving transfusional iron load in range of 0.2-0.3mg/kg/day were started initial dose of 20mg/kg/day of deferasirox and those with baseline serum ferritin level of more than 1500ng/ml and/or having transfusional iron load >0.3mg/kg/day were started an initial dose of 30mg/kg/day of deferasirox. Dose adjustments were performed based on serum ferritin

trends in steps of 5-10mg/kg /day to maximum 40mg/kg/day. Dose was increased if serum ferritin continued to rise on two or more subsequent occasions. Serum ferritin, serum creatinine, SGPT, SGOT levels were repeated at three monthly intervals. Drug was discontinued temporarily, if kidney and liver function derangements documented by serum creatinine value more than upper limit of normal or more than 5 times the ULN of SGPT and SGPT level found. To assess the compliance, parents were asked to maintain a diary for 100 days of medication taken and calculated the compliance as the number of days the drug taken out of total 100 days.

Assessment and statistical methodology

Transfusional iron load. (TIL) Annual transfusional iron load (i.e. iron load due to only blood transfusion) in milligram (mg) by the formula: (no. of transfusions in a year X volume of PRBC transfused in one transfusion [mL/year] x60x1.08)/ (weight X100) as the hematocrit of transfused PRBC to be 60% and the estimated amount of iron per ml of PRBC to be 1.08.

Total body iron overload. Serum ferritin has been taken as sole marker for measurement of body iron burden. Change in serum ferritin levels at three monthly interval from baseline to the end of the study in each group of patient cohort and evaluation of the relationship between dose adjustment regimens, percentage of reduction in serum ferritin level and transfusional iron load was done by using Pearson coefficient (r) and p value.

RESULTS

Total of 35 patients were enrolled. Out of 35 patients, 28 were male and 7 were female. Mean age of these patients was 6.0±3.65 years. Mean age at diagnosis was 13.25±8.6 months with 68% children diagnosed with in first year of life. Average weight of patients was 17.37±7.01 kg. All patients were under-transfused with mean pre-transfusion haemoglobin 6.4±0.23gm%. Average number of PRBCs transfusion in a year was 13.5±3.02 with average volume of blood transfused was 130ml/kg/year. Calculated daily transfusional iron load in 42.8% children (n=15) was in between 0.2 to 0.3mg/kg labelled as group-1 where as 37.1% (n=13) and 20% (n=7) children were having daily iron intake >0.3-0.4mg/kg and >0.4 mg/kg labelled as group-2 and group-3 respectively. Baseline mean serum ferritin level was 1828±427.08 ng/ml with 85.7% children (n=30) were having baseline serum ferritin level >1500 ng/ml. Starting dose of deferasirox in 25.7% patients (n=9) was 20mg/kg/day and in rest of 74.2% patients (n=26) starting dose was 30mg/kg/day. Baseline mean serum creatinine level of the study group was 0.7mg/dl. None of the patients had serum creatinine more than ULN. Baseline mean SGPT and SGOT were 52.01 and 70 IU/L respectively only four (11.4%) patients had baseline SGPT more than twice ULN (Table 1).

Table 1: Baseline parameters.

(n=35)	
Mean age of patients in years	6±3.65
Male: Female (n)	28:7
Average weight of patients in kg	17.37±7.01
Mean pre-transfusion haemoglobin concentration in gm%	6.4±0.23
Average number of blood transfusion in a year	13.5±3.02
Average volume of PRBC transfused in a year in ml/kg	130ml/kg/year
Calculated average annual transfusional iron load in mg/kg/day	0.33mg/kg/day
Daily iron loading in mg/kg/day	
0.2-0.3 (Group-1)	n=15 (42.8%)
>0.3-0.4 (Group 2)	n=13(37.1%)
>0.4 (Group-3)	n=7 (20%)
Mean baseline serum ferritin level in ng/ml	1828±427.08
=>1000-1500	n=5 (14.28%)
>1500-2500	n=28 (80%)
>2500	n=2 (5.71%)
Starting dose of deferasirox in mg/kg/day	
20	n=9 (25.7%)
30	n=26 (74.2%)
Mean baseline serum creatinine	0.7mg/dl
Mean baseline SGPT, SGOT level	52.01,70IU/L
Compliance to drug taken	>=96%

Table 2: Mean prescribed dose of deferasirox in children with β - thalassemia major (n=35).

Mean Dose of Deferasirox (mg/kg/day)						
Daily transfusional iron load (ml/kg/day)	Number of patients	Follow Up				Average dose
		Starting dose	Second	Third	Fourth	
0.20 -0.30 (Group-1)	15	24.28±4.95	29.03±4.77	30.23±4.21	30.71±4.17**	21.77±3.59
>0.30-0.40 (Group-2)	13	28.98±3.02*	33.32±3.26	34.82±4.18	35.17±4.40**	24.93±2.38*
>0.40 (Group-3)	7	30.00±0*	35.45±1.43	37.94±2.46	39.00±2.00**	26.45±1.00*

*Value significant as compared to group-1(p<0.05).**Value significant as compared to starting dose (p<0.05).

