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Study to Assess Safety and Efficacy of Deferasirox as an Iron Chelator in Children with B-Thalassemia Major

[1]Shweta Gupta, [2]Parag Mahankar and [3]Ramdas Dahiphale

[1]Department of Pediatrics, Naraina Medical College and Research Centre, Gangaganj Panki, Kanpur, Uttar Pradesh, India

[2,3]Department of Pediatrics, Bharati Vidyapeeth Medical College and Hospital, Pune, Maharashtra, India

ABSTRACT

In children with B-thalassemia, survival comes at the cost of repeated transfusions. The treatment for iron overload is an early and effective chelation. The approved iron chelators in the present day scenario are only three as desferrioxamine, deferiprone and deferasirox. Present study was aimed to study safety and efficacy of Deferasirox as an iron chelator in children with B-thalassemia major. Present study was single-center, prospective Interventional study conducted in children of age 2-18 years, having Serum Ferritin level >1000 ng mL, already on Deferasirox therapy, whose medical records are available, Deferasirox was started with initial dose of 30 mg kg orally once daily doses calculated to the nearest whole tablet (500 mg).The dose was increased to 35 mg kg day if serum ferritin remained unchanged or increased 3 month after Deferasirox therapy. The maximum dose is 40 mg kg day. The total number of children in this study was 30. There were 15 (50%) girls and the boys were 15 (50%) of the total sample population. The mean age of studied population was 8.29±4.883 years, including patients of 2-10 years (20) and 11-18 years (10). Hemoglobin at diagnosis(g/dL) was <7 in majority of cases (93.3%). Majority of the patients (40%) were diagnosed with B thalassemia major between the age of 6 and 12 months. A significant decrease in serum ferritin levels was observed in all age groups at the end of 1 year of treatment with Deferasirox. (p-value is 0.018). Only two patients showed adverse drug reactions (ADRs) out of 30 patients. Most common ADRs observed were Rash (n = 1) and nose bleeding (n = 1). A significant decrease in the mean serum ferritin levels was observed with deferasirox treatment. Deferasirox is relatively well tolerated among these patients.

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Key Words
Serum ferritin levels, deferasirox, B-thalassemia, chelation

Corresponding Author
Ramdas Dahiphale,
Department of Pediatrics, Bharati vidyapeeth Medical College and Hospital, Pune, Maharashtra, India
dr_ramdas@yahoo.com

Author Designation
[1]Assistant Professor
[2,3]Associate Professor

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INTRODUCTION

The B-thalassemia is an autosomal recessive genetic disease, caused mainly by point mutations within and near the B globin gene. The geographical distribution of these molecular defects is not uniform, because each ethnic population have common and rare alterations different from those of another population[1,2]. In our country the existence of thalassemia gene is said to be between 2.7-10.4%[3]. It is very high in certain communities like Punjabis, Sindhis, Gujrati's, Persians and in certain states like Delhi, Punjab, Haryana, Himachal Pradesh, Jammu and Kashmir, Maharashtra and Gujrat[3].

In such children, survival comes at the cost of repeated transfusions. The repeated transfusion coupled with enhanced iron absorption results invariably in an iron overload state, which is the cause of morbidity and mortality in children with Thalassemia. The treatment for iron overload is an early and effective chelation. Thus, our hope of effective management lies in the combination of transfusion and chelation till bone marrow transplant can become a reality for the majority.

The approved iron chelators in the present day scenario are only three as desferrioxamine, deferiprone and deferasirox[4,5]. Desferrioxime is a hexadentate compound, which binds intracellular and extracellular ion from the labile ion pool and complexes like ferrioxime are excreted both in urine (60%) and stool (40%). Chelation occurs in 1:1 molar ratio so that 1 gm of desferal can theoretically bind 85 gm of iron[4]. Present study was aimed to study safety and efficacy of Deferasirox as an iron chelator in children with B-thalassemia major.

MATERIALS AND METHODS

Present study was single-center, Prospective Interventional study conducted in department of Paediatrics, at Bharati Hospital and Research center, Pune, India. Study duration was of 2 years (1st-30th September-August 2016-2018). Study approval was obtained from institutional ethical committee.

