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Deferasirox in Chelation Naive Children with Transfusional Iron Overload in Basra, Iraq: A Two-Year Single Center Study

Basim Abdul-Kareem Abdul-Hassan[1], Mea`ad Kadhum Hassan[1, 2*], Rawshan Zuhair Jaber[1]

[1]Center for Hereditary Blood Diseases, Basra Maternity and Children Hospital, Basra, Iraq
[2]Department of Pediatrics, College of Medicine, University of Basra, Basra, Iraq

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*Corresponding author:
Mea`ad Kadhum Hassan,
Department of Pediatrics, College of Medicine, University of Basra, Basra, Iraq
Mobile: +964-780100174
Fax: +964-40-619375
Email: alasfoor_mk@yahoo.com

ABSTRACT

Background: Effective management of iron overload in patients receiving long-term blood transfusion requires assessment and monitoring of both severity of iron overload and excessive iron chelation. We aimed to evaluate the efficacy and safety of Deferasirox (DFX) in chelation naive patients with transfusion dependent thalassemia and sickle cell disease.

Methods: Chelation naive patients with transfusion dependent thalassemia (TDT) and sickle cell disease (SCD), aged 2-5 years, who had received DFX for at least 2 years were enrolled. Safety of DFX was assessed based on alanine aminotransferase (ALT) and serum creatinine levels, while efficacy was assessed based on serum ferritin levels.

Results: The study included 93 chelation naive patients; 64 (68.82%) with TDT and 29 (31.18%) with SCD. Mean SF levels declined significantly from 2297.40±1037.46 ng/ml at baseline to 1700.65±1038.7 ng/ml at the end of the study. The efficacy of DFX was increased with increasing DFX dose to ≥30 mg/kg/day. The most commonly observed adverse effects were abdominal pain in 20 (21.50%), nausea in 8 (8.60%), and vomiting in 4 (4.30%) patients, which were transient and mild to moderate in severity. A minor, although significant change in the mean serum creatinine was reported after 24 months of treatment with DFX compared to the baseline (75.72±7.87 vs. 71.59±11.14 mmol/L) ($P<0.05$). The mean ALT (17.69±1.44 vs. 21.75±3.37 U/L) and median height-SDS at the end of the study did not show significant changes compared to the baseline levels.

Conclusion: Although Deferasirox was found to be a safe, tolerable, and effective drug for reducing iron overload, monitoring safety markers and serum ferritin to ensure appropriate drug dosing can improve its efficacy.

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Introduction

Thalassemia is a common health problem in Iraq with a carrier rate ranging from 3.7–7.7% (1-3). In Basra, Southern Iraq, in addition to β-thalassemia, sickle cell disease (SCD) is also a common hemoglobinopathy, where the carrier rates for ß- thalassemia and sickle cell genes are 4.6% and 6.5%, respectively (4).

Iron overload is an inevitable complication among patients receiving long-term blood transfusion, since the human body lacks a mechanism to excrete excess iron. Iron accumulation is toxic to many tissues causing heart failure, cirrhosis, growth retardation and multiple endocrine abnormalities (5). In patients with thalassemia major, iron-induced liver disease and endocrine disorders develop earlier compared to patients with sickle cell disease (SCD) (1, 6).

Removal of stored iron is a slow and inefficient process because only a small proportion of body iron is available for chelation at any given time. Once iron is deposited in the tissues, damage is often irreversible; thus chelation therapy should be initiated before accumulation of iron has reached toxic levels to help decrease the iron burden

and to prevent and/or delay long-term complications associated with iron deposition in vital organs (7, 8).

Deferasirox (DFX), an oral agent with a once-daily dosing of 20-40 mg/kg/day which has got its approval in the US, Canada and European countries, has been used in different Asian countries for the treatment of transfusion-related iron overload (8).

Moreover, effective management of iron overload in thalassemia requires monitoring for both iron toxicity and the effects of excessive chelation (9). Serum ferritin level is the most commonly employed test to evaluate iron overload in patients with TDT. A target level of approximately 1000 ng/ml is the generally recommended standard practice in patients with TDT (7). Several studies have reported a dose-dependent effect of DFX on serum ferritin levels (10-12).

In SCD, linearity exists for serum ferritin up to 1500-2000 ng/ml or liver iron concentration (LIC) values up to 10 mg/g dry weight of liver; however, it increases more slowly due to iron overload above these levels (13).

The most common adverse events due to treatment with DFX were gastrointestinal disturbance, rash and mild increase in serum creatinine, while it may rarely result in renal and hepatic impairment and GI hemorrhage, but not agranulocytosis or growth failure (10, 14, 15).

