Effectiveness of Deferasirox in Pediatric Thalassemia Patients: Experience from a Tertiary Care Hospital of Odisha

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Abstract:
BACKGROUND AND OBJECTIVES: Patients with beta-thalassemia require lifelong blood transfusions, leading to chronic iron overload, which can lead to growth retardation, as well as hinder sexual development during the adolescent period and dysfunction of organs such as heart, pancreas, and endocrine glands. These patients are in need of lifelong transfusion therapy and hence lifelong iron chelation therapy as well. Hence, this study was aimed to assess the effectiveness of deferasirox for iron chelation in pediatric thalassemia cases in a tertiary care hospital of Eastern India.

SUBJECTS AND METHODS: This prospective, observational, hospital-based study was conducted from June 2015 to December 2016. Two hundred and fifty patients were assessed for eligibility, of which 174 were included. Effectiveness of deferasirox was observed by measuring serum ferritin levels which were monitored at the end of every 3 months till 1 year. We also evaluated the compliance with deferasirox therapy in the same study cohort.

RESULTS: The serum ferritin level reduced significantly at the end of 12 months in comparison to baseline (P = 0.04). There was a mean absolute decrease in serum ferritin only in the dose range of 21–30 mg/kg/day. Approximately 90% of the patients had 100% compliance with deferasirox therapy.

CONCLUSIONS: Deferasirox is an effective iron chelator when started at an optimum time and with optimum dose. At least 1 year of deferasirox therapy is needed for a significant lowering of serum ferritin levels of pediatric thalassemia patients on multiple blood transfusions.

Keywords: Beta-thalassemia, blood transfusions, chelating agents, deferasirox, iron

Introduction

Thalassemia is an inherited blood disorder that can result in the abnormal formation of hemoglobin. Chronic iron overload can occur in beta-thalassemia patients as they need blood transfusions throughout their life. Iron overload can lead to growth retardation, as well as hinder sexual development during the adolescent period and dysfunction of organs, such as heart, pancreas, and endocrine glands.[1-3] When the storage capacity of the body is exceeded, iron remains in free form. The formation of hydroxyl free radicals can be catalyzed by this free iron, leading to damage of cell membranes and protein denaturation. Ultimately, tissue damage occurs which can lead to significant levels of morbidity and also mortality.[4] Iron chelation helps prevent complications of iron overload due to repeated blood transfusion.[5] Indeed, the most common complication of beta-thalassemia that leads

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to death is organ failure, in patients taking regular blood transfusions and no appropriate iron chelation.[6-8] Elevated liver iron concentrations (LICs) and serum ferritin levels can manifest within 1–2 years of starting regular blood transfusions. Thalassemia patients whose serum ferritin level is more than 2500 ng/mL or LIC value is more than 15 mg Fe/kg dry weight are at high risk of development of cardiac diseases such as cardiomyopathy.[9]

Deferoxamine mesylate has remained the standard treatment for transfusional hemosiderosis for the last many years. However, there were some disadvantages such as need for parenteral administration (slow SC or IV infusion) over 8–12 h. Moreover, this had to be administered for 5–7 days in a week. Hence, it was frequently associated with decreased compliance which resulted in limited efficacy.[10,11]

Deferiprone is the first oral iron chelating agent. However, it has to be administered thrice daily. Again, it has a narrow therapeutic window also. The main adverse effects that have limited its use are arthropathy and agranulocytosis.[12]

Deferasirox belongs to new class of tridentate iron chelators. It has good oral bioavailability. The elimination t1/2 ranges from 8 to 16 h. Hence, it can be given only once per day. There are no clinically significant drug–drug interactions with deferasirox. Various preclinical studies have shown that it is able to enter and remove iron from cells.[13,14] FDA has approved deferasirox in 2005, but it came to Indian market only in April 2008.

Many western studies have proven deferasirox to be efficacious in decreasing the serum ferritin levels of transfusion-dependent anemia patients after 1 year of therapy. However, the effectiveness of this iron chelator has not been studied systematically in Eastern India and particularly in the pediatric thalassemia patients.

