DOI: 10.7860/JCDR/2017/22650.9395

Original Article

Pharmacology Section

Efficacy of Deferasirox as an Oral Iron Chelator in Paediatric Thalassaemia Patients

SHIKHA JAISWAL[1], RAJESH HISHIKAR[2], ONKAR KHANDWAL[3], MANJU AGARWAL[4], USHA JOSHI[5], AJAY HALWAI[6], BASANT MAHESHWARI[7], RAKA SHEOHARE[8]

ABSTRACT

Introduction: Thalassaemia Major patients require frequent blood transfusion leading to iron overload. Excessive iron gets deposited in vital organs and leads to dysfunction of the heart, liver, anterior pituitary, pancreas, and joints. Our body has limited mechanism to excrete iron, so patients with iron overload and its complications need safe and effective iron chelation therapy.

Aim: To assess the efficacy of Deferasirox (DFX) as an iron chelator, with specific reference to reduction in serum ferritin level.

Materials and Methods: This is a prospective; observational study done in 45 multitransfused Thalassaemia Major Children receiving DFX therapy at registered Thalassaemia society Raipur Chhattisgarh. DFX was given in an initial dose of 20 mg/kg/day and according to response increased to a maximum of 40 mg/kg/day. Serum ferritin level was estimated at time of registration and at every three monthly intervals (four times during study period). The primary end point of the study was change in serum ferritin level after 12 months of DFX therapy.

Results: The mean serum ferritin before DFX therapy of all cases was 3727.02 ng/mL. After 12 months of mean dose of 38 mg/kg/day of DFX, the mean decline in serum ferritin was 1207.11 ng/mL (drop by 32.38%, p-value <0.001).

Conclusion: DFX monotherapy has a good safety profile and effectively chelates total body iron in Thalassaemia major patients.

Keywords: Ferritin, Iron chelation, Management

INTRODUCTION

Thalassaemia Major patients require frequent blood transfusion leading to iron overload and deposition of iron in liver, anterior pituitary, pancreas joints and heart. Physiologic mechanisms to excrete iron are limited, so patients with iron overload and its complications need safe and effective chelation therapy. This therapy is required to get rid of this excess iron deposited in various vital organs of body [1]. Iron chelation therapy forms an important part of treatment for patients receiving red blood cell transfusions. Iron chelation therapy is a supportive therapy for chronic anaemias, such as β-thalassaemia, Sickle Cell Disease (SCD), and the Myelodysplastic Syndromes (MDS). Iron chelators currently available include deferoxamine (DFO), which is administered subcutaneously or intravenously, and the oral chelators' Deferiprone (DFP) and Deferasirox (DFX).

The reports stated-standard iron chelator, Deferoxamine (DFO), has a safety and efficacy profile established through many years of clinical use, but the regimen of prolonged 12 hour subcutaneous infusions, 5–7 days per week is extremely demanding and can result in poor adherence, thereby, compromising efficacy and outcomes [2].

DFP (Ferriprox; L1), a three times daily oral chelating agent, became licensed in Europe, and other regions for the treatment of iron overload in year 1999 [3]. The drug may be more effective than DFO in chelating cardiac iron [4,5]. The most common side effects of DFP are nausea, vomiting, abdominal pain, diarrhea, joint pain, liver dysfunction, and also have some rare side effects like neutropenia and agranulocytosis [6-8]. Because of the risk of agranulocytosis, a weekly assessment of white blood cell counts is recommended. In some clinical studies, it was found that DFO alone is less effective then DFO and DFP combination therapy in cardiac iron overload reduction [9].

DFX, a convenient, once-daily oral therapy, has demonstrated good efficacy and acceptable safety in adult and paediatric patients with wide range of chronic anaemias [10-12]. The unique feature of DFX, not shared with other single agent is long half life of 8-16 hour which provides sustained chelation coverage of 24 hour [13,14]. DFX, approved, by FDA in year 2005 [15] is safe, oral iron chelator. S. ferritin concentration is a convenient, nonexpensive and the most widely used measure of assessing total body iron [16,17]. We prospectively assessed serum ferritin levels in an enrolled group of multitransfused thalassaemia patients to evaluate the efficiency of DFX as an iron chelator.