Due to the significance of assessing efficacy and safety of DFX in chelation, we aimed to evaluate DFX efficacy and safety in chelation naive children with transfusion-related iron overload who were referred to the Center for Hereditary Blood Diseases (CHBD) in Basra, southern Iraq.

Patients and Methods

This single center descriptive study was conducted at CHBD in Basra on 162 multitransfused, chelation naive children with hereditary anemia and iron overload. The hereditary anemia among studied patients were TDT and SCD.

Ninety-three children who had received DFX for at least 2 years were enrolled in the study and their data were analyzed.

Treatment with Deferasirox

Patients with transfusional iron overload were scheduled to start iron chelation when their serum ferritin (SF) reached ≥ 1000 ng/ml. DFX doses were adjusted downwards with decreasing SF levels to 500 ng/ml (7). It was held when SF was consistently below 500 ng/ml (16).

The starting dose of dispersible tablets of DFX was 20 mg/kg/day, once daily, in accordance with DFX prescribing information. Dose escalations of DFX were performed based on serum ferritin levels and safety markers in increments of 5-10 mg/ kg (17).

Safety was assessed throughout the treatment period based on the incidence and type of the adverse events (AEs) (12, 18, 19). Assessment of adverse events included also the severity of AEs, mainly the gastrointestinal AEs and skin rash (16, 19).

Laboratory testing for alanine aminotransferase (ALT) and serum creatinine was performed by a fully automated chemistry analyzer, Cobas111c (Roche Cobas, Roche Diagnostic-USA) (6, 16). Serum creatinine and ALT were monitored monthly. Serum ferritin was assessed every 3 months using Cobas c 411 (Japan Roche 2013) and Ferritin Kit (Ref.No.03737551 190, Roche diagnostics, Deutschland, Germany).

All AEs were recorded by the treating pediatrician/ hematologist in the Outpatient setting.

Assessment of growth parameters (height, weight) was performed at the beginning of the study, during health visits every 3-6 months and after 2 years at the end of the study and were plotted against WHO growth charts for healthy children (6, 16, 20). The height SDS of the patients was calculated against the median for healthy children of the same age and median change in height SDS from baseline and after 2 years of DFX therapy was evaluated using the formula: SDS = X-Y/ SD, where

(X = patient height, Y= mean height for normal children of the same age and gender and SD= standard deviation of the height for normal children of the same age and gender) (21).

Transfusional iron overload was assessed based on daily iron intake and patients were categorized into low, intermediate and high transfusional iron intake groups (22, 23).

An informed consent was obtained from all patients and one of the parents before enrollment in the study. The study was approved by the Ethical Committee of the College of Medicine, Basra University.

All data were analyzed and processed using SPSS software, version 20 (IBM, Armonk, NY, USA). The safety and efficacy of DFX were assessed for patients who completed the 2-year period of the study.

Comparison of proportions was performed with crosstabs using the Chi-Square and Fisher's exact test. Mean of values was expressed as mean±SD. The statistical comparison between means was measured by paired t-tests and one-way analysis of variance (ANOVA). A $P<0.05$ was statistically significant.

Results

Ninety- three patients completed at least 2 years of treatment with DFX of whom 52 (55.91%) were boys. Children with TDT comprised 68.8% of the patients. Of the 29 (31.18%) patients with SCD, 23 had S/β^0 thalassemia and 6 had sickle cell anemia. Nine (9.67%) patients were infected by hepatitis C virus (Table 1).

Transfusional Iron Overload

The annual blood transfusion ranged from 3 to 24 transfusions/year (average 182 ml/kg/year), with a mean daily iron load of 0.26±0.12 mg/kg/day. 56 (60.2%) patients had low daily iron loading (<0.3 mg /kg/day), 34 (36.5%) had intermediate (< 0.5 mg/kg/day) and 3 (3.2%) had high daily iron loading (> 0.5 mg/kg/day).

Treatment with Deferasirox

39 (41.94%) patients started DFX with dose ≤20 mg/ kg/ day, 30 (32.25%) with >20 ≤30 mg/kg and 24 (25.81%) with a dose of ≥30 mg/ kg/day. Mean starting dose of DFX dose was 26.61±5.53 mg/kg/day. Dose escalation of DFX

Table 1: Main clinical data of chelation naive patients receiving Deferasirox

Variable		
Age (months)	Median age at starting chelation	35.00
	Mean age at starting chelation	36.05±12.27
	Mean current age	81.54±15.27
	Median current age	84.00
Gender	Male	52 (55.91%)
	Female	41 (44.09%)
Diagnosis	TDT	64 (68.82%)
	SCD	29 (31.18%)
Splenectomy		3 (3.22%)
HCV ab. Seropositivity		9 (9.67%)
Mean period of chelation (months)		45.49±9.61
Median period of chelation (months)		46.00
Median S. ferritin at start		2084.00
Mean daily iron load mg/kg/day	<0.3	56 (60.22%)
	0.3- 0.5	34 (36.56%)
	>0.5	3 (3.22%)

was based on serum ferritin, ALT and creatinine levels.

