RESEARCH PAPER

Efficacy and Safety of Deferasirox for Reducing Total Body and Cardiac Iron in Thalassemia

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Objective: To assess the efficacy of deferasirox as an iron chelator, with specific reference to reducing cardiac iron overload.

Design: Prospective, open label, single arm study between 2008-2010.

Setup: Thalassemia center at a teaching hospital.

Participants: 30 multitransfused Thalassemia Major (TM) patients receiving deferasirox (DFX) therapy.

Methods: All patients had MRI T2*evaluation for cardiac iron load before starting DFX therapy. MRI T2* was performed on a 1.5 tesla Siemens sonata machine using thalassemia tools software and the ejection fraction measured using standard cardiac magnetic resonance sequence. Quantification of cardiac iron deposit was categorized into T2* <10 ms as high cardiac risk, 10-20 ms as intermediate risk, and >20 ms as low risk. We also estimated left ventricular ejection fraction (LVEF), end systolic volume (ESV) and end diastolic volume (EDV) using standard sequence. EF <56 % was considered to be significant cardiac dysfunction. DFX was administered in an initial dose of 20mg/kg/day and increased to a maximum of 35mg/kg/day. Serum ferritin level was estimated in pretransfusion samples at 1-3 monthly intervals. The primary end point of the study was change in serum ferritin level and cardiac MRI T2* value after 12-18 months therapy.

Results: Of the 30 patients, cardiac iron value of >20 ms was seen in 15 (50%), whereas 9 (30%) had 20-10 ms, and 6 (20%) had ≤10 ms. The mean serum ferritin pre DFX therapy of all cases was 3859.8 ± 1690.70 ng/mL (1066 – 6725 ng/mL) and mean cardiac T2* was 23.8±15.2 ms (6.24-69.2 ms). After 12 to 18 months of DFX therapy on a mean dose of 33 mg/kg/day, the mean serum ferritin was 2693.4 ±1831.5 ng/mL (drop by 30.2%, *P*<0.001) and mean cardiac T2* was 24.2±12.9 ms (increase of 1.6 %, *P*=0.87). Percentage change in cardiac iron was greater in high risk (24.8%) and intermediate risk (33.4%) patients than low risk patients (8.4%), though these values were not statistically significant. LVEF was 62.0 (±7.0%) before treatment and changed to 58.9 (± 4.8%) after 18 months of therapy but the values remained within normal range and this change was not significant (*P*=0.061). Adverse effect of DFX included diarrhea, maculopapular skin rash and transient proteinuria that necessitated temporary stoppage of medication.

Conclusion: Deferasirox monotherapy has a good safety profile and effectively chelates total body iron. It is also a good myocardial iron chelator, more efficacious in moderate to severe cardiac iron overloaded patients.

Key words: *Deferasirox, Iron, Chelation, Management, Thalassemia, Heart.*

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Desferoxamine (DFO), the first effectively utilized iron chelator produced a dramatic effect on survival of patients with thalassemia. However, DFO has poor oral bioavailability and a short half life, necessitating 12 hours of subcutaneous infusion, rendering therapy extremely cumbersome [1]. Deferiprone (DFP), an orally effective iron chelator, reduces total body iron load and is also effective in removing cardiac iron [1-3]. However, it has a short life and needs to be taken thrice daily, besides having troublesome side effects of arthralgia and neutropenia. Combination of DFO and DFP has proved to be more effective in reducing cardiac iron overload than DFO alone in clinical trials [4]. Deferasirox (DFX), a recently approved, effica-cious, safe, oral iron chelator has the advantage of a longer half life and hence requires once daily administration, leading to better compliance [5,6].

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Non-invasive quantification of myocardial iron can be done using cardiovascular magnetic resonance (CMR) by measuring myocardial T2*. MRI T2* is a measure of magnetic relaxation which is easier to measure than T2 and the extent of cardiac iron on MRI T2* provides useful insight into the severity of myocardial siderosis [7]. T2* gradient echo measures decay in signal intensity as the echo time of images progressively increases. This rate of decay is enhanced in presence of iron deposition.

Serum ferritin concentration is a convenient, non-expensive and the most widely used measure of assessing total body iron but is a poor predictor of cardiac iron status [8,9]. We prospectively assessed serum ferritin levels and myocardial T2* in an enrolled group of multi-transfused thalassemia patients to evaluate the efficiency of DFX as an iron chelator.