Inclusion criteria: Children of age 2-18 years, having Serum Ferritin level >1000 ng mL, already on Deferasirox therapy, whose medical records are available, parents willing to participate in present study

Exclusion criteria:

- HIV and Hepatitis B infected children
- Creatinine clearance <60 mL min
- Hepatic impairment or renal failure

Study was explained to parents in local language and written consent was taken for participation and study. Thirty children were recruited as per the inclusion criteria. Baseline CBC, SGPT, SGOT, Bilirubin, Serum creatinine, BUN were done before starting Deferasirox. Deferasirox was started with initial dose of 30 mg kg orally once daily; doses calculated to the nearest whole tablet (500 mg).The dose was increased to 35 mg kg day if serum ferritin remained unchanged or increased 3 month after Deferasirox therapy. The maximum dose is 40 mg kg day.

Child was receive Red blood cell concentrate to maintain Hemoglobin level of 10 gm%. Adherence was checked by counting the tablets in the box and also by asking for missed doses in last 1 week. Clinical adverse effects (GI upset, skin rash) will be evaluated monthly. Laboratory adverse effects: liver enzymes (SGPT, SGOT), Serum Creatinine and hemogram were done every 3 monthly interval. Serum ferritin was done every 3 monthly using CMIA method (Abbott ARCHITECT i1000SR)

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. p-value less than 0.5 was considered as statistically significant.

RESULTS

The total number of children in this study was 30. There were 15 (50%) girls and the boys were 15 (50%) of the total sample population. The mean age of studied population was 8.29±4.883 years, including patients of 2-10 years (20) and 11-18 years (10). Hemoglobin at diagnosis (g dL) was <7 in majority of cases (93.3%). Majority of the patients (40%) were diagnosed with B thalassemia major between the age of 6 and 12 months. A significant decrease in serum ferritin levels was observed in all age groups at the end of 1 year of treatment with Deferasirox. (p-value is

Table 1: General characteristics

	No. of patients	Percentage
Age groups (in years)		
2-10	20	66.7
11-18	10	33.3
Mean age (Mean±SD)	8.294±4.883	
Gender		
Male	15	50
Female	15	50
Hemoglobin at diagnosis (g dL)		
≤7	28	93.3
7-10	2	6.6

Table 2: Age at diagnosis

Age at diagnosis	Gender		
	Female	Male	Total
≤6 months	0 (0%)	8 (33.3%)	8 (26.7%)
7-12 months	8 (53.3%)	4 (26.7%)	12 (40%)
≥1-3 years	4 (26.7%)	2 (13.3%)	6 (20%)
>3-5 years	2 (13.3%)	0 (0%)	2 (6.7%)
> 5 years	1(6.7%)	1 (6.7%)	2 (6.7%)
Total	15	15	30

Table 3: Serum ferritin distribution

Ferritin (ng mL)	At Enrollment (n = 11)	1st Follow up (n = 30)	2nd Follow up (n = 29)	3rd Follow up (n = 29)	4th Follow up (n =28)	5th Follow up (n = 28)
<1000	3 (27.3%)	Nil	Nil	Nil	Nil	Nil
1000-2000	4 (36.4)	7 (23.3%)	7 (23.3%)	3 (10.3%)	2 (7.14%)	6 (21.4%)
>2000-5000	4 (36.4)	10 (33.3%)	11 (36.6%)	14 (48.2%)	15 (53.5%)	17 (70.8%)
>5000-10,000	0 (0%)	12 (40%)	10 (33.3%)	10 (34.4%)	11 (39.2%)	5 (20.8%)
>10,000	0 (0%)	1 (3.3%)	1 (3.3%)	2 (6.8%)	0 (0%)	0 (0%)
Mean±SD	1925±2151	3743±2199	3903±2422	5135±3186.1	4637±2570	2914.9±1373.1

Table 4: Total RBC transfused per year

Total PCV transfused in last 1 year (ml kg year)	No. of patient (n = 30)	Percentage
<200	13	46
>200-300	12	40
>300	5	16.6

Table 5: Adverse effects of chelation

Adverse effects	No. of patient (n = 30)	Percentage
Rash	1	3.33
Others (nose bleed)	1	3.33
GI Upset	0	0
Dizziness	0	0

Table 6: Compliance

No. of patients (n = 30)	Compliance
20	100
10	83%

0.018). The volume of blood transfused was significantly lower in 13 patients, which was as per blood transfusion guidelines (Indian Academy of Pediatrics AP, 2006). Only two patients showed adverse drug reactions (ADRs) out of 30 patients. Most common ADRs observed were Rash (n = 1) and nose bleeding (n = 1). In present study, 100 % compliance was noted in 20 children while 83 % compliance was noted in 10 children.