By the end of 24 months, 6 (6.5%) patients were receiving DFX with dose of ≤20 mg/kg/day, 13 (14%) >20 mg/kg and 74 (79.5%) ≥30 mg/kg/day, with a mean dose of 35.69±6.32 mg/kg/day.

Safety and Tolerability

Abdominal pain, nausea, vomiting, diarrhea were observed in 20 (21.50%), 8 (8.60%), 4 (4.30%), 2 (2.15%) patients respectively, and rash, abdominal distension and gastrointestinal hemorrhage each in 1 (1.07%) patient.

The gastrointestinal AEs were predominantly transient and mild to moderate in severity with a decreasing frequency after the first year; however, the gastrointestinal hemorrhage necessitated withholding DFX.

In the case of severe skin rash, DFX was stopped for 1 month, followed by reintroduction of DFX with a lower dose (10 mg/kg) and then escalation to the required dose without reappearance of the rash.

A minor, although significant, change in the mean serum creatinine was observed after 24 months of treatment with DFX (75.72±7.87 mmol/L) compared to mean baseline readings (71.59±11.14 mmol/L), P<0.05 (Table 2 and Figure 1).

Twenty (21.50%) patients showed >33% elevation in creatinine from the baseline but none of them required interruption or dose reduction. In addition, 10 (10.75%) patients showed an elevation of more than the upper limit of normal on one reading, but none showed this for 2 successive readings.

The mean ALT level at the end of the study did not show a significant change in comparison to the baseline level

Table 2: Studied safety and efficacy markers in patients receiving Deferasirox

Variables	Mean±SD (Range) at baseline	Mean±SD (Range) at end of study	P value
S. Creatinine (mmol/L)	71.59±11.14 (44-97)	75.73±7.87 (61-94)	0.022
Serum ALT (U/L)	17.69±1.44* (4-54)	21.75±3.37* (3-190)	0.994
*Serum ferritin (ng/ml)	2297.40±1037.46 (1027-6984)	1700.65±1038.79 (69-4004)	0.003

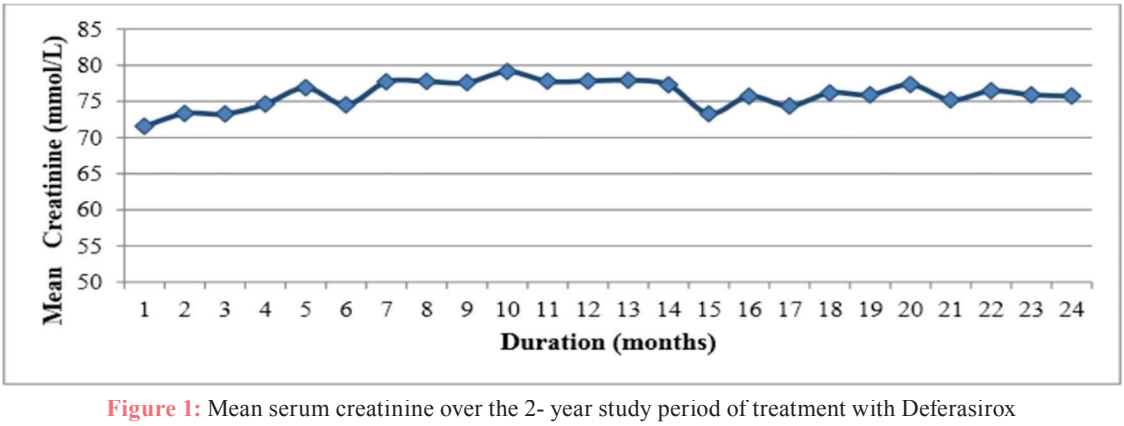

Figure 1: Mean serum creatinine over the 2- year study period of treatment with Deferasirox