Mean starting dose of deferasirox was lower in group-1 patients as compared to group-2 and group-3 patients (p < 0.05). A significant increase in the mean dose of deferasirox as compared to starting dose was observed in all groups of patients (p <0.05). Average dose of deferasirox (mg/kg/day) prescribed in group- 1, 2, and 3 were 21.77±3.59, 24.93±2.38, and 26.45±1.00 respectively. Average dose of deferasirox prescribed for one year in patients of group-1 was significantly lower as compared to group-2 and group-3 patients (p< 0.05) (Table 2).

Serum ferritin levels were analysed in study groups -1, 2 and 3 with baseline mean serum ferritin of 1599.8±256.8, 1924.38±528 and 2171.43±243 respectively. The baseline mean serum ferritin levels in group-2 and 3 were significantly higher as compared to group-1 (p < 0.05). A significant decline in mean serum

ferritin level at the end of 1 year of treatment with deferasirox as compared to baseline values was observed in all three groups (p < 0.05) with mean reduction of serum ferritin levels of 89.6±141.2, 111.38±313.3, and 266.14±182 in group-1, 2 and 3 respectively. Overall 16%, 6.8% and 16.5% of reduction in mean serum ferritin level were observed in group-1, 2 and 3 respectively (Table 3).

Statistical correlation analysis was done by using linear regression model between daily transfusional iron intake (independent variable) with average deferasirox dose required for one year (dependent variable) among the all children of study group.

As the TIL increases, dose requirement of deferasirox also goes high in linear form with Pearson coefficient(r) =0.5411 and p = 0.0007 and coefficient of determination

R2 = 0.292. Thus, there was a significant positive correlation between daily transfusional iron intake and

average drug dose prescribed (Figure 1).

Table 3: Mean serum ferritin in children with B-thalassemia major following treatment with deferasirox (n=35).

Mean serum ferritin(ng/ml)		Follow Up					Mean Reduction in Serum Ferritin Level
Daily transfusional iron load (ml/kg/day)	Number of patients	Baseline	First	Second	Third	Fourth	
0.2-0.3 (Group-1)	15	1599.8± 256.83	1701.7± 308.48	1599.40± 294.39	1404.20 ± 233.52	1335.13± 223.66**	89.6± 141.21
>0.3-0.4 (Group-2)	13	1924.38± 526.56*	1841.46± 331.24	1834.85±2 63.35	1815± 356.98	1760.46± 421.23**	111.38± 313.38
>0.4 (Group-3)	7	2171.43± 243 *	2021± 341.59	1910±241. 73	1890.57 ±237.4	1799.29± 221.33**	266.14± 182.09

*Value significant as compared to Group-1(p<0.05).**Value significant as compared to baseline (p<0.05).

Likewise percentage reduction in serum ferritin level (dependent variable) after one year of deferasirox therapy correlated with daily transfusional iron intake (independent variable) as shown in (Figure 2) as TIL increases the percentage reduction in serum ferritin goes down with Pearson coefficient (r) = 0.0027 and p = 0.98.

This signifies a negative although insignificant correlation between TIL and percentage reduction in serum ferritin level.

None of the patients treated with deferasirox in study group showed any serious adverse effects or significant derangements in renal and liver functions tests which required dose adjustment or discontinuation of chelation therapy except for abdominal pain in two (5.7%) patients. The study group recorded a good compliance of >96%.

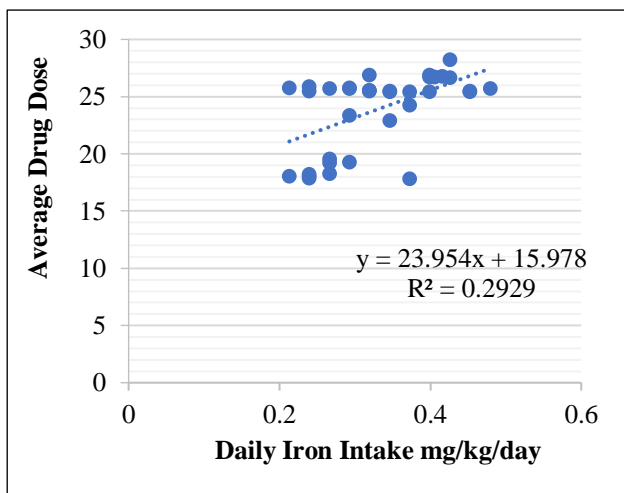


Figure 1: Relationship between daily transfusional iron intake and average drug dose prescribed.

