Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Comparative Efficacy and Safety of Once-Daily Dosing and Twice-Daily Dosing of Deferasirox in Reducing Serum Ferritin Levels in Children with Thalassemia Major Patients

Ifra Rasool, Rajnesh Kumar, Audil Mateen, Mohammad Irfan Dar

Department of Pediatrics, Government Medical College, Jammu, Jammu and Kashmir, India

Abstract

Objectives: The objectives of the study were to assess the efficacy and tolerability of two divided dosing of deferasirox in comparison to once-daily dosing.

Materials and Methods: Pediatric thalassemia patients more than 2 years of age who were receiving deferasirox as the only chelator over the past 6 months or more were included in the study group. Deferasirox administration schedule was switched from "once-daily" to "two divided daily" dosing schedule with the total dose per day remaining the same which the patient had been receiving earlier as once-daily dose. Serum ferritin levels that were done 6 months before "switch over" were taken as baseline. Serum ferritin levels were done at the time of "switch over" and subsequently at the end of 3rd and 6th month and were compared to the baseline serum ferritin levels. Duration for which patient had received single-dose deferasirox acted as control.

Results: The mean serum ferritin at baseline of the study group on "once-daily" dosing was 2501.52 ± 1392.03 ng/ml. At enrolment of patients (total 25) on "once-daily" dosing of deferasirox, 14 patients had decreasing serum ferritin levels, 10 patients had increasing trend of serum ferritin while in one patient, there was no change in serum ferritin when observed retrospectively for the past 6 months. After 6 months of "two divided daily dosing," serum ferritin decreased statistically in 4 (16%) subjects and increased significantly in 21 (84%) subjects. The mean ferritin of the four subjects with decreased serum ferritin at the baseline was 1800 ± 400 which subsequently decreased to 721.5 ± 301.96 ng/ml. Mean decrease in serum ferritin in four patients was 1078.5 ng/ml. No significant changes were observed in complete blood count, renal function test, liver function test, and blood sugar levels when compared to the baseline.

Conclusion: Two divided dosing of deferasirox was better tolerated with no adverse effects being reported.

Key words: Deferasirox, Iron chelators, Thalassemia

INTRODUCTION

Thalassemia is a group of inherited blood disorders caused by defects in one or more genes responsible for producing the globin chains in hemoglobin synthesis, characterized by a reduction in the synthesis of one or more of the globin chains, leading to imbalanced globin chain synthesis, defective hemoglobin production causing anemia.[1] Thalassemia is considered the most common genetic disorder worldwide.[2] The management of thalassemia is guided by the severity of anemia, suppression of excessive erythropoiesis, and prevention of excess iron overload. Patients who receive more than 100 units of packed red blood cells per annum usually develop iron overload.[3] To prevent iron overload and its complications, iron-chelating agents are started early when starting transfusion therapy. Commonly used chelating agents are deferoxamine, deferiprone, and deferasirox.[4]

Deferasirox has been developed in response to an overwhelming clinical need for a convenient effective and well-tolerated iron-chelating age. Studies have confirmed

Access this article online

www.ijss-sn.com

Month of Submission : 04-2022
Month of Peer Review : 05-2022
Month of Acceptance : 05-2022
Month of Publishing : 06-2022

Corresponding Author: Mohammad Irfan Dar, Department of Pediatrics, Government Medical College, Jammu, Jammu and Kashmir, India.

its ability to chelate cardiac iron, thus reducing cardiac iron overload.[5] It is currently administered as once-daily dose. Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain are common and are reported in one-third of patient.[6] Skin rashes are the other common adverse effect. The most concerning effect is increase in serum creatinine that is reported in up to 1/3 of patients. Dividing deferasirox in twice-daily dosing will provide sustainable therapeutic levels of deferasirox throughout 24 h resulting in better clinical efficacy. Twice-daily dosing may lead to decreased dose-dependent side effect thus improved tolerability. Hence, this study was planned to assess the efficacy and tolerability of two divided dosing of deferasirox in comparison to once-daily dosing.[7]

MATERIALS AND METHODS

The study was conducted at the thalassemia day care center in the postgraduate department of pediatrics SMGS Hospital, Government Medical College, Jammu, Jammu and Kashmir, where 290 patients are registered. Forty patients were receiving deferasirox as iron chelator. In this study, all the pediatric thalassemia patients more than 2 years of age who were receiving deferasirox as the only chelator over the past 6 months or more were included in the study group. Deferasirox administration schedule was switched from "once-daily" to "two divided daily" dosing schedule with the total dose per day remaining the same which the patient had been receiving earlier as once-daily dose. Serum ferritin levels that were done 6 months before "switch over" were taken as baseline. Serum ferritin levels were done at the time of "switch over" and subsequently at the end of 3rd and 6th month and were compared to the baseline serum ferritin levels. Duration for which patient had received single-dose deferasirox acted as control.