Thalassemia patients are in need of lifelong transfusion therapy, and hence, iron chelation is also needed throughout the life. Hence, it is very much essential to evaluate the effectiveness of this newer oral iron chelator deferasirox, particularly in pediatric patients of Eastern Indian region. Pediatric population is a very specific and vulnerable population, in whom drug therapy is mostly given as off-label without any direct clinical evidence. The pharmacokinetics and pharmacodynamics of a drug can vary significantly in pediatric population compared to their adult counterparts.[15] Hence, we have selected pediatric thalassemia patients for our study.

With this background, the current study was undertaken with the aim to evaluate the clinical effectiveness and safety of deferasirox therapy in once daily dosing in pediatric thalassemic patients attending a tertiary care hospital of Eastern India. In this article, we have published the data related to effectiveness and compliance. The safety data of deferasirox in pediatric thalassemia patients will be published separately.

Subjects and Methods

This open-label, prospective, observational, hospital-based study was conducted by the collaborative efforts of the Department of Pharmacology and Clinical Haematology of S. C. B. Medical College, Cuttack, where deferasirox is provided free of cost by the State Government.

Study setting

A study team was constituted comprising the principal investigator and the study guides of both the departments. The study protocol, written assent form, and informed consent form were designed by the team. Patients attending the Outpatient Department of Clinical Haematology, diagnosed with thalassemia, and on deferasirox therapy were assessed for the inclusion in the study. For the purpose of case collection, prior permission from the Head of the Department, Clinical Haematology, was obtained.

Study period

The study was conducted between June 2015 and December 2016 for a total duration of 1 year and 7 months.

Study population

The diagnosed patients of thalassemia of either sex, between the age of 2 and 18 years, with chronic iron overload predominantly by blood transfusions as evident by elevated serum ferritin level (>1000 ng/mL) or annual blood transfusion requirement of 8 or more were included in this study, irrespective of chelation status at baseline. Patients having one of the following conditions were excluded from this study: alanine aminotransferase level >250 U/L in the previous 1 year before enrolment, positive hepatitis serology, positive HIV test, serum creatinine 1.2 mg/dL, urinary protein–creatinine ratio of >0.5, hypertension not controlled by medications, increased QTc interval, or systemic infection within previous 10 days, intestinal malabsorptive conditions or a history of ocular adverse effects with previously used iron chelators.

Enrolment

Baseline evaluations were performed for patients providing assent and/or consent from the legally acceptable representative, as applicable. These included hepatitis serology, HIV status testing, electrocardiogram,
Effectiveness assessments
Effectiveness was defined as any decrease in serum ferritin from baseline value or maintenance of the same value in the presence of ongoing blood transfusions. Serum ferritin values were noted at baseline and then 3 monthly till 1-year follow-up period. The dose of deferasirox used and compliance of the patients were also noted in a predesigned case record form at 3-monthly intervals. The flow diagram of study design has been shown in Figure 1.

Compliance assessment
The compliance of the patients was calculated by proportion of days covered. It is the number of days covered over a time interval.

Ethical considerations
The institutional ethics committee of study center approved our study protocol. Verbal (for 7–12 years) or simplified written (for >12–18 years) assent was taken from the participants. Written informed consent was taken from each patient’s legally acceptable representative.

Statistical analysis
Data entry was done in Microsoft Excel sheet. Data analysis was performed using MedCalc version 12 - © 1993-2013 MedCalc Software bvba (Acacialaan 22,840 Ostend,Belgium). Summary statistics was used to express the variables as mean ± SD, median (range), etc., Repeated-measures ANOVA was used for comparing mean serum ferritin values at each of the defined time points.

Results

The baseline and demographic parameters of the study participants are summarized in Table 1.

| Parameters                  | Numbers          |
|-----------------------------|------------------|
| Number of patients          | 174              |
| Sex, n (%)                  |                  |
| Male                        | 103 (59.2)       |
| Female                      | 71 (40.8)        |
| Age (years)                 |                  |
| Mean±SD                     | 8.7±3.7          |
| Median (range)              | 9 (2.25-18)      |
| Age groups (years), n (%)   |                  |
| 2–<12                       | 135 (77.6)       |
| 12-18                       | 39 (22.4)        |
| Serum ferritin (ng/mL)      |                  |
| Mean±SD                     | 3942.3±2658.3    |
| Median (range)              | 3740 (652-16,500)|

Initially, 34.7% of the patients had their serum ferritin values below 2500 ng/mL. This percentage increased to 45.4% at the end of 12 months.

