

## Original Article

# A 3-Year Study of Deferasirox Therapy in Sickle Cell Disease Patients in Basra, Southern Iraq

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ABSTRACT

**Background:** Patients with sickle cell disease (SCD) may require repeated transfusions, which inevitably lead to iron overload (IOL). **Aims:** This study aims to assess the effectiveness and safety of oral deferasirox (DFX) in patients with SCD and transfusional IOL. **Patients and Methods:** A descriptive study has been performed on patients with SCD who have completed at least 3 years on DFX. Height and weight were checked every 3–6 months. The efficacy was assessed based on serum ferritin (SF) levels. The safety was assessed based on adverse events (AEs), alanine aminotransferase (ALT), and serum creatinine (S. Cr) levels. **Results:** A total of 102 patients (61 males and 41 females) were recruited. Their mean daily iron intake was  $0.13 \pm 0.06$  mg/kg. SF levels declined significantly from  $2434.1 \pm 132.9$  ng/ml at the start of the study to  $1655.8 \pm 154.2$  ng/ml at the end of the study ( $P < 0.05$ ), with significant decreases observed after increasing the DFX dose to  $\geq 30$  mg/kg/day. ALT ( $12.8 \pm 9.9$  vs.  $12.1 \pm 7.1$  U/L) and S. Cr ( $72.4 \pm 9.2$  vs.  $74.1 \pm 7.9$  mmol/L) levels did not show significant differences from the start to the end of the study ( $P > 0.05$ ). Thirty-eight patients (37%) developed AEs. The most common were abdominal pain (24.5%), diarrhea (8.0%), and nausea (7.8%). AEs were predominantly transient and mild to moderate in nature. **Conclusions:** This study has revealed that DFX is a safe, tolerable, and effective drug for reducing IOL in SCD patients, though it is associated with mild and transient adverse events.

**KEYWORDS:** Basra, deferasirox, sickle cell disease

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## INTRODUCTION

Sickle cell disease (SCD) represents a major public health problem due to its associated morbidity and mortality. It is a multisystem disease that is associated with episodes of acute illness and progressive organ damage and is one of the most common monogenic disorders worldwide.<sup>[1]</sup>

Approximately 5% of the world's population carries trait genes for hemoglobin (Hb) disorders, mainly, SCD and thalassemia. Each year, approximately 300,000 infants are born with major hemoglobin disorders, including more than 200,000 cases of sickle cell anemia (SCA) in Africa.<sup>[2]</sup> It is also common in persons from Mediterranean countries, the Arabian Peninsula, and the Indian subcontinent.<sup>[3]</sup> In Middle Eastern Arab countries,

the frequency of carriers for Hb S ranges from <1% to 18.1%.<sup>[4]</sup>

In Basra in Southern Iraq, the overall prevalence of the sickle cell trait is 6.48%, with a gene frequency of 0.0324. The sickle cell gene is reported in all areas of Basra but with different frequencies in different governorate districts ranging from 2.3% to 8.1%.<sup>[5]</sup>

Improved care for patients with SCD has inevitably led to extended survival, and patients today have an average life expectancy ranging from 40 to

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50 years. This may be attributed to neonatal screening, vaccination and prophylactic antibiotics, the introduction of hydroxyurea (HU), early detection of cerebral vasculopathy using transcranial Doppler ultrasonography (TCD), improved healthcare facilities, and the effective management of complications.<sup>[6]</sup>

In contrast to many inherited anemias, iron overload (IOL) does not occur without blood transfusion in SCD. The rate of transfusional iron intake in SCD depends on the blood transfusion regimens; the rates are similar to thalassemia major (TM) with simple hypertransfusion regimes, though IOL can be minimal with automated erythrocyte apheresis.<sup>[7,8]</sup> In SCD, a lower proportion of transfused iron is extrahepatically distributed, and this occurs later than in TM; thus, IOL complications associated with the heart and endocrine system are less common.<sup>[7,9]</sup>