MATERIALS AND METHODS

This prospective, observational study assessed the serum ferritin levels of thalassaemia patients who were on DFX and evaluated the efficacy of DFX in these patients. Study was conducted in registered thalassaemia society Raipur, between January 2013 to December 2013, on 45 multitransfused thalassaemic patients of age 1- 18 years and were receiving DFX. Study is done to monitor the effect of DFX on total body iron load. This study was conducted in accordance with Good Clinical Practice guidelines and was approved by the college Ethical Committee.

Inclusion Criteria

1. Male/female between 1-18 years
2. Receiving multi blood transfusion and Chelation therapy
3. Base line S. ferritin >1000 ng/ml

Exclusion Criteria

1. Patients of other chronic medical illnesses (SLE, Rheumatoid arthritis, Hepatitis ABC, Epstein Barr virus infection).
2. Patient of severe kidney problem, abnormal decrease in platelet count, dehydration.

Patients who received Packed RBC transfusions at one to two week intervals to maintain the haemoglobin concentration at a level above 10 gm/dl were enrolled in study. Informed consent was obtained in written from the patient's guardian recruited in our study. The nature of study was discussed with each patient's guardian in the manner they understand. Single peripheral venous blood sample was drawn

from the ante cubital vein. Serum ferritin was estimated by using an automatic immunoassay analyser (360 clinitek Siemens). Serum ferritin estimated at time of registration in study and subsequently every three monthly (i.e., four times in a year). The recommended initial dose of DFX was 20 mg/kg per day given empty stomach in morning for patients receiving approximately 6 to 8 units of Packed RBC Per year, which could be discontinued or adjusted in increments of 5 to 10 mg/kg per day done to a maximum of 40 mg/kg/day when necessary based on serum ferritin levels [1]. Serum ferritin level is directly proportional to total body iron store. Iron chelation therapy decrease total body iron and hence, decline the serum ferrtin level. Dose reduction was done if any side effect was noted or if S. ferritin fall below 500 ng/ml. The relevant data were recorded in specified proforma. The primary end point of the study was to evaluate the difference in serum ferritin after 12 months of DFX therapy as compared to baseline values.

STATISTICAL ANALYSIS

The data was compiled in the formats and subjected to descriptive and statistical analysis. Data were presented as mean±SD and variables analysed by paired t-test for statistical significance. The p <0.05 was considered statistically significant.

RESULTS

Fifty patients were enrolled for the study; five were lost to follow up; 45 patients completed the study. In our study, maximum affected age group of thalassaemia requiring iron chelation therapy is between ages of 0-5 years (20%), 6-10 years (48.89%), 11-15 years (24.40%) and 16-18 years (6.67%) [Table/Fig-1].

Twenty seven males (60%) and18 females (40%) received regular transfusion with a mean age of 8.68±3.9 years (3.6-17 years) [Table/Fig-2].

Mean decline in serum ferritin level after three months is 270.36±1274.86: p-value of 0.08 (non-significant) after six months is 549.24±1206.22: p-value of 0.0019 (significant) after nine months is 1079.71±1466.28: p-value of $5.8x10^{-6}$ (highly significant) and after 12 months is 1207±1315.50; p-value of $9.96x10^{-8}$ (highly significant) [Table/Fig-3].

Significant decline in S. ferritin observed after 6 months of DFX therapy 3177.78±1379.10 p-value-0.06 (<.05) [Table/Fig-4].

DFX 20 mg/kg/day was started initially but due to non-appreciable decline in S. ferritin, upgradation of dose was done to 30 -40 mg/kg/day over next six month. A total of 16 (35.5%) patients required 35-40 mg/kg/day dose for control of ferritin level. Dose of 30-35mg shows max decline of S. ferritin level from 4450±2717.08 to 2176.67±1391.56 over one year. The p-value 0.001 (<0.05) which is highly significant [Table/Fig-5].