Of the 174 patients included in the study, 113 patients could give the serum ferritin data at baseline and after 3 and 6 months. These patients were analyzed for effectiveness assessments. It was found that the highly iron overloaded patients (serum ferritin at baseline >4000 ng/mL) responded better. The percentage of the patients in which deferasirox was found to be effective at the end of 6 months was 25%, 19%, 48%, and 63% in patients with baseline serum ferritin >1000, 1000–<2500, 2500–<4000, and >4000 ng/mL, respectively [Figure 2].

Of the 113 patients, five patients were given deferasirox at a mean dose between 10 and 20 mg/kg/day, 84 patients between 21 and 30 mg/kg/day, and 24 patients between 31 and 40 mg/kg/day. The percentage of the patients in each group in whom deferasirox was found effective was 25%, 45%, and 42%, respectively [Figure 3].

The mean absolute change in the serum ferritin from baseline to month 6 was highest for the most heavily iron-overloaded patients, i.e., −1080 ± 3610.2 ng/mL, in patients whose baseline serum ferritin was >4000 ng/mL. For those with baseline serum ferritin between 2500 and <4000 ng/mL, the mean absolute change was −57 ± 1172.2 ng/mL. In patients with baseline serum ferritin <2500 ng/mL, there was no decrease in the mean serum ferritin level [Figure 4].

As per the mean dose of deferasirox used, there were three dose categories. In the five patients who were given deferasirox in the dose range of 10–20 mg/kg/day, there was no decrease in the mean serum ferritin from baseline to the end of 6 months. However, there was a decrease of −106 ± 2804 ng/mL in the 84 patients who got
deferasirox at a dose range of 21–30 mg/kg/day. Again, in the 24 patients who were given deferasirox in the dose range of 31–40 mg/kg/day, there was an increase in the mean serum ferritin level [Figure 5].

Of 174 patients included, 11 patients could give the serum ferritin data till month 12. When repeated-measures ANOVA was applied for comparing the mean serum ferritin levels at baseline and that at completion of every 3 months till 1 year, a statistically significant decrease was observed between the mean serum ferritin level at baseline and that after 12 months ($P = 0.04$) [Figure 6].

Approximately 90% of the patients had 100% compliance with deferasirox therapy [Table 2]. An extensive study of the adverse effects of deferasirox has been done, and the detailed safety analysis data will be published in a separate article.

**Discussion**

Chronic iron overload in the thalassemia patients as a result of repeated blood transfusions is an important problem in day-to-day treatment and care. It can cause significant morbidity as well as early mortality if adequate chelation therapy is not given. Therapy with
Deferasirox is an orally administered iron chelating agent that has to be given by dissolving in water or fruit juice once per day. Previous trials have shown that deferasirox was efficacious as an iron chelator. Deferasirox has become available in India only recently. It is recommended for the treatment of chronic transfusional hemosiderosis in adults and pediatric patients (more than or equal to 2 years). As per our knowledge, this is the first study that has evaluated the effectiveness and safety profile along with the compliance to the novel oral iron chelator deferasirox in the pediatric thalassemia patients of Eastern Indian region. Although deferasirox is an FDA-approved drug, this study is very much essential as the Eastern Indian pediatric population can have a different pattern of bioavailability and hence effectiveness and safety profile due to pharmacogenomic variations.

In our study, male patients are more than female patients (male: female ratio = 1.45); Ladis et al. did a study on 85 patients with transfusion-induced iron overload in which female patients were more than male patients (female: male ratio = 1.3). This difference in gender distribution might be because mostly female patients are neglected in our society and male patients are better taken care of and hence brought to the hospital setup for treatment. Furthermore, Ladis et al. have included beta-thalassemia (67.1%), thalassemia intermedia (20%), and sickle cell anemia (12.9%) in their study. However, we included all kinds of thalassemia patients including Hb-E-beta-thalassemia and sickle-beta-thalassemia combinations.

Studies showing data of pediatric patients are limited as most studies done on deferasirox were in adults. As per the Indian Academy of Paediatrics, the 'paediatric age group' includes up to 18 years of age. Hence, we have included adolescents also in our study. We excluded children <2 years because deferasirox is not recommended in them. More than three-fourth of the study participants were children aged between 2 and <12 years. The rest were adolescents between 12 and 18 years of age. The median age of our study participants was 9 years (range = 2.25–18 years). Hence, our data signify an outcome primarily in children.