DISCUSSION

Definitive treatment of thalassemia includes bone marrow transplantation and gene therapy, however both treatment options are expensive. In developing countries, repeated blood transfusions remain the mainstay of management. However, in resource-limited settings, repeated blood transfusions lead to iron overload and deposition of iron in various tissues of the body[6,7]. Iron overload is associated with a variety of complications affecting skeletal, cardiovascular, hepatobiliary and endocrine systems. To prevent these complications, hematologist recommends prophylactic iron-chelating therapy to transfusion-dependent thalassemic patients. Deferasirox is a newer iron chelator which requires once daily oral administration. Efficacy and safety of deferasirox in children have been reported to be similar to that in adults. In our study, 15 (50%) girls and 15 (50%) boys were studied. In other similar studies, a male preponderance were recorded. Thakor *et al.*[8] reported 36 were boys and 19 were girls (male female ratio of 1.89:1). A similar preponderance of males (69.5%) was observed in studies conducted by Chhotray *et al.*[9] at Orissa, India and by Qurat-ul-Ain *et al.*[10] at Faisalabad, Pakistan (65.66%). However the reason for male gender dominance in this disease has not been documented in above studies. In our study the majority of patients (40%) were diagnosed with B thalassemia major between the age of 6 and 12 months. Similarly, in Thakor *et al.*[8] study, patients (n = 46, 83.6%) were diagnosed with B thalassemia major between the age of 6 and 12 months. These findings were also observations by Nigam *et al.*[11] who reported 12.7 months as a mean age of thalassemia diagnosis in Gujarat. Parakh *et al.*[12] also reported 33 patients with a mean age of 12.67 years (7.5-17.5 years). Availability of advanced diagnostic techniques, media attention, increased awareness and better access to healthcare has helped screen and diagnose this disease at an early age.

Serum iron level were analyzed in 30 patients. In the present study the mean serum ferritin level was detected to be significantly higher in patients at baseline. Parakh *et al.*[12] also a mean ferritin of 4835.23±1443.85 pg L. Higher mean serum ferritin levels in these patients could have been because of a higher number of blood transfusions received in these patients before enrolment. A significant decrease in serum ferritin levels was observed in all age groups at the end of 1 year of treatment with Deferasirox ($p<0.05$). These findings suggest that deferasirox effectively reduced iron overload. A phase III study also showed a significant decrease in serum ferritin levels with Deferasirox (ICL670) treatment in 96 transfusion-dependent B thalassemia patients over a period of 1 year[6]. Pennell *et al.*[13] also reported a median reduction of 1048 ng mL in serum ferritin from baseline over 1 year in transfusion-dependent B thalassemic children after treatment with deferasirox at doses of 20-30 mg kg day. Additionally, this study also concluded that continuous treatment with deferasirox for 2 years with a target dose of 40 mg kg d continued to remove iron from the heart in patients with B-thalassemia major and mild, moderate and severe cardiac siderosis.

In our study, two patients showed adverse effects of chelation, rash (n = 1) and nose bleeding (n = 1). In an 18-month trial by Alavi *et al.*[14] at IRAN showed that safety and tolerability was reached by 93.33%. The most common adverse events were skin rash and gastrointestinal disturbance in their study. In

Thakor *et al.*[8] study, most common ADRs observed were diarrhea (n = 24), raised serum creatinine (n = 15), raised hepatic enzymes (n = 14), abdominal pain (n = 14) and rashes (n = 14) and no abnormalities were observed on ophthalmological examination at baseline and at end of the study. In a phase 3 study of deferasirox (ICL670) by Cappellini *et al.*[15] the most common adverse events included rash, gastrointestinal disturbances, and mild nonprogressive increases in serum creatinine.

Iron overload usually affects skin, liver, pituitary, pancreas, heart, thyroid, para thyroid, gonads and adrenals. The terminal event commonly being cardiomyopathy and arrythmias occurring around the later half to second decade. Emphasis should therefore be laid on educating the patient/caretakers at each visit to ensure better drug compliance and to reduce the incidence of adverse reactions such as rash and bleeding.

CONCLUSION

A significant decrease in the mean serum ferritin levels was observed with deferasirox treatment. Deferasirox is relatively well tolerated among these patients. Periodic monitoring of laboratory and clinical parameters along with suitable dose modification can help optimize the drug therapy and improve the safety of this drug.

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