DISCUSSION

Iron overload is one of the serious side effects associated with frequent blood transfusion in thalassaemia patients. Since, regular blood transfusion is mainstay of thalassaemia therapy, iron chelation therapy become mandatory when serum ferritin level crosses 1000 ng/ml. DFX is commonly used as oral iron chelator among various iron chelators available. DFX shows significant decline in serum ferritin level.

S. No.	Age group (year)	Number (n = 45)	Percentage
1	0-5	9	20.00
2	6-10	22	48.89
3	11-15	11	24.44
4	16-18	03	6.67
	Total	45	100

[Table/Fig-1]: Distribution of cases according to age group.

S. No.	Gender	Number	Percentage
1	Male	27	60
2	Female	18	40
	Total	45	100

[Table/Fig-2]: Distribution of cases according to gender.

S. No	Baseline S.Ferritin (ng/ml)B	D1 After 3mths (B-FU1)	D2 After 6mths (B-FU2)	D3 After 9mths (B-FU3)	D4 After 12mths (B-FU4)
Mean	3727.02	270.36	549.24	1079.71	1207.11
SD	1405.10	1274.86	1206.22	1466.28	1315.50
95% CI		372.48	352.42	428.40	384.35
p-value		0.08	0.0019	$5.8x10^{-6}$	$9.96x10^{-8}$

[Table/Fig-3]: Time Vs mean difference in serum ferritin level.
D1= Mean decline in serum ferritin level after three months D2=Mean decline in serum ferritin level after six month D3=Mean decline in serum ferritin level after nine months is and D4=Mean decline in serum ferritin level after 12 months. CI=Confidence Interval, SD=standard deviation. FU=Follow up B=Baseline

S. No.	Time	Mean SF	SD	95%CI	p-value
1	Baseline	3727.02	1405.10		
2	3 month (fu1)	3456.67	1595.01	900.06	0.39
3	6 month (fu2)	3177.78	1379.10	1132.49	0.06
4	9 month (fu3)	2647.31	1335.21	1653.93	0.003
5	12 month (fu4)	2519.91	1204.97	1755.46	0.001

[Table/Fig-4]: Time Vs Mean serum ferritin level.
FU=Follow up SF= Serum Ferritin

In our study, 60% patients were males and mean age group was found to be 8.6±3.9 years.

Rashid Merchant et al., have found 73.3% males as sufferer and in his study, mean affected age group was 15.7±6.8 years (study population of age 6.5 years to 29 years) [18].

In our study 80% patients were on Mean dose of 38 mg/kg.

Reports of Rashid Merchant et al., M. Domenica Cappellini et al., YR Lai et al., suggested mean DFX dose 21.6±6.4 mg/kg and 33mg/kg and 33.6 mg/kg respectively for iron chelation [18-20].

This study shows significant decline in serum ferritin from 3727.02 to 2519.91 ng/ml i.e., 1207.11 ng/ml at end of one year, p-value 9.96×10^{-8} (<.05). The mean difference 1207.11 is >1000 ng/ml indicating that all of them need further chelation therapy in forthcoming years.

M. Domenica Cappellini et al., found median decline in S. ferritin from 2117 to 1124 (p-value <.001) [19]. Ali Taher et al., in Escalator Study found median decline in S. ferritin of 517 ng/ml (p-value

		Serum Ferritin Levels (Time in Interval)																	
		Baseline		3 month				6 month				9 month				12 month			
S. No	Dose (mg/kg)	Mean	SD	Mean	SD	95%CI	p	Mean	SD	95%CI	p	Mean	SD	95%CI	p	Mean	SD	95%CI	p
1	20-25	3370	2729.43	3050	2899.14	1499.6	0.591	3000	2828.43	1534.43	0.5294	2675	2368.81	1765.64	0.204	2465	1887.17	1887.17	0.07
2	25-30	3406.67	1773.28	2965	1781.83	1186.39	0.2417	2430	941.44	1578.44	0.0015	1443.33	347.9	2498.68	0.001	1576.67	87.37	2355.96	0.001
3	30-35	4450	2717.08	3610	2025.41	1843.96	0.099	2895	1844.34	2527.85	0.0021	2091.67	1364.81	3259.1	0.001	2176.67	1391.56	3177.68	0.001
4	35-40	3752.67	1244.29	3539.58	1569.96	806.55	0.477	3302.08	1347.12	993.86	0.102	2807.61	1334.84	1485.66	0.0008	2644.61	1225.62	1625.46	0.001
	Total	3727.02	1405.1	3456.66	1595.01			3177.78	1379.1			2647.31	1335.21			2519.91	1204.97		

[Table/Fig-5]: Effect of different dose of deferasirox on serum ferritin level.