The gold standard for assessing liver iron stores in the absence of cirrhosis is the liver iron content (LIC), which is determined mainly by liver biopsy. Noninvasive blood tests (ferritin and iron saturation) and magnetic resonance imaging (MRI) methods have also been evaluated as predictors of LIC.<sup>[9,10]</sup>

Serum ferritin (SF) has been shown to correlate with LIC in TM, but the correlation in SCD is less clear because it has some particular limitations in SCD. Ferritin disproportionately increases compared to iron loading for several weeks after a vaso-occlusive sickle crisis (VOC) and may account for the highly variable correlation with LIC. If measured during steady state, SF shows a significant correlation with total transfused units by simple topup. However, aspects of this relationship are qualitatively and quantitatively nonlinear.<sup>[11-13]</sup>

In SCD, linearity exists up to SF values of <1500–2000 µg/L or LIC values up to 10 mg/g dry weight, but SF increases more slowly due to IOL above this level.<sup>[7]</sup>

Deferasirox (DFX) is an oral chelator that is given once daily as an oral suspension (in water or fruit juice). The efficacy and safety of DFX have been evaluated in patients with TM, thalassemia intermedia (TI), SCD, and myelodysplastic anemia.<sup>[14-16]</sup>

This study was performed to assess the effectiveness and safety of oral DFX in patients with SCD and secondary IOL in Basra.

## PATIENTS AND METHODS

### Patients

This descriptive study was performed on patients with SCD, homozygous cell anemia (SCA), and sickle/β thalassemia, who have attended the Center for Hereditary Blood Diseases (CHBD) for transfusional

IOL (SF >1000 ng/ml) and who have completed at least 3 years on DFX (from March 2010 to August 2014).

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

These patients' medical records were reviewed for the age, gender, SCD type, transfusion history, history of splenectomy, hepatitis B and C, and history of previous chelation therapy, mainly deferoxamine (DFO); its duration and dose.

The patients' records of transfused blood were reviewed to assess the transfusional iron intake including the volume of the administered units, the hematocrit of the units or the average hematocrit of units, and the patient's weight. The iron intake calculated as total amount of red blood cells transfused × 1.08. Then, the daily IOL was calculated (mg/kg/day).<sup>[17]</sup>

Patients were categorized into low, intermediate, and high transfusional iron intake groups.<sup>[18]</sup>

### Deferasirox therapy

This retrospective study was completed to assess the long-term safety and efficacy of DFX in patients with SCD. To assess the efficacy, we examined SF levels as we do not have facilities to assess IOL through MRI or LIC. To assess the safety, we collected clinical and biochemical data.

Patients with SCD and on DFX were followed at the CHBD monthly to assess the efficacy and safety of DFX.

The efficacy was assessed based on SF levels, and the DFX dose was reviewed every 3 months according to the SF levels.<sup>[19,20]</sup> The starting dose of DFX was determined according to number of blood transfusions and daily iron intake (loading).<sup>[17]</sup> SF measurements were taken when the patients were in steady state and had no history of blood transfusion for at least 2 weeks, history of infection, fever, and/or VOC.<sup>[21-23]</sup>

In our center, SCD patients with transfusional IOL are started on iron chelators when their SF reaches ≥1000 ng/l; we stop this therapy when SF levels are <1000 ng/l.<sup>[19]</sup>

The safety was assessed throughout the treatment based on the incidence and type of adverse events (AEs), serious AEs, and routine laboratory testing for alanine aminotransferase (ALT) and serum creatinine (S. Cr) levels.<sup>[19,20]</sup>

Growth measures (height and weight) were checked every 3–6 months;<sup>[19,20]</sup> the data for pediatric patients were plotted against WHO growth charts for normal children.<sup>[24]</sup>

Heights at the start of therapy and at the 3-year interval were assessed together with the corresponding normal values in terms of medians. The height-standard deviation score (h-SDS) of patients was calculated against the median for healthy children of the same age, and median change in h-SDS from baseline and after 3 years of DFX therapy was evaluated using the formula:

$$SDS = \frac{X - Y}{SD}$$

(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).<sup>[25]</sup>

Echocardiography was completed for each patient at the start of the therapy and followed up every 6–12 months.<sup>[20,26]</sup>

### Laboratory evaluation

Patients underwent the following investigations before starting DFX and during follow-up: (1) complete blood count (Hb, WBC, and platelet counts) using a hematological analyzer (Sysmex KX-21 N, 2006), Japan; (2) SF assessment at the start of the DFX treatment and every 3 months with a COBAS analyzer, Germany (kit 03737551 V 14); and (3) assessments for S. Cr and ALT and AST that were completed with a COBAS analyzer (kit c 111-05401755 01 04 and c 111-04718569 01 02, respectively).

