VOLUME-6 | ISSUE-2 | FEBRUARY-2017 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 78.46

Evaluation of efficacy and safety of Deferasirox in children of Thalassemia Major

Paediatrics

KEYWORDS: Deferasirox, Thalassemia major, Ferritin, Iron chelation.

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ABSTRACT

Introduction Repeated blood transfusions and iron chelation therapy improves survival rate in thalassemia major. The novel oral iron chelator deferasirox have been approved by Food and Drug Administration (FDA). **Objective** The present study aims to evaluate the efficacy of deferasirox in thalassemia major patients. **Material and Method** Thirty patients of thalassemia major fulfilling the inclusion criteria formed case group. The patients were given treatment in the form of tablet deferasirox 20 mg/kg/day OD for one month and in the absence of any serious side effects the dose was increased to 30 mg/kg/day OD over 1 year period. The patients were followed up monthly and investigated as per protocol. The records of blood transfusion and level of serum ferritin and other investigations were maintained. **Results** The decrease in serum ferritin at 6, 9, and 12 months of study was statistically significant ($p<0.001$). **Conclusion** Deferasirox is an effective drug which decreases serum ferritin significantly and a good safety profile in thalassemia.

Introduction

Blood transfusion at regular interval from an early age is an essential therapy for thalassemia major patients. Deferoxamine has been the established chelation therapy for iron-overload for more than 40 years. Deferiprone, oral iron chelator is available as second-line therapy in thalassemia patients where deferoxamine is contraindicated. Despite, the availability of these chelating agents, mortality due to iron overload and resulting organ failure is high.

Deferasirox is an oral iron chelating agent and approved by Food and Drug Administration.[1] Its molecular formula is $C_{21}H_{15}N_3O_4$ and its molecular weight is 373.4. It represents a new class of tridentate iron chelators with a high specificity for iron.[2] Deferasirox acts by mobilizing tissue iron by forming soluble, stable complexes that are then excreted in faeces. Iron is chelated, both from the reticuloendothelial cells as well as various parenchymal tissues. The chelated iron is cleared by the liver and excreted through the bile. It also has the ability to prevent myocardial cell iron uptake, remove iron directly from myocardial cells.[3] The efficacy and safety of deferasirox in various transfusion dependent anemia patients was established during Phase II/III trials in over 1000 patients.[4-8]

Our study was an effort to evaluate the efficacy and safety of deferasirox in a small group of thalassemia major patients.

Material and methods

Sample

The study was done over a period of one year at thalassemia day care centre in the department of Pediatrics in collaboration with Biochemistry and Radiology department at Pt. B.D. Sharma University of Health Sciences, Rohtak, Haryana. Thirty patients of thalassemia major attending the thalassemia day care centre who fulfilled the inclusion criteria were selected as cases.

Inclusion criteria: Patients with thalassemia major

1. age between 3 years to 18 years
2. who gave consent for the study
3. who can afford the drug
4. who were on at least 2 years of regular blood transfusion,
5. who had serum ferritin > 1000 ng/ml on at least two occasions, at least two weeks apart, before starting therapy and patient
6. who were taking Deferiprone as iron chelator and having persistently high serum ferritin i.e. >1000 ng/ml

Exclusion criteria: Patients

1. who were non-compliant, potentially unreliable, not co-operative, could not be followed up,
2. who were terminally ill
3. serum creatinine above the upper limit of normal,
4. AST or ALT > 500 IU/ml during screening,
5. evidence of active hepatitis B or C or HIV positive, severe anemia or bone marrow suppression,
6. ocular or auditory toxicity and
7. systemic diseases (cardiovascular, renal, hepatic etc)
8. who did not give consent.

The serum ferritin 6 months preceding the study of the cases was taken, hence, these cases also served as controls for themselves.

A written informed consent from the parents/guardian of the patients was taken to ensure compliance and regular follow up.