Inclusion Criteria

- Thalassemia patients more than 2 years of age who have been receiving deferasirox as the only chelator for the past 6 months or more and whose serum ferritin levels have been documented in the past 6 months were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

- Thalassemia patients <2 years
- HbsAg positive and HBC positive
- Patients with deranged renal function tests (RFTs) (serum creatinine >2 times the age appropriate upper limit of normal before and during the study)
- Deranged liver function tests (LFTs) (transaminases more than 5-fold)
- Patients receiving more than 1 chelator.

Clinical examination of subjects was done monthly to monitor any organ or endocrine dysfunction. Complete blood counts (CBCs), RFTs, LFTS, and pancreatic enzyme assays were done monthly to monitor any adverse effect. At the end of 6 months of "two divided dosing," patients were evaluated for decrease in serum ferritin levels and were compared to the baseline serum ferritin levels. All the data from the patients of the study group were noted on the pro forma and were put in tabulated form and analyzed using appropriate statistical technique.

RESULTS

There were 16 males (64%) and 9 females (36%) in the study group with male-female ratio of 1.78:1.

- Mean age of the study group was 6 ± 2.09 years
- The mean dose of deferasirox in the study patients was 34.10 ± 3.62 mg/kg/day
- The mean serum ferritin at baseline of the study group on "once-daily" dosing was 2501.52 ± 1392.03 ng/ml. Subsequently after 6 months of two divided dosing, serum ferritin levels increased to 2873.96 ± 1434.60 ng/ml which was not significant
- At enrollment of patients (total 25) on "once-daily" dosing of deferasirox, 14 patients had decreasing serum ferritin levels, 10 patients had increasing trend of serum ferritin while in one patient, there was no change in serum ferritin when observed retrospectively for the past 6 months
- After 6 months of "two divided daily dosing," serum ferritin decreased statistically in 4 (16%) subjects and increased significantly in 21 (84%) subjects
- The mean ferritin of the four subjects with decreased serum ferritin at the baseline was 1800 ± 400 which subsequently decreased to 721.5 ± 301.96 ng/ml
- Mean decrease in serum ferritin in four patients was 1078.5 ng/ml
- The mean age of the above four patients was 6.5 years
- No significant changes were observed in CBC, RFT, LFTS, and blood sugar levels when compared to the baseline
- At the end of study, no significant change was observed in the number of blood transfusions when compared with the baseline
- Two divided dosing was better tolerated with no adverse effects being reported.

DISCUSSION

Thalassemia patients on chronic transfusion are susceptible for developing iron overload. Patients who receive more than 100 units of packed RBCs (annually) usually develop iron overload. Serum ferritin, liver biopsy, and

imaging modalities such as magnetic resonance imaging and superconducting quantum interference device can measure iron overload in the body. Complications arising from iron overload are cirrhosis, endocrine dysfunction, glucose intolerance, hypogonadism, hypothyroidism, hypoparathyroidism, and cardiomyopathy.[3] To prevent these complications, iron-chelating agents such as deferoxamine and deferasirox are used early when starting transfusion therapy.

Deferoxamine was the first iron chelator used for the treatment of chronic iron overload. It is administered parentally due to its poor oral bioavailability. Given its short half-life, it requires frequent administration, typically 57 times per week. It can be given by both intravenous and subcutaneous routes (Callender *et al.*, 1962). It requires prolong infusion time which affects the quality of life and increases the risk of noncompliance with therapy. Early and aggressive deferoxamine administration can adversely affect the skeletal maturation and results in growth retardation (De Virgillis, 1988). The cumbersome nature and complications associated with deferoxamine therapy pushed investigators to identify oral agents that would be suitable for long-term iron chelation in those with chronic iron overload.

Deferiprone was the first oral chelator to be used for the treatment of iron overload. Deferiprone results in more significant reduction in iron levels in those with higher burden. It may not be as helpful for those with less significant iron overload.[8] Deferiprone is associated with several adverse effects. Most concerning is agranulocytosis. In clinical trials, neutropenia is reported in up to 5% with agranulocytosis reported in <l%.[9] Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain have been reported in up to 33% of patients**.** Elevation of liver transaminases has also been reported. Arthralgia and arthritis have been associated with deferiprone. Large joints such as knees are commonly affected. About 50% of cases develop within the 1st year of therapy.[8] Due to these side effects and non compliance of Deferipirone, investigators looks for oral iron chelators with more favorable attributes.

Deferasirox has been developed in response to an overwhelming clinical need for a convenient, effective, and well tolerated iron-chelating agent. It was approved by the US Food and Drug Administration in 2005.