### Statistical methods

All of the statistical analyses were performed using the Statistical Packages for Social Sciences (SPSS) software version 18 Chicago, IL, USA. The data are reported for all patients who received at least one dose of DFX during the 3-year study period, while the safety and efficacy of DFX were assessed for patients who completed the 3-year study period.

Comparisons of the proportions were performed with crosstabs using the Chi-square test when each cell had an expected frequency of five or more. The Fisher's exact test was used when one or more of cells have an expected frequency <5 in 2 × 2 table.

The S. Cr and ALT data were expressed as the mean ± SD, and while for SF, the values were expressed as mean ± standard error (SE). The statistical significance of the differences in the mean SF, serum creatinine, ALT levels, and h-SDS from the beginning of DFX treatment to the end of the study (EOS) was determined using the paired *t*-test.

For both S. Cr and ALT, we assessed the variability of the data; thus, we used the SD, while for the SF, we were

interested in the precision of the means and in comparing and testing differences between means; thus, the SE was used. *P* < 0.05 was considered to be statistically significant.

## RESULTS

### Patient characteristics

One hundred and twenty-nine patients on DFX were initially enrolled between March 2010 (first patient, first visit) and August 2014. One hundred and two patients had completed 3 years of DFX treatment; of the recruited patients, 61 (59.8%) were males, and 41 (40.2%) were females. Out of the 102 enrolled patients, 85 (83.3%) were ≤16 years of age and 24 (23.5%) were on HU [Table 1]. Twenty-two (21.5%) patients were positive for hepatitis C antibodies, and 10 have chronic hepatitis C, which was confirmed by PCR.

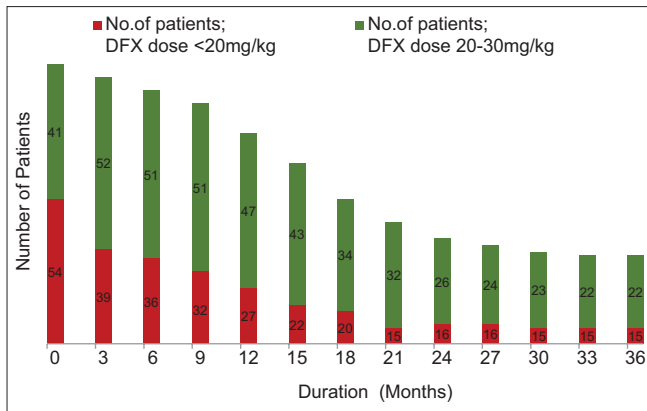
Seventy-nine patients were diagnosed with hemoglobin S/β thalassemia (74.5%), both sickle/β° thalassemia and sickle/β+ thalassemia, and the rest with hemoglobin SS. Twenty-two patients had a splenectomy.

Eighty-seven patients were on prior chelation therapy with subcutaneous DFO (30–42 mg/kg daily, 5 days/week).

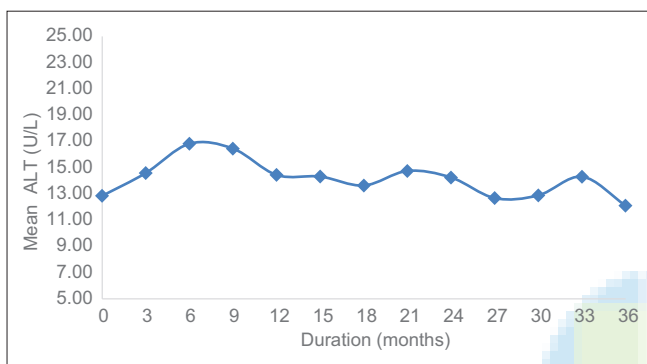
**Table 1: Selected demographics and clinical variables for the patients with sickle cell disease on deferasirox therapy**