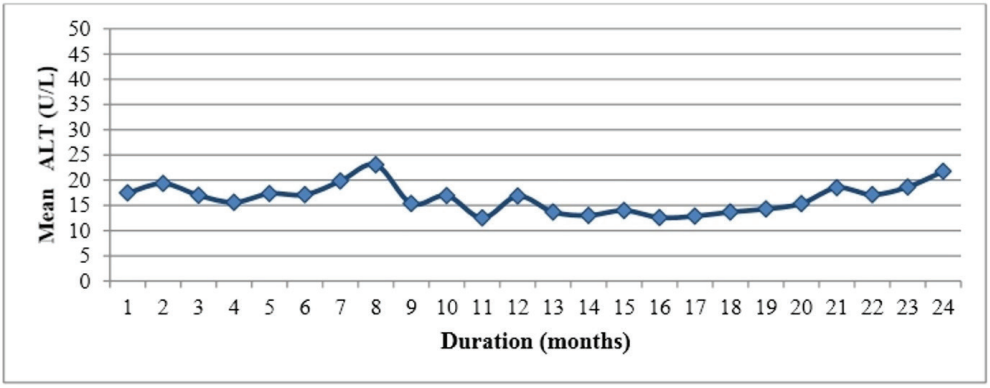

Figure 2: Mean ALT level over the 2-year study period of treatment with Deferasirox

(P >0.05, Table 2 and Figure 2).

Forty-six (49.4%) patients showed ALT elevation >1.5 times the ULN for at least 1 reading, only 2 (2.15%) patients showed elevation of >5 fold the ULN and none had ALT elevation of >10 times the ULN. Only one patient required interruption of the treatment due to increased ALT to eight folds of normal upper limits. None of the patients with increased ALT were positive for hepatitis C.

No significant hematological AEs (anemia or leukopenia) were reported throughout the period of observation.

The difference in median height of male and female patients were compared with the WHO standard. No significant difference in the median height SDS was detected among the patients between the beginning and end of the study. (P>0.05, Figure 3).

Efficacy

Transfusion was continued during the period of the observation and the mean daily iron load remained relatively stable for most of the patients (60.21%) receiving daily iron loading of <0.3 mg/kg/day.

By the end of the study, 17 patients achieved a serum ferritin level <500 ng/ml. Median serum ferritin levels decreased steadily with treatment during the study period with the greatest (633 ng/ml) decrease observed in those with daily iron loading < 0.3 mg /kg/day. The efficacy of DFX increased with increasing DFX dose to >30 mg/kg/day. (Table 3 and Figure 4).

Mean SF levels was 2297.40±1037.46 ng/ml at baseline. Its levels decreased from 2687.12±1358.41 ng/ml after 6 months to 2528.77±1581.70 ng/ml at 1 year of treatment, to 2202.21±1406.24 ng/ml at 18 months and to 1700.65±1038.7 ng/ml at the end of the study.

The efficacy of DFX in decreasing SF for both TDT and SCD was also evaluated.

For TDT patients, SF declined significantly from

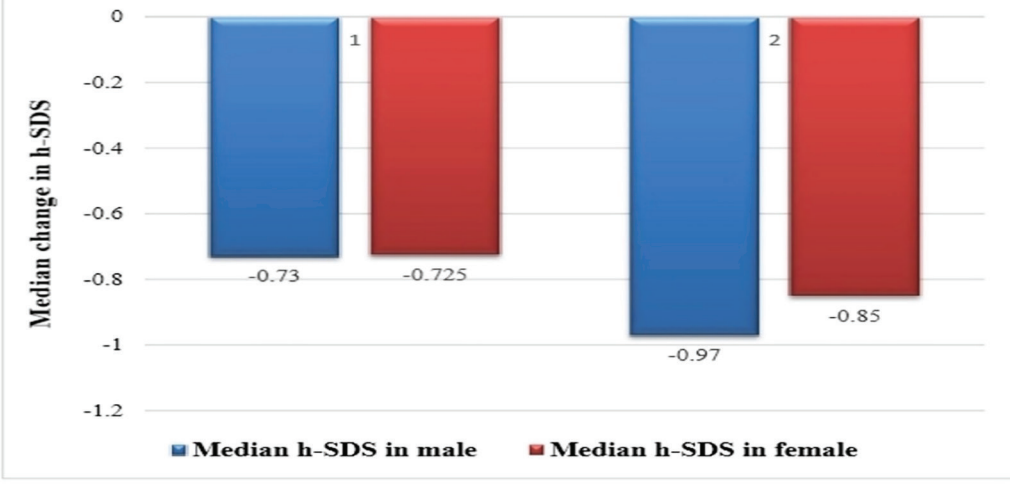

Figure 3: Height-SDS for the studied patients at the beginning and end of the study. P=0.210

