ORIGINAL ARTICLE

EFFICACY AND TOLERABILITY OF ORAL IRON CHELATOR, DEFERASIROX

Awais Tahir, Syed Ibrar Hussain, Huma Saleem Khan, Sumaira Khalil, Syed Zulfiqar Haider, Munir Akmal Lodhi

Fauji Foundation Hospital, Rawalpindi

Background: Thalassemia major is the severe form of β thalassemia characterized by severe anaemia, hepatosplenomegaly and facioskeletal changes due to increased haemolysis of defective red blood cells. In iron overload states, high levels of iron exceed the iron-carrying capacity of transferrin within the plasma, leading to the formation of nontransferrin-bound iron form. These nontransferrin-bound iron forms can be taken up into cells, including liver, heart, and endocrine cells leading to organ damage. To prevent complications associated with hemosiderosis, iron chelation therapy remains one of the main objectives of clinical management of the patients affected by Thalassemia Major. **Methods:** Thirty-seven patients were enrolled using non randomized convenience sampling technique after the written consent from patients. Patients age 2–30 years were enrolled in this study. Serum Ferritin, ALT, Serum Creatinine were checked at the start of the study, 3 months, 6months and then at the end of the study, i.e., at 9 months of the commencement of the study. They were also assessed for other side effects pertaining to oral tolerability of the drug like vomiting, nausea, GI upset, diarrhoea, urinary complaints or any other subjective complaint. **Results:** Of the 37 patients, 20 were male (54.1%) and 17 were female (45.9%). Mean age of the patients was 10.2 years (Min. 3 years, Max 21 years). The average serum Ferritin at baseline was noted as 3440 which increased after a period of 3 months, 6 months and 9 months with average of 3359, 3677 and 4394 respectively. After the period of 9 months largest 95% confidence interval of serum Ferritin levels was observed in the range of 3420.17 to 5368.63. In our study, 17 patients required alternative chelation (46%). These patients needed IV Deferioxamine because of the rising trend of Serum Ferritin after the study. **Conclusion:** From the results of our study, we infer that oral Deferasirox is not an effective iron chelator. If the patients are taking oral deferasirox, their Serum Ferritin should be checked 3 monthlies. The drug is effective only in maintaining Serum Ferritin levels with levels less than 1500ng/ml. Intravenous Deferioxamine still should be preferred over oral iron chelators for effective control of iron overload and its complications.

Keywords: Thalassemia major; Haemolysis; Serum Ferritin; ALT; Serum Creatinine

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INTRODUCTION

Thalassemia is an autosomal recessive hemoglobinopathy, leading to reduced synthesis of globin chains required for haemoglobin synthesis. Pattern of presentation depends upon the degree of impairment of the globin chain synthesis and concomitant presence of other abnormal globin genes.[1] According to WHO, Haemoglobinopathies pose a health in 71 out of 229 countries, and these countries are responsible for 89% of all new births internationally. Amongst 330000 affected neonates 83% have sickle cell disorders while17% have thalassaemia's. Haemoglobin disorders account for about 3.4% of under 5 mortality.[2] Globally, 80–90 million people are estimated to be carriers for β thalassemia. In India, β thalassemia is estimated to be to commonest monogenetic disorder, with estimated carriers, nearly 36 million.[3] Thalassemia patients are dependent on Blood transfusion in order to maintain their haemoglobin levels and also to prevent ineffective erythropoiesis. Iron load contained in a single unit of packed red blood cells is around 200–250 mg.[3] These patients, therefore, accumulate excess iron an approximate rate of 0.5 mg/kg/day. This is further worsened by an increased absorption dietary iron from the gastrointestinal tract. This increased bioavailability of dietary iron is mediated by upregulation of ferroportin and down-regulation of hepcidin.[4] Plasma iron bind with transferring and is transported to cells. Iron overload saturated the transferring capacity and results in non-transferrin bound iron being accumulated. Nontransferrin-bound form of iron has the capability to enter hepatocytes, myocytes and endocrine cells and cause organ damage.[3] Iron chelation therapy is the

main tertiary prevention strategy in patients with Thalassemia Major.