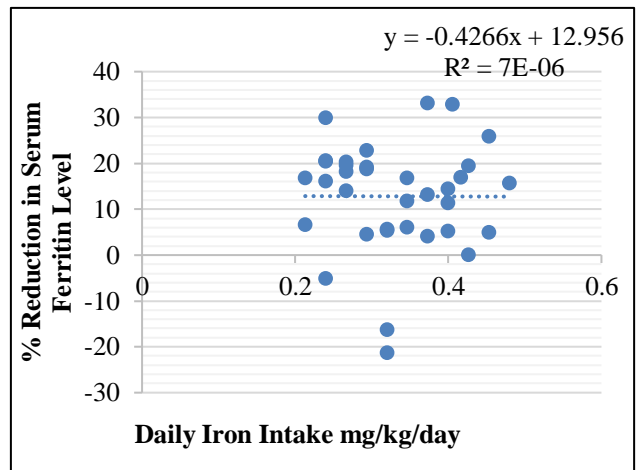


Figure 2: Relationship between daily transfusional iron intake and percentage of reduction in serum ferritin.

DISCUSSION

In our study group a male preponderance was observed. Only Indian studies have reported male preponderance up to 70% and 75%.^{7,8} Mean age at diagnosis in our study was similar to study done by Trehan A. et al who observed mean age at diagnosis of 13.2±9.7 months.⁷ Average volume of PRBC transfused in our study was much lower than study done by Thakor DR et al who found it to be 180.3ml/kg/year.⁹ So as per number and volume of PRBC transfusion our children were under-transfused. The rate of transfusional iron loading is relatively well defined in thalassemia major. According to recommended transfusion scheme, patients usually receive between 100 and 200ml of PRBC/kg per year with this volume of transfusion, the rate of transfusional iron loading is 0.30 to 0.59 mg of iron/kg/day.² Because

of under-transfusion in our study group calculated average transfusional iron load (TIL) was 0.33mg/kg/day with 80% children were having TIL<0.4mg/kg/day. Mean baseline serum ferritin in our study group children was similar to study done by Kumari V et al and Shah N. et al showed 82.4% and 93.7% children respectively having serum ferritin level > 1500ng/ml.^{8,10} In our study mean starting dose of deferasirox in patients having TIL <0.4 was 27.16 mg/day whereas mean starting dose of deferasirox was 30mg/kg/day in patients having TIL> 0.4mg/kg/day. Post-hoc analysis of 1 year phase III deferasirox data suggested that, at TIL of 0.4mg/kg/day, negative iron balance was achieved in approximately 50% of patients at a deferasirox dose of 20mg/kg per day and neutral or negative iron balance was more consistently achieved in most of the patients with a deferasirox dose of 30mg/kg per day.^{4,5} Our study showed, mean reduction of serum ferritin level in patients group having TIL> 0.4mg/kg/day who were treated with average dose of deferasirox 26. 45±1.00mg/kg/day for a year was 266.14±182.09 ng/ml. This was similar to the multicenter Evaluation of Patients Iron Chelation with Exjade (EPIC) study done by Cappellini et al 2010 showed patients treated with deferasirox at dose of 20-30mg/kg/day, the mean reduction in serum ferritin level was 198ng/ml while receiving mean TIL of 0.44mg/kg/day.¹¹ Mean reduction in serum ferritin level in patients of our study group-2 and group-3 (TIL >0.3mg/kg/day) treated with deferasirox average dose of 25.47mg/kg/day was significantly higher as compared to group-1 patients (TIL < 0.3mg/kg/day) treated with deferasirox average dose of 21.77±3.59 mg/kg/day over time of one year. A significant positive correlation of TIL with the average dose of deferasirox in our study was similar to the study done by Porter J. et al 2007 which showed deferasirox at 20 and 30 mg/kg/day, stabilised or reduced mean serum ferritin levels across a variety of transfusion-dependent anaemias having different level of transfusional iron intake and the linear regression model which has been used in this study showed only dose of deferasirox and iron intake category had a statistically significant effect on change in LIC.^{12,13} A negative but insignificant correlation of TIL with percentage reduction of serum ferritin was observed in our study. This insignificant correlation is because of very narrow gap in daily transfusional iron intake level among the patients of study group-1,2 and 3. Adverse effect of deferasirox, was almost similar to that seen in other studies.⁹ In the pivotal phase III trial, in which 296 patients with β - thalassemia major received deferasirox for one year, the most common adverse events related to deferasirox therapy were gastrointestinal disturbances (15.2%) and rash (10.8%), neither of which required dose adjustment or discontinuation. Drug compliance was excellent similar to study done by Mahajan A. et al with > 96%.¹⁴

Limitation of our study was that serum ferritin was taken as sole criteria to measure total body iron load rather than other predictive values of iron toxicity like liver iron concentration. Study done by Porter J.B et al 2016

showed that the mean changes from study baseline for serum ferritin and LIC generally correlate more strongly in patients on deferasirox therapy whom serum ferritin is < 4000ng/ml (3). In our study the highest baseline serum ferritin level was 3800ng/ml.