Table 3: Average Reduction in serum ferritin in terms of daily iron loading

Daily iron load mg/kg/day (No)	Mean daily iron load (mg/kg)	Average reduction in median ferritin (ng/ml)	Median ferritin (ng/ml)	P value*
<0.3 (56)	0.17±0.07	633	1994.00	0.039
<0.5 (34)	0.36±0.04	117	2410.50	
>0.5 (3)	0.53±0.02	-208.5	2158.00	

*Kruskal-Wallis test. For assessment of serum ferritin median reduction between 2 groups, Mann-Whitney U test was used. For the groups which have DIL (<0.3 and < 0.5), P=0.010. For the groups which have DIL (<0.5 and >0.5), P>0.05

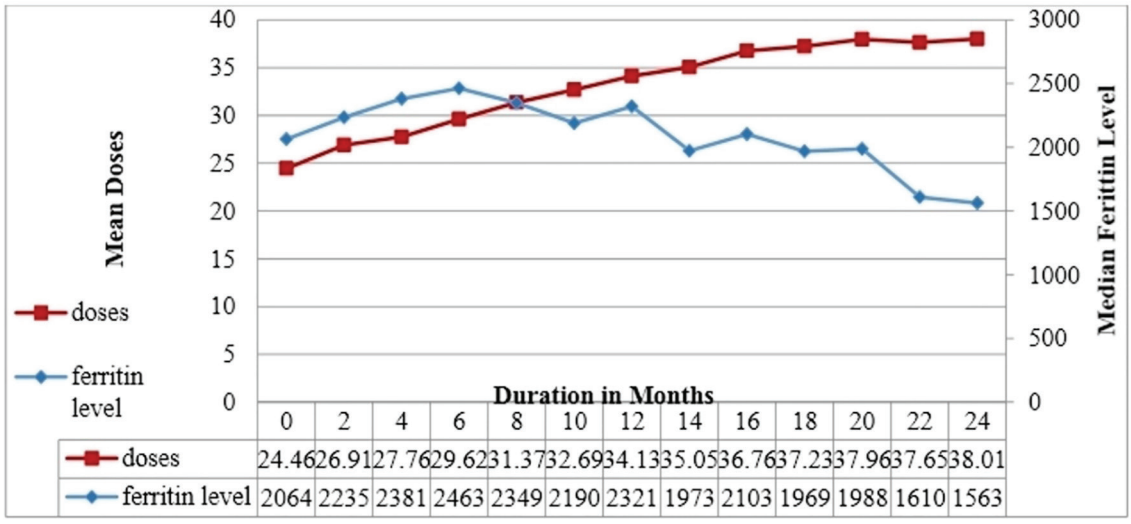

Figure 4: Relation between ferritin levels and Deferasirox dose escalation

2410.14±1288.17 ng/ml at baseline to 1847.85±1361.33 ng/ml at the end of the study (P=0.027). A decrease in SF was also observed for patients with SCD, from 2415.77±955.21 ng/ml at baseline to 1996.68±1255.01 ng/ml at the end of the study; however, the decrease in SF was not significant (P>0.05). After 2 years, 17 (18.2%) patients achieved at least once ferritin level less than 500 ng/ml who discontinued DFX treatment.

Discussion

The present study evaluated 64 pediatric patients with TDT and 29 with SCD, with a median age of 35 months at diagnosis, who received iron chelation therapy using DFX for at least two years and the results showed that Serum ferritin showed a steadily decreasing trend among patients over the study period in both TDT and SCD patients. Deferasirox dose adjustments were based on serum ferritin changes and safety markers (ALT, serum creatinine and clinical adverse events). The efficacy of DFX increased with increasing DFX dose to >30 mg/kg/day. Furthermore, daily iron loading had a significant impact on serum ferritin changes; at low level of transfusional iron intake, achievement of iron balance with DFX was significantly better than with intermediate and high iron intake.

Children ≥2 years of age with TDT may have severe iron overload as estimated by serum ferritin and LIC. Iron chelation is important for the treatment of iron overload and prevention of iron accumulation and iron-induced end organ complications (24).

Cappellini and colleagues, in a multicenter study, reported a significant decline in iron overload in pediatric patients on Deferasirox during 5 years of follow-up (25), which confirm the results of the present study. Efficacy and safety of Deferasirox has also been proved in other studies from Taiwan and India (26, 27). Vichinisky and co-workers reported that the median serum ferritin declined from 1,702 ng/ml at baseline to 1,127 ng/ml following 5 years of Deferasirox therapy in pediatric patients (aged 2-6 yrs) with TDT, SCD and other rare anemias (28). The results of the above-mentioned studies are consistent with that of ours and confirm the decreasing trend of serum ferritin in children receiving DFX. On the other hand, other studies report contrary results. In a study in Turkey, no significant absolute changes in serum ferritin were reported from baseline to the end of the study (median duration of the study 2.29 yrs) which contradicts the results of the present study; although they showed that daily iron loading and DFX doses had a major impact on serum ferritin changes (29) which is similar to the results of the present study. In another study in Oman, the researchers also reported a nonsignificant increase in serum ferritin in children with transfusion naïve thalassemia major in one year of Deferasirox therapy with lower doses of DFX (< 25 mg/kg/day) followed by achieving safe ferritin levels after increasing the dose (30).