Most of the complications of iron overload are reversible with appropriate Iron chelation therapy.[5,6]Different iron chelating agents available have variable pharmacokinetics, mode of administration, frequency of dosing and iron binding capacity resulting in variable efficacy. There is also variation in organ specificity (hepatic, cardiac) and side effects and safety profile among chelators. Because of variable pharmacokinetics of different drugs, patient compliance, side effects and iron chelation efficacy vary between drugs. Deferoxamine is a naturally occurring iron binding agent produced by *Streptomyces pilosus.* The first ever approved iron chelator was also deferoxamine and is being used over past 40 years.[7] However, it needs parenteral administration because of poor absorption from the intestinal tract.[8] Short half-life of this drug makes slow continuous infusion mandatory for it to be effective. Deferoxamine 25–50 mg/kg is usually administered as a continuous slow subcutaneous infusion lasting between 8–12 hours, 5 days a week to daily. Both intravenous and subcutaneous infusions are time consuming and painful. This results in poor adherence and treatment failure. Deferasirox is the first oral iron chelator approved for use in number of countries. Iron binding ratio of Deferasirox is 2:1 (tridentate chelator). The drug is highly specific for iron, binding only minimally to copper and zinc in the stomach.[9,10] Deferasirox has been reported to be equally effective as deferoxamine in doses of 20–30 mg/kg/day in reducing serum ferritin and liver iron concentration in patients with Thalassemia major.[11] Data also suggests that Deferasirox can also remove cardiac iron.[12] Compliance is also much better with deferasirox in comparison with deferoxamine. Subjective patient satisfaction and convenience is also much high with Deferasirox in comparison with deferoxamine.[13,14] As a larger number of patients have now been exposed to deferasirox doses of >30 mg/kg per day for a prolonged period of time, this study aims to assess the efficacy, safety profile and tolerability of the oral iron chelator, Deferasirox.

MATERIAL AND METHODS

This study was conducted in both paediatric outdoor and indoor departments at Fauji Foundation hospital, Rawalpindi. Thirty-seven patients were enrolled using non randomized convenience sampling technique after the written consent from patients. Patients age 2–30 years were enrolled in this study. Patients with ALT more than 250/L, Serum Creatinine >2 mg/dl were not enrolled in this study. Patients with poor compliance were to be excluded from the study as well.

Serum Ferritin, ALT, Serum Creatinine were checked at the start of the study, 3 months, 6months and then at the end of the study, i.e., at 9 months of the commencement of the study.

Patients were started at 20 mg/kg dose of deferasirox and then dose was escalated to maximum of 40 mg/kg /day based on serum ferritin levels. Patients who were already receiving higher doses were kept at same dose and their serum creatinine, ferritin and LFTs were done at the first contact. These patients were kept on 2 weekly follow up visits in OPD. They were also assessed for other side effects pertaining to oral tolerability of the drug like vomiting, nausea, GI upset, diarrhoea, urinary complaints or any other subjective complaint. The above-mentioned laboratory parameters were rechecked at 3 months, 6 months and then at the end of the study, i.e., at 9 months. Any patient with side effects like GI upset, anaphylaxis, deranged RFTs and ALT levels, the dose was tapered. The same strategy shall be adopted with the other side effects of oral tolerability and subjective complaints. The data was analysed on computer programme SPSS version 20.

RESULTS

Of the 37 patients, 20 were male (54.1%) and 17 were female (45.9%). Mean age of the patients was 10.2years (Min. 3 years, Max 21 years). Our patients showed good oral tolerability to the drug (Table-1). Of 37 patients, only one patient complained of having nausea and vomiting (2.7%), three patients complained of abdominal pain and diarrhoea (8.1%), only one patient complained of nonspecific rash (2.7%) which resolved spontaneously without any remedy. 10 patients had urinary problems (27%). Nine patients had dysuria (24.3%.) while one patient had frequency, urgency (2.7%). All of these patients only had minor symptoms which were relieved with symptomatic management. None of the patients required dose tapering/omission of drug therapy.

From table-2 it can be seen that, the average serum Ferritin at baseline was noted as 3440 which increased after a period of 3 months, 6 months and 9 months with average of 3359, 3677 and 4394 respectively. After the period of 9 months largest 95% confidence interval of serum Ferritin levels was observed in the range of 3420.17 to 5368.63. Serum Ferritin increased highly from the baseline to end of the study period

except the period of after 3 months in which serum ferritin decreased. Hence, it can be concluded that the most suitable interval for the serum ferritin is 2546.61 to 4170.88 with average 3359 and standard error 399.625. The trend of estimated means of Serum Ferritin is depicted in figure-1.

We can observe from Table 3, that all multivariate tests show a significant result, meaning that the intervention induced in the participant had a significant effect over time. Table-4 reveals about the assumption of sphericity. The significance value of 0.109 indicates that, we are unable to reject the null hypothesis that the variances of the differences between Serum Ferritin levels are same. From Table-5 of Within-Subjects Effects we are able to discover the significant results (F (2.784, 94.641) = 4.017, p<0.05).