Measures:

A semi-structured clinical interview was designed to collect sociodemographic variables and relevant medical history including age at presentation, age at diagnosis, consanguinity of parents, frequency of blood transfusion, serum ferritin, HIV, HBsAg and HCV status. Complete physical examination was also done at the time of enrollment.

Following investigations were done at start of therapy : Complete hemogram including absolute platelet count, Liver function tests, Renal function tests, Serum ferritin, ECG, M-mode Echocardiography, HIV, HBs Ag, HCV Status, Slit lamp examination and dilated fundoscopy, Audiometric examination.

During the study, the patients were followed up monthly and history of any specific symptoms were asked. Routine physical examination and complete hemogram with absolute platelet count were done at every follow up.

Serum ferritin was done at monthly interval which was used as primary outcome measure. It was estimated by chemiluminiscent method done by ADVIA centaur CP ferritin assay. Liver function tests, renal function tests were done at one month and then after every three months interval.

ECG, Echocardiography, slit lamp examination, dilated fundoscopy, audiometric examination, HIV, HBs antigen and HCV were done once at enrollment and once at the end of the study.

Statistical analysis

The data collected during the study was entered in the Microsoft excel format and was analysed using SPSS.17 version Microsoft software. Student's paired t-test was used for comparing before and after the start of therapy, serum ferritin levels. The p values were two tailed and probability level of significant difference was set at <0.05.Results obtained were classified into different categories depending upon the percentage change in serum ferritin. Responses were categorized as mild, moderate and marked. For changes in serum ferritin, change as 0-10%, 10-20%, >20% respectively formed the basis for categorization.

Results

Table 1 shows baseline epidemiological profile of cases. The mean ageSD of the patients at the time of enrollment in study was 10.93.81 years. There were 22 (73%) male cases and 8 (27%) female cases. None of the patient was HIV, HBsAg and HCV positive at enrollment and at the end of study. The mean duration of chelation therapy was 6.453.3 years. Deferasirox was given for the period of one year at an average dose of 29.110.21 mg/kg/day single oral dose.

Table 1
Baseline epidemiological profile of the cases at enrollment

	MeanSD	Range
Age at enrollment for study (years)	10.93.81	5.5-18
Weight (kg)	29.4710.21	14-52
Height (cm)	129.0514.36	108-155
Mean age at diagnosis (months)	10.64.74	5-22
Duration of chelation therapy (years)	6.453.3	2-14
No. of patients with splenectomy	3	
Spleen size at enrollment (cm) n=27*	3.70.89	2.5-6.0
Liver size at enrollment (cm)	3.470.76	2.0-5
Dose of deferasirox used (mg/kg/day)	29.110.21	28.35-29.17

(*3 patients already splenectomized)

During one year of study patients received mean iron over load of 3511.64622.24 mg from 26.44.68 packs of PCV with mean Hb of 8.30.58 g%.

Table 2 shows variation in serum ferritin levels during the study period. Over one year of study period mean serum ferritin levels decreased from 1st month onwards and found to be statistically significant after 6th months.

Table 2
Variation in serum ferritin levels (ng/dl)

Time	Serum ferritin (ng/dl)	p value compared with control	
	MeanSD	Range	
In prior 6 months (controls)	5736.72088.69	2317.3-11675.4	
At enrollment	5782.492081	2591.3-11945.3	>0.05
At 1 month	5829.822146.93	2563.6-11663.5	>0.05
At 3 months	5654.382137.77	2481.7-11521.6	>0.05
At 6 months	5435.312125.43	2070.3-10973	<0.001
At 9 months	5208.392065.07	1941.1-10561.4	<0.001
At 12 months	4982.362020.81	1672.6-9913.7	<0.001

Table 3 shows variation in biochemical parameters of the cases during the study period. It was found that total leukocyte count, platelets count, and other biochemical parameters did not show any significant change at the end of the study.