Variable	n (%)
Age (years)	
<6	7 (6.8)
6-10	35 (34.3)
10-16	43 (42.2)
>16	17 (16.7)
Gender	
Male	61 (59.8)
Female	41 (40.2)
Type of SCD	
Sickle cell anemia	23 (22.5)
Sickle-β thalassemia	79 (77.5)
Splenectomy	
Yes	23 (22.5)
No	79 (77.5)
Hydroxyurea therapy	
Yes	24 (23.5)
No	78 (76.5)
HCV antibody positive	22 (21.6)
Prior chelation therapy (DFO)	87 (85)
Blood transfusion	
Range	10 50
Median	22
Daily iron load (mg/kg)	
Range	0.06-0.29
Mean±SD	0.13±0.06

SCD=Sickle cell disease; DFO=Deferoxamine; HCV=Hepatitis C virus; SD=Standard deviation



**Figure 1:** Distribution of patients in relation to deferasirox dose over the 3-year study period



**Figure 3:** Mean serum alanine aminotransferase levels of sickle cell disease patients over the 3-year study period of deferasirox therapy

### Transfusional iron intake

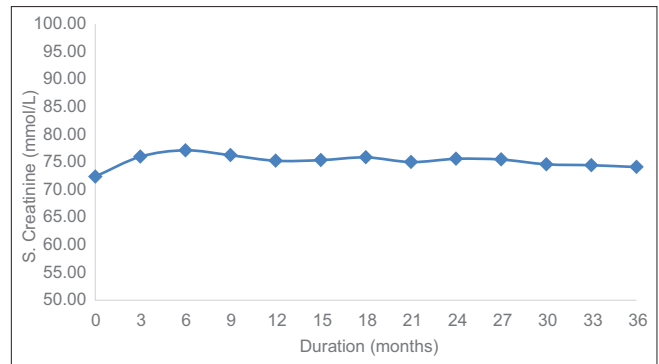
The number of blood transfusion varied from patient to patient, it ranged from 10 to 50 units, with a mean of  $4333 \pm 1907.7$  ml red blood cells during the 3-year study period, which is equivalent to a mean daily iron intake of  $0.13 \pm 0.06$  mg/kg depending on the hematocrit of the units or the average hematocrit of units of our blood bank if an individual hematocrit was missing or not available [Table 1].

Out of the 129 patients initially enrolled, 27 (20.9%) were excluded from the study; 6 (4.7%) because of poor compliance, 17 (13.2%) for loss of follow-up, 2 (1.5%) due to abnormal laboratory findings, and 2 (1.5%) for unsatisfactory therapeutic responses (indicated by rising SF despite increasing DFX dose to a maximum of 40 mg/kg).

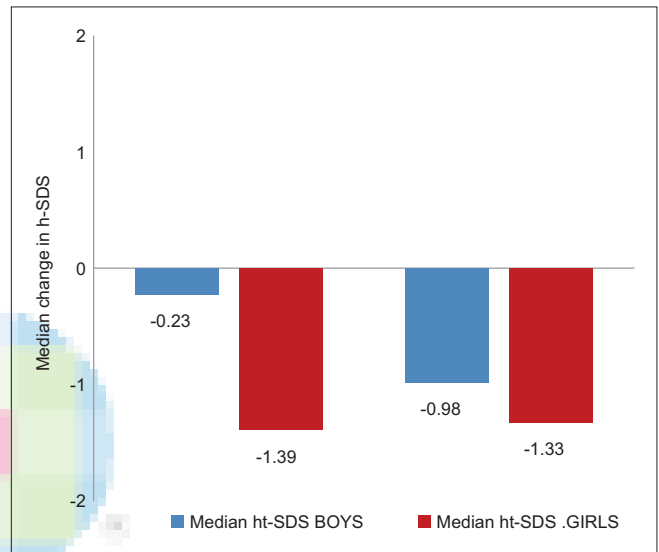
By the end of the 3-year study period, 31 (30.4%) patients had stopped DFX therapy because they had achieved their therapeutic goal (SF <1000 ng/ml).