We can report that as our data meets the assumption of sphericity, when using an ANOVA with repeated measures with a Huynh-Feldt correction, the mean scores for Serum Ferritin levels were statistically significant (F (2.784, 94.641) = 4.017, p<0.05). We can, therefore, conclude that there was a significant difference (rise) in all time periods of Serum Ferritin. The suitable interval of serum ferritin was noted in the range of 1000–1500. In this interval the proportion of patients reduced gradually from baseline to end of the study period. At baseline the proportion of patient was 24.3% which reduced to 21.6% after 3 months of study, after 6 months this proportion reduced to 13.5% and after 9 months it was 8.1%. The trend of estimated means of Serum Ferritin is depicted in figure-1.

From Table-2 the average serum ALT at baseline was noted as 75.86 (mg/dl) which increased after a period of 3 months, 6 months and 9 months with average rate of 76.657(mg/dl), 91.029(mg/dl) and 93.171(mg/dl) respectively. The smallest variation in serum ALT was noted in the period of after 3 months and 95% confidence interval obtained for this sample was observed in the range of 60.114(mg/dl) to 93.201(mg/dl). Results of ANOVA with repeated measures on ALT levels (Table-6) with a Huynh-Feldt correction, the mean scores for ALT levels were statistically significant (F (2.458, 83.555) = 1.931, p >0.05). We can, therefore, conclude that there was no significant difference observed in the periods of ALT.

From Table-2 the average Serum Creatinine at baseline was noted as 73.143 (mg/dl) which reduced with the passage of time and after an intervention period of 3 months, 6 months and 9 months average rate was 74.314 (mg/dl), 66.143 (mg/dl) and 69.743 (mg/dl) respectively. The maximum variation in Serum Creatinine was observed in the period of after 6 months and 95% confidence interval obtained for this sample was in the range of 61.481(mg/dl) to 70.805 (mg/dl). Due to lowest average Serum Creatinine of 69.743 (mg/dl) and small standard error the confidence interval for 5% level of confidence was 66.712(mg/dl) to 72.774(mg/dl). Results of ANOVA with repeated measures on Serum Creatinine levels (Table 7) with a Greenhouse-Geisser correction, the mean scores for Serum Creatinine levels were statistically significant (F (2.175, 73.938) = 4.504, p<0.05). Therefore, it can be concluded that a significant difference was observed in all time periods of Serum Creatinine levels.

In our study, 17 patients required alternative chelation (46%). These patients needed IV Deferioxamine because of the rising trend of Serum Ferritin after the study.

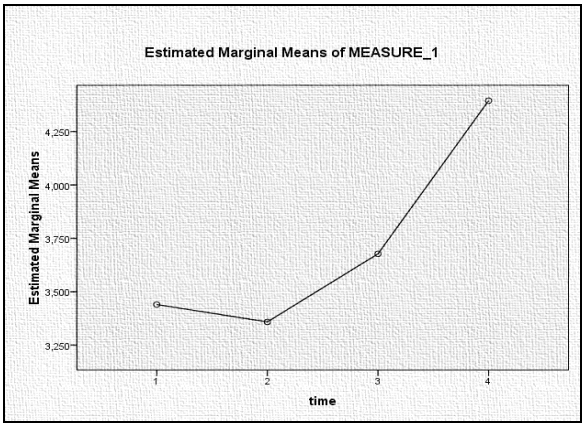

Figure-1: Profile plot of Serum Ferritin

Table-1: Frequency of Subjective complaints

Count		Frequency	Percentage
Nausea	Yes	1	2.70
	No	36	97.30
vomiting	Yes	1	2.70
	No	36	97.30
Abdominal pain	Yes	3	8.11
	No	34	91.89
Diarrhoea	Yes	1	2.70
	No	36	97.30
Rash	Yes	1	2.70
	No	36	97.30
Urine Problems	No	27	72.98
	Dysuria	9	24.32
	Frequency	1	2.70
Alternative chelation	Nil	20	54.05
	Deferioxamine	17	45.95