Deferasirox is an orally active chelator that is highly selective for iron (III) and binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of iron, primarily in the feces. Deferasirox has very low affinity for zinc and copper and does not cause constant low serum levels of these metals.[10] Deferasirox is effective in lowering serum ferritin levels and decreasing overall iron burden. A dose-dependent effect on serum ferritin has been observed.[4,8] Studies have confirmed its ability to chelate cardiac iron, thus reducing cardiac iron overload.[5] In an iron balance metabolic study in iron overloaded adult thalassemia patients, deferasirox at daily doses of 10, 20, and 40 mg/kg induced the mean net excretion of 0.119, 0.329, and 0.445 mg Fe/kg body weight/day, respectively. Phase 2 and 3 trials involving deferasirox have shown that a dose between 20 and 30 mg/kg/day generally produces a net negative iron balance. The current maximum dose of deferasirox has been increased to 40 mg/kg/day. It is currently administered in single dose and is well tolerated. Adverse effects associated with its use are mild and self-limiting. Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain are common and are reported in one-third of patient.[6] Skin rashes are the other common adverse effect. The most concerning effect is increase in serum creatinine that is reported in up to 1/3 of patients. In general, these are mild and transient and resolve on discontinuation of drug.[8]

Dividing deferasirox in twice-daily dosing will provide sustainable therapeutic levels of deferasirox throughout 24 h resulting in better clinical efficacy. Twice-daily deferasirox dosing may yield more homogenous suppression of non-transferrin bound plasma and lower peak levels. In addition, some adverse effects may be dose dependent and related to peak levels. Twice-daily dosing may lead to decreased dose-dependent side effect, thus improved tolerability.[7]

In our study, deferasirox in two divided dosing given at a median dose of 34.1 mg/kg/day for a duration of 6 months in 25 subjects with median age of 6 years showed statistically significant fall in serum ferritin in four subjects whose mean age was 6.1 years and baseline mean serum ferritin of 1800 ng/ml. Twenty-one subjects had significant rise in serum ferritin levels. However, deferasirox was better tolerated in "two divided" dosing as compared to "once-daily" dosing.

A longer study with a maximum dose of deferasirox, that is, 40 mg/kg/day started early at lower serum ferritin levels with an assessment of more reliable markers such as hepatic and cardiac iron are required for further evaluation of chelation efficacy of two divided dosing of deferasirox.

CONCLUSION

There is no significant difference in efficacy of once daily dosing versus twice daily dosing of Deferasirox in thalassemia. Although Two divided dosing of deferasirox

was better tolerated with no adverse effects being reported. Futher study with a higher dose of deferasirox, with an assessment of more reliable markers such as hepatic and cardiac iron are required for further evaluation of chelation efficacy of two divided dosing of deferasirox.

REFERENCES

1. Kelly N. Thalassemia. Pediatr Rev 2012;33:434-5.
2. Fawdry AL. Erythroblastic anaemia of childhood (Cooley's anaemia) in Cyprus. Lancet 1944;1:171-6.
3. Prakash A, Aggarwal R. Thalassemia major in adults: Short stature, hyperpigmentation, inadequate chelation, and transfusion-transmitted infections are key features. N Am J Med Sci 2012;4:141-4.
4. Porter J, Viprakasit V. Iron overload and chelation. In: Cappellini MD, Cohen A, Porter J, Taher A, editors. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 3rd ed., Ch. 3. Nicosia, CY: Thalassaemia International Federation; 2014.
5. Wood JC, Otto-Duessel M, Gonzalez I, Aguilar MI, Shimada H, Nick H, *et al.* Deferasirox and deferiprone remove cardiac iron in the iron-overloaded gerbil. Transl Res 2006;148:272-80.
6. Cohen AR, Galanello R, Piga A, De Sanctis V, Tricta F. Safety and effectiveness of long-term therapy with the oral iron Chelator deferiprone. Blood 2003;102:1583-7.
7. Chang H, Lu MY, Lio YM, Lin PC, Yang YL, Lin DT, *et al.* Improved efficacy tolerability of oral deferasiroc by twice-daily dosing for patients with transfusion-dependent β-Thalssemia. Pediatr Blood Cancer 2011;56:420-4.
8. Cappellini MD. Long-term efficacy and safety of deferasirox. Blood Rev 2008;22:S35-41.
9. Piga A, Galanello R, Forni GL, Cappellini MD, Origa R, Zappu A, *et al.* Randomized phase II trial of deferasirox (Exjade, ICL670), a once-daily, orallyadministered iron chelator, in comparison to deferoxamine in Thalassemia patients with transfusional iron overload. Haematologica 2006;91:873-80.
10. Steinhauser S, Heiz U, Bartholoma M, Weyhermüller T, Nick H, Hegetschweiler K. Complex formation of ICL670 and related ligands with FeIII and FeII. Eur J Inorg Chem 2004;21:4177-92.

How to cite this article: Rasool I, Kumar R, Mateen A, Dar MI. Comparative Efficacy and Safety of Once-Daily Dosing and Twice-Daily Dosing of Deferasirox in Reducing Serum Ferritin Levels in Children with Thalassemia Major Patients. Int J Sci Stud 2022;10(3):115-118.

Source of Support: Nil, **Conflicts of Interest:** None declared.