### Exposure to treatment

Overall, 54 patients (52.9%) started on DFX doses of  $\leq 20$  mg/kg/day, 41 (40.2%)  $>20-30$  mg/kg/day, and 7 (6.9%) at  $\geq 30$  mg/kg/day; the mean DFX dose was  $23.1 \pm 4.7$  mg/



**Figure 2:** Mean serum creatinine levels of sickle cell disease patients over the 3-year study period of deferasirox therapy



**Figure 4:** Height standard deviation scores for the studied patients with sickle cell disease aged 2-16 years at the start and end of the study

kg/day at the start of the study. However, the DFX dose was gradually increased according to SF levels; thus, 3 years after starting therapy, 65 (63.7%) patients were on a DFX dose of  $\geq 30$  mg/kg/day, 22 (21.6%) between 20 and 30 mg/kg/day, and 15 (14.7%) at  $\leq 20$  mg/kg/day, with a mean DFX dose of  $30.4 \pm 7.3$  mg/kg, [Figure 1].

### Safety and tolerability

#### Adverse events

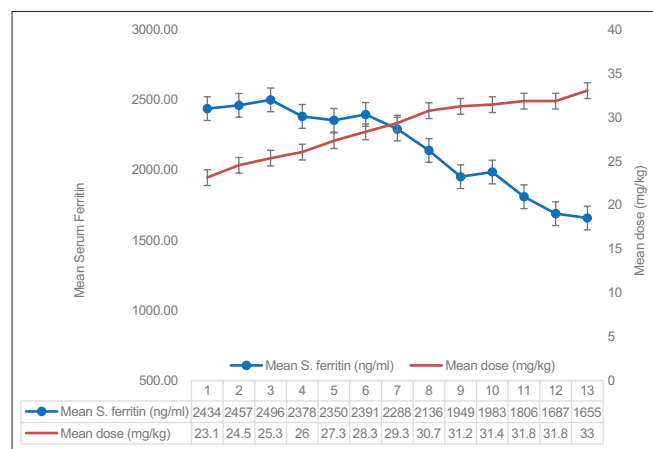
Thirty-eight patients (37%) developed AEs during DFX treatment. The most common DFX-related AEs were abdominal pain in 25 (24.5%), diarrhea 9 (8.0%), nausea 8 (7.8%), vomiting 4 (3.9%), rash 3 (2.9%), dyspepsia 4 (3.9%), and anorexia in 4 (3.9%).

The AEs were predominantly transient and mild to moderate in nature. Their incidence generally decreased after the 1<sup>st</sup> year of DFX treatment. Overall, the frequency of the AEs related to DFX was higher in patients receiving their first doses although there was no marked increase in AE frequency in patients treated with higher doses.

**Table 2: Selected biochemical parameters of studied patients with sickle cell disease**

Parameter	At baseline		At the end of study		P
	Median (range)	Mean±SD	Median (range)	Mean±SD	
ALT (U/L)	10 (4-54)	12.8±9.9	10 (7-19)	12.1±7.1	0.563
Serum creatinine (mmol/L)	70 (33-126)	72.4±9.2	74 (61-79)	74.1±7.9	0.180
Serum ferritin* (ng/ml)	2274 (954-12,000)	2434.1±132.9	1161 (379-1282)	1655.8±154.2	0.001

\*Mean±SE, P value was assessed by paired t-test. ALT=Alanine aminotransferase; SD=Standard deviation; SE=Standard error



**Figure 5:** Mean serum ferritin levels and the average deferasirox dose (mg/kg). Three monthly serum ferritin values were included

### Renal parameters

S. Cr levels remained stable during DFX treatment for up to 3 years, with no significant difference in the mean levels at starting DFX therapy and after the 3-year study period,  $P > 0.05$  [Figure 2 and Table 2]. This nonsignificant difference in the mean creatinine levels during the 3-year period of DFX therapy was observed among both types of SCD patients (SCA and sickle/ $\beta$  thalassemia). One patient (0.9%) reported an increase in S. Cr values greater than the upper limit of normal (ULN) and  $>33\%$  above their value at the start of DFX treatment on two consecutive visits during the study. S. Cr levels normalized in this patient following temporary interruptions in DFX treatment, and they went on to complete the therapy. This patient had history of chronic hepatitis C and was already on HU treatment.