Table-2: Descriptive Statistics of Serum Ferritin, Serum ALT, Serum Creatinine

		Mean	Std. Error	Lower Bound	Upper Bound
Serum Ferritin	Baseline	3440	425.316	2575.77	4304.46
	After 3 Months	3359	399.625	2546.61	4170.88
	After 6 Months	3677	436.181	2790.92	4563.77
	After 9 Months	4394	479.385	3420.17	5368.63
Serum ALT	Baseline	75.857	9.320	56.916	94.798
	After 3 Months	76.657	8.141	60.114	93.201
	After 6 Months	91.029	10.802	69.076	112.981
	After 9 Months	93.171	9.057	74.766	111.577
Serum Creatinine	Baseline	73.143	1.770	69.547	76.739
	After 3 Months	74.314	1.531	71.203	77.426
	After 6 Months	66.143	2.294	61.481	70.805
	After 9 Months	69.743	1.491	66.712	72.774

Table-3: Multivariate Test for Serum Ferritin

Multivariate Tests[b]						
Effect		**Value**	**F**	**Hypothesis df**	**Error df**	**Sig.**
Time	Pillai's Trace	.343	5.576[a]	3.000	32.000	.003
	Wilks' Lambda	.657	5.576[a]	3.000	32.000	.003
	Hotelling's Trace	.523	5.576[a]	3.000	32.000	.003
	Roy's Largest Root	.523	5.576[a]	3.000	32.000	.003

Table-4: Mauchly's Test of Sphericityfor Serum Ferritin

Mauchly's Test of Sphericity[b]							
Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.760	8.993	5	.109	.853	.928	.333

Table-5: Tests of Within-Subjects Effects for Serum Ferritin

Measure: MEASURE_1						
Source		**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Time	Sphericity Assumed	2.329E7	3	7763649.112	4.017	.010
	Greenhouse-Geisser	2.329E7	2.558	9105996.817	4.017	.014
	Huynh-Feldt	2.329E7	2.784	8367303.635	4.017	.011
	Lower-bound	2.329E7	1.000	2.329E7	4.017	.053
Error(time)	Sphericity Assumed	1.971E8	102	1932713.901		
	Greenhouse-Geisser	1.971E8	86.964	2266883.314		
	Huynh-Feldt	1.971E8	94.641	2082990.076		
	Lower-bound	1.971E8	34.000	5798141.703		

Table-6: Tests of Within-Subjects Effects for Serum ALT

Measure: MEASURE_1						
Source		**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
ALT	Sphericity Assumed	8876.421	3	2958.807	1.931	.129
	Greenhouse-Geisser	8876.421	2.284	3886.241	1.931	.146
	Huynh-Feldt	8876.421	2.458	3611.958	1.931	.142
	Lower-bound	8876.421	1.000	8876.421	1.931	.174
Error (ALT)	Sphericity Assumed	156268.329	102	1532.042		
	Greenhouse-Geisser	156268.329	77.658	2012.259		
	Huynh-Feldt	156268.329	83.555	1870.238		
	Lower-bound	156268.329	34.000	4596.127		

Table-7: Tests of Within-Subjects Effects for Serum Creatinine

Measure: MEASURE_1						
Source		**Type III Sum of Squares**	**Df**	**Mean Square**	**F**	**Sig.**
Time	Sphericity Assumed	1422.421	3	474.140	4.504	.005
	Greenhouse-Geisser	1422.421	2.175	654.092	4.504	.012
	Huynh-Feldt	1422.421	2.329	610.813	4.504	.010
	Lower-bound	1422.421	1.000	1422.421	4.504	.041
Error(time)	Sphericity Assumed	10737.329	102	105.268		
	Greenhouse-Geisser	10737.329	73.938	145.220		
	Huynh-Feldt	10737.329	79.177	135.612		
	Lower-bound	10737.329	34.000	315.804		

DISCUSSION

Thalassemia major is a growing health and economic problem in our region, with the modified guidelines for transfusion and iron chelation that improved survival of these patients. Iron overload and hemosiderosis are the leading causes of morbidity and mortality, and therefore effective iron chelation remains the target of research that aims to reduce serum ferritin levels to between 500 and 1500 μg/L, which equates transfusional iron burden and maintains acceptable hepatic, cardiac hemosiderosis with negligible side effects[15]. We aimed at assessing the efficacy and safety profile of oral iron chelator, Deferasirox. In our study, we found the drug to be ineffective in controlling Serum Ferritin especially in patients with higher Ferritin levels (>1500). A constant rise in mean Serum ferritin was observed at all three time points of estimation during study despite of good compliance, dose escalation and adequate treatment duration. Invariably, statistically insignificant results were also found in couple of studies. Muzamil Shabana Ejaz conducted an efficacy and drug safety assessment trial[16], they found a slight decrease in serum ferritin levels in patients after 6 months use of Deferasirox but the results were statistically insignificant (p=0.929). Furthermore, they also inferred that there was no significant correlation between serum ferritin levels and prolonged duration of deferasirox treatment. The duration of chelation therapy had insignificant impact on serum ferritin in patients who received chelation for less than 36 months, 56.9% had value above 2500 ng/ml, between 37–60 months of chelation therapy 50% and for more than 60 months 100% had value above 2500 ng/ml. In our study, the mean scores for Serum Ferritin levels had shown a statistically significant rise (F (2.784, 94.641) = 4.017, p<0.05). We conducted this study for a span of 9 months and had to put patients on IV chelation with elevated serum ferritin towards the end of the study since the oral drug was ineffective in lowering serum ferritin.