CONCLUSION

With present study authors conclude that deferasirox 30mg/kg/day significantly reduces serum ferritin and well tolerated in majority of patients with thalassemia major having daily transfusional iron intake of 0.3-0.4mg/kg/day where as 20mg/kg/day is required in patients having low transfusional iron intake. A significant positive correlation of TIL with the average dose of deferasirox and negative correlation of TIL with the mean reduction in serum ferritin level signifies that TIL should be monitored on an ongoing basis while deciding starting dose and subsequent dose adjustment during course of iron chelation therapy in thalassemic patients.

ACKNOWLEDGEMENTS

Authors would like to grateful for the biostatistic help and support of Dr. Gyan Prakash Assistant Professor (Statistics) department of community medicine, M.L.N. Medical college Prayagraj.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

- Porter JB. Practical management of iron overload. *British J Haematol.* 2001;115:239-52.
- Porter J, Viprakasit V. Iron overload and chelation. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the management of transfusion dependent thalassemia (TDT). 3rd edition. Thalassemia International Federation; 2014:42-97.
- Porter JB, Elalfy M, Taher A, Aydinok Y, Lee SH, et al. Limitation of serum ferritin to predict liver iron concentration responses to deferasirox therapy in patients with transfusion-dependent thalassemia. *Europ J Haematol.* 2017 Mar;98(3):280-8.
- Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in β -thalassemia major. *Blood.* 2008 Jan 15;111(2):583-7.
- Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. A phase 3 study of dererasirox (ICL670), a once-daily oral iron chelator, in patients with β -thalassemia. *Blood.* 2006;107(9):3455-62.
- Taher A, Cappellini MD, Vichinsky E, Galanello R, Piga A, Lawniczek T, et al. Efficacy and safety of

- deferasirox doses of > 30 mg/kg per d in patients with transfusion dependent anemia and iron overload. *Br J Haematol.* 2009;147(5):752-9.
7. Trehan A, Sharma N, Das R, Bansal D, Marwaha R.K.; Clinicoinvestigational and Demographic Profile of Children with Thalassemia Major. *Indian J Hematol Blood Transfus;* 2015 Mar;31(1):121-6.
 8. Shah N, Mishra A, Chauhan D, Vora C, Shah NR. Study on effectiveness of transfusion program in thalassemia major patients receiving multiple transfusions at a transfusion centre in Western India. *Asian journal of transfusion science.* 2010 Jul;4(2):94-8.
 9. Thakor DR, Desai CK, Kapadia JD, Dikshit RK, Mehariya KM. Efficacy and safety of Deferasirox in Pediatric Patients of Thalassemia at Tertiary Care Teaching Hospital. *Ind J Med Pediatr Oncol.* 2017;38 (2):102-10.
 10. Kumari V, Upadhyay SK, Gupta V, Piplani KS, Bhatia BD. Growth Retardation and Malnutrition in Children with Thalassemia Major. *Indian J. Prev. Soc. Med.* 2012;43(2);149-52.
 11. Cappellini MD, Porter J, El-Beshlawy A, Li CK, Seymour JF, Elalfy M, et al. Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. *haematologica.* 2010 Apr 1;95(4):557-66.
 12. Porter J, Galanello R, Saglio G, Neufeld EJ, Vichinsky E, Cappellini MD, et al. Relative response of patients with myelodysplastic syndromes and other transfusion-dependent anaemias to deferasirox (ICL670): a 1-yr prospective study. *Europ J haematol.* 2008 Feb;80(2):168-76.
 13. Porter JB, Lin KH, Beris P, Forni GL, Taher A, Habr D, Domokos G, Roubert B, Thein SL, EPIC Study Investigators. Response of iron overload to deferasirox in rare transfusion-dependent anaemias: equivalent effects on serum ferritin and labile plasma iron for haemolytic or production anaemias. *Eur J Haematol.* 2011 Oct;87(4):338-48.
 14. Dhamija M, Mahajan A, Kalra M, Virmani A. Deferasirox in Indian children with thalassemia major: 3 years' experience. *Indian J Med Paediatr Oncol.* 2013 Jan-Mar; 34(1):16-20.

Cite this article as: Shukla SK, Shrivastava A, Mishra PC. Effect of deferasirox on serum ferritin level in children with thalassemia major: impact of transfusional iron load. *Int J Contemp Pediatr* 2019;6:2081-6.