### Hepatic parameters

No progressive increases in ALT levels were observed during long-term DFX treatment, for patients with both SCA and sickle/ $\beta$  thalassemia,  $P > 0.05$  [Table 2 and Figure 3]. Four patients (3.9%) had increased ALT values  $>40$  U/L on two consecutive assessments during DFX treatment. All of the patients had ALT levels  $>$  ULN before entering the study. Two patients (1.9%) had a history of chronic hepatitis C, though only one of them had temporary DFX treatment interruptions, and reassumed the treatment at the same dose after normalization of their values and went on to complete the therapy. The other patient with hepatitis

C and two other patients had transient increases  $>40$  but  $<100$  U/L, meaning that interference was not required.

### Other safety parameters

Thrombocytopenia which is defined as having a platelet count  $<100000/\text{mm}^3$  at two consecutive assessments after starting DFX was reported in 6 (5.8%) patients.

Four of these patients had hypersplenism, which ended by splenectomy, and two patients had transient thrombocytopenia. DFX therapy was stopped until platelets count became normal (2 weeks later), then DFX therapy resumed for the two patients without further complications.

Gastrointestinal hemorrhage was reported in one patient (0.9%). This event was resolved by medical intervention, and DFX treatment was temporarily interrupted during the event.

Rashes (of all types) were reported as AEs in 3 patients (2.9%); one patient had a temporary interruption in their DFX treatment.

### Pediatric growth and development

The differences in median heights for male and female patients with SCD aged 2–16 years were evaluated in comparison with WHO median standards. Our results show that for all males (2–16 years of age), the difference in the median h-SDS at the start of the study increased significantly from  $-0.23$  to  $-0.98$  at the EOS ( $P = 0.002$ ). However, there was no significant changes in the baseline median h-SDS for females from that at the EOS ( $-1.39$  and  $-1.33$ ), respectively,  $P > 0.05$  [Figure 4].

### Efficacy

Patients continued their regular transfusion regimens during the study, and the mean overall iron intake remained relatively stable, with most patients receiving  $<0.3$  mg/kg/day of iron during and up to 3 years of DFX treatment.

SF levels steadily decreased with DFX treatment for up to 3 years, with the largest decreases observed after the average DFX dose increased to  $\geq 30$  mg/kg/day [Figure 5].

Among patients who received DFX treatment for at least 1 year, mean SF levels decreased significantly from  $2434.1 \pm 132.9$  ng/ml at the start of DFX

treatment to  $2350.8 \pm 143.4$  ng/ml after 1 year of treatment,  $1949.1 \pm 165.7$  ng/ml at 2 years, and  $1655.8 \pm 154.2$  ng/ml at the EOS [Table 2].

The efficacy of DFX in decreasing SF was observed for both types of SCD. For patients with homozygous HbS, the SF declined significantly from  $2640.5 \pm 471.2$  ng/ml at baseline to  $1180.6 \pm 248$  ng/ml at the EOS,  $P = 0.019$ , and for patients with sickle/ $\beta$  thalassemia, a significant decrease in SF was also observed;  $2381 \pm 109.9$  ng/ml at baseline versus  $1780.2 \pm 180.2$  ng/ml at the EOS,  $P = 0.002$ .

DFX treatment was stopped in 31 patients because they reached their target SF levels. Their mean daily iron intake was  $0.12 \pm 0.03$  mg/kg, and 9 of them were adults (29%).

Concerning echocardiography, no significant difference was observed in the ejection fraction  $59.1 \pm 5.1\%$  at baseline versus  $59.3 \pm 5.4\%$  at the EOS,  $P = 0.806$ .