The difference in serum ferritin decline between different studies can be attributed to difference in daily iron loading of studied patients, different drug dosages and the duration of follow-up.

As suggested in the present study, the efficacy of DFX increases with increasing dose to >30 mg/kg/day, which has been previously suggested as the effective dose for reduction of iron burden in TDT patients (31). In a recent study in Iraq, Basra, significant decrease in serum ferritin levels of patients with SCD was observed after increasing DFX dose to >30 mg/kg/day (32), which confirm the results of the present study on children. Therefore, the highest approved dose, 30 mg/kg/day, seems to be the most effective dose.

The second most important finding in the present study was the AEs. In the present study, Chelation therapy with Deferasirox was generally well tolerated the most common reported adverse events included GI complications, such as abdominal pain (transient, and mild to moderate) and non-progressive increase in serum creatinine. This was while we only had one case of skin rash. These results are in line with the results of the meta-analysis of studies that reported GI complications as the most common AEs of DFX (33). The predominance of GI adverse events

and low rate of discontinuation of the treatment with Deferasirox due to safety issues was in agreement with previous reports from four countries including Egypt, Jordan, Spain and UK (34). However, other studies have reported different frequencies for AEs of DFX. Cappellini and colleagues reported increased blood creatinine (11.2%), abdominal pain (9.0%), and nausea (7.4%) as the most common AEs of DFX in patients aged ≥2 years (25).

Skin rash was reported in 48.3% of TDT patients in another study, and GI complications was reported as the second most common AEs (abdominal pain in 38.3% and diarrhea in 26.7%) (26). The difference in the AE rates in the studies could be attributed to the different formulation and brands of DFX used in each study (35, 36).

The current study reported a transient increase in serum creatinine and ALT levels that did not require dose adjustments (except in one patient for raised ALT). Similar to other AEs of DFX, each study has reported a different frequency in this regard (19). Consistent with the results of our study, Antmen and co-workers showed a slight increase in serum creatinine levels, which remained within normal range in TDT and SCD patients aged 2-18 years (37). Nonetheless, another study showed fluctuations in liver enzymes and nonprogressive increase in serum creatinine as the most common AEs of DFX in transfusion-dependent children <5 years (29).

Also in a study in Pakistan, 69% of Pakistani children with β-thalassemia major on Deferasirox had abnormal ALT (38), while Soliman and colleagues in Qatar found a significant decrease in serum ALT among β-thalassemia major patients (with hepatitis negative screening) on DFX for four years (39).

None of our patients developed leucopenia, neutropenia or thrombocytopenia which was similar to that reported by Tony et al. in Oman (30). It seems that episodes of neutropenia and thrombocytopenia during treatment with Deferasirox have occurred in patients with preexisting hematologic disorders such as bone marrow failure and even the relationship of these episodes with Deferasirox may be uncertain (40, 41).

Another interesting finding in our study was that only one patient developed skin rash during the study period which was quite different from most other studies (11, 29, 40-42).

Pediatric linear growth continued among studied patients during the study period which was similar to the effects of Deferasirox in Italian and Turkish children with TDT (25, 29). Deferasirox did not impair the linear growth in SCD pediatric patients (32).

One of the limitations of the present study was the evaluation of the efficacy of Deferasirox only through measuring serum ferritin levels as it was the only available tool in our country.

Conclusion

Deferasirox is a safe and effective drug for reducing transfusional iron overload in pediatric patients with TDT and SCD. Most of the reported adverse events were transient and mild to moderate. Efficacy of Deferasirox can be improved with appropriate dose adjustment according to serum ferritin levels and safety markers.

Conflict of Interest: None declared.