<.001) [16]. Rashid Merchant et al., in year observed mean decline in serum ferritin of 30.2% (p-value < 0.001) over 12-18 months of DFX therapy [18]. YR Lai et al., found median ferritin decline of -756 ng/ml (p-value 0.0397) [20]. Kamrthi et al., found, the decrease in the S. ferritin levels from 4362.5 ng/ml (range 1337.8-17217 ng/ml) to 1869.25 ng/ml (range 634.4-3486.1 ng/ml) during DFX therapy [21].

In this study, 47% cases (n=21) had drug compliance of 80-100% and 53% cases (n=24) had drug compliance of 100%.

In 2.2% (n=1) cases by changing drug brand desired response was obtained, which can be explained by difference in bioequivalence of different brands.

In current study out of 50 patients registered, one patient died due to cardiac haemosiderosis.

LIMITATION

The limitations of present study were that, liver biopsy was not done for estimation of ferritin level due to lack of facilities, patient's number were limited and follow-up was done for one year only.

CONCLUSION

In conclusion we state that, our findings underline the importance of iron chelation therapy and regular monitoring of S. ferritin levels in thalassaemia patients treated with frequent blood transfusion. If S. ferritin level is > 1000 ng/ml then three monthly estimation of serum ferritin should be practiced. Iron chelation therapy, if given concurrently with blood transfusion, decreases the risk of morbidity and mortality due to iron overload in thalassaemia. DFX monotherapy has a good safety profile and effectively chelates total body iron. Our results should serve as a benchmark for using DFX chelation therapy in heavily iron overloaded Indian Thalassaemia major cases.

ACKNOWLEDGEMENTS

Dr. Vikas Goel, Haematologist, Sanjeevni Hospital, for guidance. Mrs. Preeti Singh, Mr. Anant shrivastava, Mr. Heera sahu for their inputs and analysis of statistical data. Mr. Durgadas Madnani, Director of Thalassaemia Society Raipur, for co-operation during the study.