## DISCUSSION

The CHBD in Basra was established in 1998. It offers services for patients with hemoglobinopathies, Fanconi anemia, and hereditary bleeding disorders. DFX therapy began at the end of 2009 for all patients with transfusional IOL.

SF levels continued to decrease over the 3-year period with DFX treatment. Patients also continued their regular transfusion regimens during the study, with mean overall patient iron intake remaining relatively stable. Most patients received  $<0.3$  mg/kg/day of iron during the 3-year DFX treatment period. This result is similar to that reported by Vichinsky *et al.* in a multicenter study<sup>[27]</sup> and Agarwal in India.<sup>[28]</sup>

The increased efficacy of DFX by increasing the dose to  $\geq 30$  mg/kg/day is also consistent with previous reports that showed that DFX doses  $>30$  mg/kg/day have been found to effectively reduce IOL without increasing the incidence of AEs or worsening renal or liver functions.<sup>[15,29]</sup>

The majority of these AEs were mild in severity. The most frequently reported AE in this study are predominantly gastrointestinal, transient, and mild to moderate in nature. The frequency of these AEs was found to decrease as time progressed, suggesting that tolerability to DFX improves with long-term treatment.

Renal and liver functions were closely monitored throughout DFX therapy, especially with the relatively high frequency of hepatitis C antibody seropositivity in our patients. We did not observe progressive increases in S. Cr or liver transaminase levels during the 3-year

DFX treatment. This result is similar to that reported by Vichinsky *et al.* in two multicenter studies<sup>[27,30]</sup> and Cancado *et al.* in Brazil.<sup>[31]</sup> Furthermore, Brittenham GM<sup>[20]</sup> and Meerpohl *et al.*<sup>[32]</sup> mentioned similar observations in their review about the safety and efficacy of DFX in SCD. However, Tsouana *et al.* in the UK reported that 53% of patients with SCD developed reversible transaminases elevation (transaminitis), probably due to drug-induced hepatitis following DFX therapy.<sup>[33]</sup>

The mean difference in the median height for male patients with SCD at the start of the study increased significantly compared to the EOS, which indicates a progressive decline in height as patients become older.

The mean difference in the median height for male patients with SCD at the start of the study increased significantly compared to the EOS, which indicates a progressive decline in linear growth rate as patients become older. However, many studies on pediatric patients with SCD receiving DFX found a steady increase in weight in the height of both genders and that growth had proceeded normally in these patients.<sup>[27,34,35]</sup>

Although our findings differ from that of other studies concerning the effect of DFX on the growth of male pediatric SCD patients, these findings are consistent with that of other studies on SCD patients compared to healthy controls. Zemel *et al.* reported that 70% of the children's length/height Z score declined during a 4-year observational study on patients with SCA (mean age of  $9.1 \pm 4.7$  years) who were not receiving HU or other drugs that may affect growth and were free from other chronic illnesses. They also reported that boys were more likely to have growth failure than girls for all measures.<sup>[36]</sup> Rhodes *et al.* in the USA reported also that in males with SCA, growth in height declined over time, while females did not show significant change in height compared to control group.<sup>[37]</sup> However, in a recent study from Nigeria, Odetunde *et al.* found that all the anthropometric variables were comparable in patients with SCA and control group (both males and females) aged 6–20 years ( $P > 0.05$ ).<sup>[38]</sup>

The gender differences in linear growth can be attributed to the higher total energy expenditure in males, in addition to other hematological status including hemoglobin and hemoglobin F concentration.<sup>[36-39]</sup>

The current study has many limitations. First, we have only examined SF to monitor IOL, as other methods for assessing IOL are currently not available (LIC and MRI). This limitation is present in many developing countries and countries with limited resources. Despite this limitation, our results revealed a significant decrease in SF levels with DFX therapy. The other limitation is

that the sample size was small for assessing growth, particularly in relation to age groups. This made it difficult to explain the results, as growth failure in SCD patients is multifactorial.

## CONCLUSIONS

DFX is a safe and effective drug for reducing IOL in SCD patients although there are some mild and transient adverse events. Therefore, the findings from this study support the efficacy data for DFX for the treatment of SCD patients with IOL.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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