References

1. Al-Allawi NA, Al-Dousky AA. Frequency of haemoglobinopathies at premarital health screening in Dohuk, Iraq: implications for a regional prevention programme. East Med Health J. 2010; 16(4):381–5.
2. Polus RK. Prevalence of hemoglobinopathies among marrying couples in Erbil Province of Iraq. Iraqi J Hematol 2017;6:90-3.
3. Alnakshabandi AA, Muhammad HA. Prevalence of β-Thalassemia carriers among a cohort of University students in Hawler Province of Iraqi Kurdistan. Iraqi J Pharm Sci. 2009; 18(2):15- 9.
4. Hassan MK, Taha JY, Al-Naama LM, Widad NM, Jasim SN. Frequency of haemoglobinopathies and glucose-6-phosphate dehydrogenase deficiency in Basra. East Med Health J. 2003; 9(1 and 2): 45-54.
5. Hashemieh M. Assessment of Organ Specific Iron Overload in Transfusion-dependent Thalassemia by Magnetic Resonance Imaging Techniques. Iranian Journal of Blood and Cancer. 2019;11(2):39-46.
6. Brittenham GM. Iron-chelating therapy for transfusional iron overload. N Engl J Med. 2011; 364: 146- 56.
7. Porter J, Viprakasit V. Iron overload and iron chelation. In: Capellini MD, Cohen A, Porter J, Taher A and Viprakasit V (eds.). TIF Guidelines for the Management of Transfusion Dependent Thalassemia (TDT) 3rd ed. Nicosia, Cyprus 2014: 42-89.
8. Saliba AN, Harb AR, Taher AT. Iron chelation therapy in transfusion-dependent thalassemia patients: current strategies and future directions. J Blood Med. 2015; 6: 198- 209.
9. Mishra AK, Tiwari A. Iron Overload in Beta Thalassemia Major and Intermedia Patients. Maedica (Buchar) 2013; 8(4): 328-32.
10. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood 2006; 107(9):3455- 62.
11. Vichinsky E, Bernaudin F, Forni GL, Gardner R, Hassell K, Heeney MM, et al. Long-term safety and efficacy of deferasirox (Exjade) for up to 5 years in transfusional iron-overloaded patients with sickle cell disease. Br J Haematol. 2011; 154(3): 387-97.
12. Taher A, El-Beshlawy A, Elalfy MS, Al Zir K, Daar S. Efficacy and safety of deferasirox, an oral iron chelator, in heavily iron-overloaded patients with β-thalassaemia: the ESCALATOR study. Eur J Haematol. 2009; 82(6): 458– 65.
13. Porter J, Garbowski M. Consequences and management of iron overload in sickle cell disease. Hematology Am Soc Hematol Educ Program 2013; 2013: 447- 56.
14. Berdoukas V, Chouliaras G, Moraitis P, Zannikos K, Berdoussi E, Ladis V. The efficacy of iron chelator regimes in reducing cardiac and hepatic