Table 3 Variation in biochemical parameters of the cases

Parameters	Mean ± SD	P value			
	6 months prior	At 3 months	At 6 months	At 12 months	
TLC (1000/mm3)	7.28±1.79	8.22±1.52	6.78±2.23	7.95±1.80	>0.05
APC (lakh/mm3)	2.17±0.56	2.16±0.47	2.25±0.53	2.03±0.39	>0.05
AST (U/L)	83.07±34.32	85.50±34.92	87.50±40.31	80.57±35.80	>0.05
ALT (U/L)	90.70±34.32	87.40±35.23	90.07±39.77	87.10±32.40	>0.05
S. Alk PO4 (U/L)	264.10±70.68	271.53±69.52	273.33±69.21	265.67±68.52	>0.05
B.Urea (mg/dl)	29.13±4.76	31.30±4.18	31.57±5.10	30.5±6.01	>0.05
S.Creat (mg/dl)	0.89±0.18	0.91±0.20	0.89±0.19	0.83±0.11	>0.05

Four (13%) patients developed GIT related side effects [2 (50%) nausea, 1(25%) abdominal pain, 1 (25%) diarrhea] at start of therapy, improved within two three days without discontinuation of therapy. One patient (3%) developed rash at 3rd month of therapy, improved without discontinuation of therapy. Two patients (7%) developed transient thrombocytopenia at 6th and 9th months of therapy settled after fifteen days of discontinuation of therapy.

Two (7%) patients having transient rise in serum creatinine, which improved after dose reduction to20mg/kg/day from 30mg/kg/day for a period of one month.
None of the cases showed ophthalmic and auditory side effects.

Discussion

The present study was done to access the efficacy and safety of deferasirox in patients who were previously on other iron chelator therapy having considerably high iron overload despite the previous chelation therapy. The average dose of deferasirox used in our study 29.110.21 mg/kg/day as a single oral dose. Piga et al found that a daily dose of deferasirox 20mg/kg/day was as effective as desferrioxamine 40mg/kg/day for removing excess iron.[4] Nisbet et al also concluded that deferasirox 20-30 mg/kg/day offered the most effective chelation combined with reasonable tolerability.[9]

This prospective study suggests that deferasirox is effective in reduction or maintenance of iron overburden achieved by the patients of thassemia major. The reduction in serum ferritin levels started from 1st month onwards and statistically significant at 6 month onwards (p<0.001). These findings are in line with the previous studies.[10] Taher et al in a prospective, open label, 1 year escalator study found that after 1 year's deferasirox treatment, the intent to treat population experienced a significant treatment success rate of 57% (p=0.016). Changes in serum ferritin appeared to parallel dose increases at around 24 weeks. Most patients (78.1%) underwent dose increasing above 20mg/kg/d, primarily to 30mg/kg/day.[11] Cappallini et al also reported a significant reduction in median Serum ferritin levels (p<0.0001). A dose of 30mg/kg/day deferasirox produced the largest reduction in serum ferritin as compared to baseline.[12] List et al conducted a phase II, open label, efficacy and safety of deferasirox and gave 20-40 mg/kg/day of deferasirox over a period of 1 year + extension phase. The decrease in

VOLUME-6 | ISSUE-2 | FEBRUARY-2017 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 78.46

serum ferritin level was found statistically significant.[13] Thus, present data and previous findings highlight the importance of dose adjustments of deferasirox to ensure patients achieve their therapeutic goal of reduction in iron overload.

Cardiac function

In our study, M mode echocardiography is done at enrollment and at the end of study. All the parameters showed statistically non significant difference when compared to the baseline. Taher et al reported statistically significant increase in mean left ventricular ejection fraction in the study group over the course of the study, from 65.1 (7.0SD) at baseline to 66.86.7 at week 52 (p=0.0002). Possibly, larger duration of study on larger number of patients could yield a significant data regarding cardiac function.[11] Pannell et al reported that deferasirox treatment at a mean dose of 32.6 mg/kg/day significantly improved on T2* from a geometric mean of 11.2 at baseline to 12.9 ms after one year. It was also found that left ventricular ejection fraction was maintained at 67% which supports the finding of our study.[14]

Safety

There was no statistically significant difference observed in total leucocyte counts over the study period. This suggests that deferasirox did not cause myelosuppression.