In another study by AcicekA, Koc A[17] efficacy of deferasirox was assessed in children with B-Thalassemia. This study was conducted for a period of 3 years. Mean (median) serum ferritin level showed a gradual riseduring the first 22 months of treatment, from 3.161±1.683 ng/mL (2.760 ng/mL) to 3.679±1.997 ng/mL (3.071 ng/mL; p<0.001) followed by a gradual decline to 2.907±1.436 ng/mL (2.670 ng/mL; p=0.023) at 36 months. Mean dose of deferasirox was 21.2±8.6, 23.7±8.1, 30.7±8.2 and 32.4±7.6 mg/kg per day at 0, 12, 24 and 36 months, respectively. The serum ferritin levels increased during the first 2 years of the study period which concurs with our results. However, Aycicek A *et al* found a slight decrease in serum ferritin levels during the third year of therapy though it was still insignificant, i.e., 2.907±1.436 ng/mL (2.670 ng/mL; p=0.023) at 36 months.

Almost similar statistically insignificant results were found with Deferasirox monotherapy by Maggio A etal[18]and Wood JC *et al.*[19]

Hossein Karami *et al*[20] studied the efficacy of combination oral chelation therapy using both Deferasirox and Deferiprone in B-Thalassemia patients with iron overload. The mean doses of DFP and DFX were 53.9±22.2 and 29.3±6.8 mg/kg/day, respectively. The duration of treatment was 11.5±4.6 months. Serum ferritin in this study was 2800±1900 at the start of treatment and 3400±1600 ng/mL after treatment respectively (p<0.6). Again the results of this study cocur with the findings of our study, even the combined oral chelation failed to lower the serum ferritin levels. However, the author further studied the effects of combined oral chelation therapy on Liver and Cardiac iron overload and he found promising results.

A similar trial by Elalfy MS *et al*[21] assessed efficacy and safety of a combination of two oral chelators deferasirox/deferiprone with combination of deferoxamine/deferiprone in beta thalassemia major patients with iron overload. A noteworthy dissimilarity between slopes of the two groups regarding cardiac T2* (p=0.001 with more improvement in DFP/DFX patients) was found. However, the slopes of Serum ferritin and Liver iron concentration (p=0.218 and 0.340) were almost alike. On the contrary, there are a number of studies which found deferasirox as an effective drug in reducing Serum ferritin. The famous THETIS study[22], EXJADE trial[23], CONIFER study[24] and ESCALATOR study[25] not only established the efficacy of Deferasirox, but also lamented the safety profile of this drug negating many studies and case reports questioning drug safety[26–28] and efficacy. Our study results did not show any significant side effects. Patients had good oral tolerability and compliance. There wasn't a significant effect of drug on Serum ALT and Serum Creatinine during the study. However, 10 (27%) patients had urinary symptoms, predominantly dysuria, which got better with symptomatic treatment.

CONCLUSION

From the results of our study, we infer that oral Deferasirox is not an effective iron chelator. If the patients are taking oral deferasirox, their Serum Ferritin should be checked 3 monthlies. The drug is effective only in maintaining Serum Ferritin levels with levels less than 1500ng/ml. Intravenous Deferioxamine still should be preferred over oral iron chelators for effective control of iron overload and its complications.

AUTHORS' CONTRIBUTION

AT: Conceptualization, data search, data analysis, interpretation, write-up. SIH: Data collection, literature

search. HSK: Literature search, interpretation. SK: Write-up, literature search. SZH: literature search. MAL: Study design, conceptualization, proof reading.

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Address for Correspondence:

Awais Tahir, Children department, Fauji foundation Hospital, Rawalpindi-Pakistan
Email: doctorsbin@yahoo.com