For monitoring the iron overload, we used serum ferritin values. It is a reflection of body iron stores. It is inexpensive and also very easy to estimate repeatedly. It is very much useful to identify trends. The average interval between two blood transfusions was 25.9 days in our patients. Their baseline mean serum ferritin (3942.3 ± 2658.3 ng/mL) showed that our patients were heavily iron overloaded. Chandra et al. did a study on 40 North Indian children with β-thalassemia major whose baseline serum ferritin was 5909.6 ± 5832.82 ng/mL. This higher serum ferritin level could be because they have included only β-thalassemia major patients who are all transfusion dependent, but we have included all types of thalassemic patients whose blood transfusion requirement was more than 8/year.

After 12 months of deferasirox therapy, the percentage of patients who achieved a serum ferritin value of 2500 ng/mL or less was 45% compared to only 35% at baseline. Cappellini et al. in 2011 did a study on 371 patients, and at 4–5 years of follow-up, they found that the percentage of patients who achieved serum ferritin value of 2500 ng/mL or less was 73% as compared to 64% at baseline.

As per the mean dose of deferasirox used, we found deferasirox to be effective only in the dose range of 21–30 mg/kg/day. Further, the percentage of responders was highest in this subgroup of patients. Most of the studies pertaining to efficacy profile of deferasirox have been done in adults, and hence, data regarding pediatric population are limited. Cappellini et al. in 2006 showed that deferasirox 30 mg/kg/day could achieve a negative iron balance. In this study, 20% of the patients belonged to the pediatric age group. ESCALATOR study reported that decrease in LIC in the pediatric patients was not as much as in adults. The authors explained that this was because pediatric patients had 30% higher intake of iron from transfusions as compared to adults. In addition, the doses in pediatric patients were escalated after a larger median time gap than in adult patients.

Previous studies on pharmacokinetics of deferasirox have found that children have lower exposure to deferasirox than adults. We noticed that similar to previous studies, deferasirox was ineffective in the dose range of 10–20 mg/kg/day, but it was effective in patients getting deferasirox in the dose range of 21–30 mg/kg/day.
21–30 mg/kg/day. However, unexpectedly, it was again not effective in the subgroup of 24 patients who were given deferasirox in the dose range of 31–40 mg/kg/day. There could be many reasons for this unexpected result. These patients could be taking a higher number of transfusions, or they could be having some infections at the time of serum ferritin estimation which raised the acute-phase reactants (including serum ferritin), or some could be having hepcidin gene polymorphism. Moreover, on inquiry, many patients were found to be taking highly iron-rich food. Further, they used to dissolve deferasirox tablets in metallic containers which are not recommended.

A statistically significant fall in the mean serum ferritin level was observed from baseline to month 12. EPIC study which included 1744 transfusion-dependent anemia patients, of which 1115 were thalassemia major, showed that a significant fall in the serum ferritin was achieved at 1 year.25 Hence, we can conclude that serum ferritin levels decrease significantly only after the thalassemia patients on multiple transfusions have taken at least 1 year of deferasirox therapy.

For the detection of organ iron overload, T2* MRI and superconducting quantum interference device are the better diagnostic techniques. However, we could not use them because of nonavailability in our hospital. Hence, we have used serum ferritin to monitor the iron overload in our study. A rapid increase in the serum ferritin could be due to hepatitis or any other infectious or inflammatory conditions. Hence, if a patient’s serum ferritin does not fall, it is not necessary that he/she is a “nonresponder” to the chelation therapy. Moreover, many patients were reluctant to do even serum ferritin estimation and other special investigations, due to lack of motivation and ignorance. Thus, it was difficult to generate all the data properly.

**Conclusions**

Deferasirox is an effective iron chelator when started at an optimum time and with optimum dose. Serum ferritin levels decrease significantly only if at least 1 year of deferasirox therapy is taken by pediatric thalassemia patients who are on multiple transfusions. A proper dose-escalation protocol can ensure a better response. In resource-constraint setting, the effectiveness of chelation and deferasirox dose adjustment can be done by serum ferritin estimation although the gold standard is LIC measurement. Government cooperation for deferasirox distribution may play a vital role in thalassemia management.

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**Conflicts of interest**

There are no conflicts of interest.

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