The variation in absolute platelet counts was also not found statistically significant. Two patients showed a transient decline in platelet counts but improved on temporarily stoppage of deferasirox for 15 days. Resumption of treatment did not cause thrombocytopenia suggesting that transient thrombocytopenia may be related to disease process itself and not be related as drug side effect.There was no statistically significant difference found in variation of serum creatinine over study period. Two patients showed rise in serum creatinine during deferasirox therapy – one at 3 month and second at 6 month of study. In these patients, the dose of deferasirox decreased to 20mg/kg/day from 30mg/kg/day for a period of one month. Level of serum creatinine became normal within one month with dose reduction. These findings suggest that deferasirox does not alter renal functions significantly over one year of study and can be maintained by reduction of doses. At every follow up blood urea levels were found within the physiological range for the age and sex. Four (13%) patients developed GIT related side effects [2 (50%) nausea, 1(25%) abdominal pain, 1 (25%) diarrhea] at start of therapy, settled within two three days without discontinuation of therapy. One patient (3%) developed rash at 3rd month of therapy, settled without discontinuation of therapy. Cappellini et al conducted a phase III study of deferasirox and reported most common adverse effects - rash, gastrointestinal disturbances and mild non progressive increase in serum creatinine. No agranulocytosis, arthropathy, or growth failure was associated with deferasirox.[6] It was also found that deferasirox was generally well tolerated, with the frequency of investigator reported adverse effects decreasing over long term treatment. There were no changes in liver or renal function that differed significantly from the one year core trials, and there was no evidence of progressive liver / renal dysfunction.[15] List et al conducted a phase II, open label study and concluded that the most common adverse effects were diarrhea, rash, and nausea. Of 147 patients with normal baseline serum creatinine, 18% increased on at least two occasions. 5 and 13% of patients experienced new onset cases of thrombocytopenia and neutropenia, respectively, none suspected related to deferasirox.[13] Vichinsky et al found that adverse effects were mostly mild, transient nausea, vomiting, diarrhea, abdominal pain and skin rash. There was mild non progressive increase in serum creatinine and reversible elevation in liver function tests.[16] Taher et al concluded that deferasirox related adverse effects were mostly mild to moderate and resolved without discontinuing treatment. Most adverse effects resolve spontaneously.[11] Galanello et al reported no serious adverse events related to deferasirox. One withdrew due to skin rash. Five patients briefly interrupted treatment due to elevated transaminases with no recurrences when treatment resumed.[5] Thus, findings of present study are in line with previous studies findings highlighting a good safety profile of deferasirox.

Conclusion

Though the study was done using sound methodology, there were certain limitations.A small sample-size and a single-cited study limits the genelizability of the results. As this was open label study, lack of blinding is also a limitation. A placebo control group could have increased the reliability of the results. Serum ferritin concentration is a convenient, non expensive measure of assessing total body iron but is poor predictor of cardiac iron status.[17,18] In the present study, echocardiography was done to assess cardiac changes. Cardiovascular magnetic resonance (CMR) could have increased the reliability of assessing myocardial iron load.[19] Based on our results and previous study literature, it is indicated that deferasirox decreases serum ferritin significantly after 6 months of treatment at an average dose of 29.110.21 mg/kg/day. Deferasirox did not cause any serious side effects in patients. Finally we can conclude that deferasirox is an effective drug which decreases serum ferritin significantly without any serious side effects. Further multi-central and meta-analysis studies should be considered to establish the efficacy of this drug in large group of patients.

Conflict of interest

None

Funding of study

None

Acknowledgements

None

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