REFERENCES

[1] Jaiswal S, Hishikar R, Maheshwari B, Khandwal O, Sheohare R. Safety of deferasirox as an oral iron chelator in thalassaemic children. Int J Basic Clin Pharmacol. 2016;5:647-50.
[2] Hershko CM, Link GM, Konijn AM, Cabantchik ZI. Iron chelation therapy. Curr Haematol Rep. 2005;4:110-11.
[3] Vichinsky E. Clinical application of deferasirox: Practical patient management. American Journal of Haematology. 2008;83(5):398-402.
[4] Anderson LJ, Wonke B, Prescott E. Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in β-thalassaemia. Lancet. 2002;360:516-20.
[5] Pennell DJ, Berdoukas V, Karagiorga M. Randomized controlled trial of deferiprone or deferoxamine in β-thalassaemia major patients with asymptomatic myocardialsiderosis. Blood. 2006;107:3738-44.
[6] Neufeld EJ. Oral chelators deferasirox and deferiprone for transfusional iron overload in thalassaemia major: new data, new questions. Blood. 2006;107(9):3436-41.
[7] EMEA: Deferiprone summary of product characteristics. 2006. Available at http://www.ferriprox.com.
[8] Jamuar SS, Lai AHM. Safety and efficacy of iron chelation therapy with deferiprone in patients with transfusion-dependent thalassaemia. Therapeutic Advances in Haematology. 2012;3(5):299-307.
[9] Tanner MA, Galanello R, Dessi C, Smith G, Westwood MA, Agus A, et al. A randomized, placebocontrolled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassaemia major using cardiovascular magnetic resonance. Circulation. 2007;115:1876-84.
[10] Vichinsky E, Onyekwere O, Porter J. A randomized comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. Br J Haematol. 2007;136:501–08.
[11] Cappellini MD, Cohen A, Piga A. A phase III study of deferasirox (ICL670), a once daily oral iron chelator, in patients with β-thalassaemia. Blood. 2006;107:3455–62.
[12] Cazzola M, Gattermann N, Greenberg P. ICL670, a once daily iron chelator, is effective and well tolerated in patients with myelodysplastic syndrome (MDS) and iron overload. Haematologica. 2005;90 (Suppl 2):306.
[13] Daar S, Taher A, Pathare A. Deferasirox (Exjade, ICL670) provides 24 hour protection from labile plasma iron (LPI), in iron overloaded β-thalassaemia patients previously chelated with mono- or combination therapy. Haematologica. 2006;91(Suppl 1):31 (abstract).
[14] Cabantchik ZI, Breuer W, Zanninelli G, Cianciulli P. LPI-labile plasma iron in iron overload. Best Pract Res Clin Haematol. 2005;18:277-87.
[15] Vichinsky E, Pakbaz Z, Onyekwere O, Porter J, Swerdlow P, Coates T, et al. Patient reported outcomes of deferasirox (Exjade ICL670) versus deferoxamine in sickle cell disease patients with transfusional haemosiderosis. Substudy of randomized open label phase II trial. Acta Haematol. 2008;119:133-41.
[16] Taher A, Al Jefri A, Elalfy MS, Al Zir K, Daar S, Rofail D, et al. Improved treatment satisfaction and convenience with deferasirox in iron overloaded patients with β thalassaemia results from the ESCALATOR trial. Acta Haematol. 2010;123:220-25.
[17] Kirk P, Roughton M, Porter J, Walker J, Tanner M, Patel J, et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassaemia major. Circulation. 2009;120:1961-68.
[18] Merchant R, Ahmed J, Krishnan P, Jankharia B. Efficacy and safety of deferasirox for reducing total body and cardiac iron in thalassaemia. Indian Pediatrics. 2012;49:281-85.
[19] Domenica Cappellini M, Bejaoui M, Agaoglu L, Canatan D, Capra M, Cohen A, et al. ron chelation with deferasirox in adult and pediatric patients with thalassaemia major. Blood Journal Haematology. 2011;118:884-93.
[20] Lai YR, Liu RR, Li CF, Huang SL, Li Q, Habr D, et al. Efficacy of deferasirox for the treatment of iron overloads in Chinese thalassaemia major patients: Results from a prospective, open-label, multicentre clinical trial. Transfusion Medicine. 2013;23(6):389-96.
[21] Kamrthi U, Kumar B. Study on safety and efficacy of deferasirox in the treatment of thalassaemia in a South indian tertiary care hospital. Indian Journal of Pharmacy Practice. 2015;8(1).

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pharmacology, PT JNM Medical College, Raipur, Chhattisgarh, India.
2. Professor and Head, Department of Pharmacology, PT JNM Medical college, Raipur, Chhattisgarh, India.
3. Professor, Department of Paediatrics, PT JNM Medical College, Raipur, Chhattisgarh, India.
4. Assistant Professor, Department of Pharmacology, PT JNM Medical College, Raipur, Chhattisgarh, India.
5. Associate Professor, Department of Pharmacology, PT JNM Medical College, Raipur, Chhattisgarh, India.
6. Assistant Professor, Department of Pharmacology, PT JNM Medical College, Raipur, Chhattisgarh, India.
7. Associate Professor, Department of Pharmacology, PT JNM Medical College, Raipur, Chhattisgarh, India.
8. Consultant Diabetologist and Non Invasive Cardiologist, Lifeline Hospital, Raipur, Chhattisgarh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shikha Jaiswal,
Assistant Professor, Department of Pharmacology, PT JNM Medical College, Raipur, Chhattisgarh, India.
E-mail: dr.shikhajaiswal @gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Aug 04, 2016**
Date of Peer Review: **Sep 08, 2016**
Date of Acceptance: **Oct 22, 2016**
Date of Publishing: **Feb 01, 2017**