iron in patients with thalassaemia major: a clinical observational study. J Cardiov Magn Reson. 2009; 11:20. https://doi.org/10.1186/1532-429X-11-20.
15. Galanello R, Origa R. Beta – thalassemia. Orphanet J Rare Dis. 2010; 5: 11. DOI: 10.1186/1750-1172-5-11.
16. EXJADE (deferasirox) dispersible tablets: EU Summary of Product Characteristics. Novartis; September 2014 (/tools-and resources/ references. jsp#102).
17. Agarwal MB. Deferasirox. Oral, once daily iron chelator - an expert opinion. Indian J Pediatr. 2010; 77(2): 185- 91.
18. Cappellini MD, Porter J, El-Beshlawy A, Li CK, Seymour JF, Elalfy M, et al. Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. Haematologica | 2010; 95(4): 557 – 66.
19. Chaudhary P, Pullarkat V. Deferasirox: appraisal of safety and efficacy in long-term therapy. J Blood Med 2013; 4: 101- 10.
20. The WHO child growth standard 2006; (http://www.who.int/ childgrowth /en/) and (http://www.who.int/ growthref/en/) . Accessed 21/2/2016.
21. Moayeri H, Oloomi Z. Prevalence of growth and puberty failure with respect to growth hormone and gonadotropins secretion in Beta-Thalassemia Major. Arch Iran Med. 2006; 9: 329 – 34.
22. Trompeter S, Cohen A. Blood transfusion. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V (eds). Guidelines for the management of transfusion dependent thalassemia. 3rd ed. Nicosia, Cyprus. Thalassemia International Federation 2014: 34 - 5.
23. Cohen A, Glimm E and Porter J. Effect of transfusional iron overload intake on response to iron chelation therapy in β- thalassemia major. Blood 2008; 111(2):583- 7.
24. Aydinok Y, Kattamis A, Viprakasit V. Current approach to iron chelation in children. Br J Haematol. 2014; 165: 745–55.
25. Cappellini MD, Bejaoui M, Agaoglu L, Canatan D, Capra M, Cohen A, et al. Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. Blood 2011; 118(4):884 – 93.
26. Chang HH, Lu MY, Peng SS-F, Yang Y-L, Lin D-T, Jou S-T, et al. The long-term efficacy and tolerability of oral Deferasirox for patients with transfusion-dependent β-thalassemia in Taiwan. Ann Hematol. 2015; 94:1945–52.
27. Jaiswal S, Hishikar R, Khandwal O, Agarwal M, Joshi U, Halwai A, et al. Efficacy of Deferasirox as an Oral Iron Chelator in Paediatric Thalassaemia Patients. J Clin Diagn Res. 2017;11(2):FC01- 3.
28. Vichinsky E, El-Beshlawy A, Alzoebie A, Kamdem A, Koussa S, Chotsampancharoen T, et al. Long-term safety and efficacy of deferasirox in young pediatric patients with transfusional hemosiderosis: Results from a 5-year observational study (ENTRUST). Pediatr Blood Cancer 2017; 64. DOI: 10.1002/ pbc.26507.
29. Aydinok Y, Unal S, Oymak Y, Vergin C, Tu¨rker ZD, Yildiz D, et al. Observational study comparing long-term safety and efficacy of Deferasirox with Desferrioxamine therapy in chelation naïve children with transfusional iron overload. Eur J Haematol. 2012; 88:431-8.
30. Tony S, Al-Khabori MK, Saad, AA, Daar S, Zachariah M, Wali Y. Dose Optimization of Deferasirox in Chelation Naïve Children with Thalassemia Major. Blood 118:5294.
31. Taher A, Cappellini MD, Vichinsky E, Galanello R, Piga A, Tomasz Lawniczek T, et al. Efficacy and safety of deferasirox doses of >30 mg/kg per d in patients with transfusion-dependent anaemia and iron overload. Br J Haematol. 2009; 147: 752- 9.
32. Mohsin AM, Hassan MK. A 3-Year Study of Deferasirox Therapy in Sickle Cell Disease Patients in Basra, Southern Iraq. Niger J Clin Pract 2018; 21(6): 735- 42.
33. Dou H, Qin Y, Chen G, Zhao Y. Effectiveness and Safety of Deferasirox in Thalassemia with Iron Overload: A Meta-Analysis. Acta haematologica. 2019;141(1):32-42.
34. El-Beshlawy A, Inusa B, Pastor DB, Xicoy B, Nieto MSD, Bruederle A, et al. International sentinel site surveillance of patients with transfusional hemosiderosis treated with deferasirox in actual practice setting. Hematology 2019; 24(1): 238-46.
35. Taher AT, Origa R, Perrotta S, Kourakli A, Ruffo GB, Kattamis A, et al. New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or lower-risk MDS: Results of the randomized, phase II ECLIPSE study. American journal of hematology. 2017;92(5):420-8.
36. Eshghi P, Amin Asnafi A, Shamshiri A, Alavi S, Molavi M, Tamaddoni A, et al. The Comparison of Efficacy of Original Brand Deferoxamine with Generic Iranian Made Deferoxamine in Urinary Iron Excretion in Patients with Thalassemia Major. Iranian Journal of Blood and Cancer. 2017;9(4):108-11.
37. Antmen B, Karakaş Z, Yeşilipek MA, Küpesiz OA, Şaşmaz İ, Uygun V, et al. Deferasirox in children with transfusion-dependent thalassemia or sickle cell anemia: a large cohort real-life experience from Turkey (REACH-THEM). Eur. J. Haematol. 2018; 102: 123-30.
38. Ejaz MS, Baloch S, Arif F. Efficacy and adverse effects of oral chelating therapy (deferasirox) in multi-transfused Pakistani children with β-thalassemia major. Pak J Med Sci. 2015; 31(3):621-5.
39. Soliman A, Yassin M, Al Yafei F, Al-Naimi L, Almarri N, Sabt A, et al. Longitudinal Study on Liver Functions in Patients with Thalassemia Major before and after Deferasirox (DFX) Therapy. Mediterr J Hematol Infect Dis. 2014; 6(1): e2014025.
40. Pilo F, Di Tucci AA, Dessì L, Angelucci E. Management of Transfusional Chronic Iron Overload: Focus on Deferasirox. Clinical Medicine:

Therapeutics 2009; 1: 735- 45.
41. Vichinsky E. Clinical application of deferasirox: Practical patient management. Am J Hematol. 2008; 83:398–402.
42. El-Beshlawy A, Elalfy M, Chan L, Lai Y, Lin K, Aydinok Y, et al. Deferasirox Treatment for up to 3 Years in Iron-Overloaded Pediatric Patients Reduces Serum Ferritin with a Manageable Safety Profile. Blood 2012; 120(21):1028.