METHODS

This prospective single arm study was conducted between October 2008 and October 2010, on 30 multi-transfused thalassemic patients to monitor the effect of DFX on myocardial and total body iron load. To quantify change in cardiac iron load, myocardial T2* was measured at baseline and then after 12-18 months of DFX therapy, on a 1.5 Tesla Siemens Sonata machine. Though all chelating agents have a short half-life of less than a day, a washout period of a week was given before starting DFX to avoid any confounding. Patients were scanned using a single 8 mm thick, short axis mid ventricular slice, acquired at 8 different echo times. End systolic and diastolic ventricular volume and ejection fraction (EF) were measured using a standard reproducible CMR sequence as per published norms [10,11]. For T2* measurement we used the software CMRtools created by Imperial College and utilized the Argus software on the Siemens workstation for EF evaluation. Cardiac T2* value of <20 ms is indicative of iron overload as below this value there is progressive decline in the LV function. Values of <10ms are suggestive of severe cardiac siderosis [7,10,11]. EF of <56% was considered to be significant cardiac dysfunction and such patients were not included in this study as continuous DFO or combined DFO+DFP form the standard care for them [12]. All 30 patients studied were asymptomatic from cardiac prospective. The radiologists performing MRI T2* scan were blinded to the details of therapy of the patients.

Serum ferritin (SF) level was estimated by ELISA from pretransfused blood sample when the first MRI was done i.e. pre DFX therapy and subsequently every 3 months. Urine examination was done every month for albuminuria, serum creatinine and ALT levels were estimated monthly for the first 3-6 months, and subsequently every 3 months. All adverse events were documented. Patients were started on single dose DFX at 20-25 mg/kg/day given on an empty stomach in the morning and further dose escalation done to a maximum of 35 mg/kg/day. Dose reduction was done if any side effect was noted or if serum ferritin fell below 500 ng/mL. This study was conducted in accordance with Good Clinical Practice guidelines and was approved by the Hospital Ethical Committee. Informed consent was obtained from parents, guardian or patients themselves. The primary end point of the trial was to evaluate the difference in serum ferritin and cardiac MRI T2* after 12-18 months of DFX therapy as compared to baseline values. Data are presented as mean ± SD and variables analyzed by paired and unpaired *t*- test for statistical significance. P <0.05 was considered statistically significant.

RESULTS

There were 30 patients (22 males, 73.3%) receiving regular transfusion with a mean age of 15.7 ±6.8 years (range 6.5 to 29 years) and average weight of 34.2±12.5kg. The mean blood transfusion requirement was 219.4 mL/kg/year with a range of 180-260 mL/kg/year and median transfusion duration was 180 months (range 96-310 months). 6 patients (20%) had baseline T2* <10ms, 9 (30%) had T2* between 10 to 20 ms while 15 (50%) patients had T2* >20ms. All the patients were started on DFX 20mg/kg/day initially but due to non appreciable decline in serum ferritin, required upgradation to 30 mg/kg/day dose over next 6 month. Only 4 of our patients required 35 mg/kg/day dose for control of ferritin level. ***Table* I** shows the serum ferritin, cardiac iron load (as T2*) and cardiac functions before and after deferasirox therapy. ***Table* II** shows the mean and percentage change of T2* in various risk groups and their corresponding serum ferritin change (***Fig*.1**).

Significant decrease in serum ferritin also occurred in those with cardiac T2* <10 ms and between 10 to 20 ms

TABLE I CHANGE IN SERUM FERRITIN, CARDIAC IRON (T2*) AND CARDIAC FUNCTION PRE AND POST DEFERASIROX THERAPY

Parameter	Pre therapy Mean ± SD (range)	Post therapy Mean ± SD (range)	% change	*P* value
Serum ferritin (ng/mL)	3859.8 ± 1690.7 (1066 – 6725)	2693.4 ± 1831.5 (660-8702)	30.2	0.001
Cardiac T2* (ms)	23.8±15.2 (6.2- 69.2)	24.2 ± 12.9 (7.6-48.5)	1.6	0.870
Ejection fraction (%)	62.0 ±7.0	58.9 ± 4.8	4.9	0.061
End diastolic volume (mL)	84.9 ±31.8	108.2 ±42.0	27.5	0.001
End systolic volume (mL)	32.2 ±14.3	44.8 ±19.7	39.1	0.001

(P<0.05). In the subgroup of patients with cardiac T2* <10ms and between 10 to 20 ms, there was a greater improvement in cardiac iron overload with a 24.8 % and 33.4% increase in T2* value from the baseline, indicating greater reduction of cardiac iron overload in this group as compared to mildly iron overloaded patients who had 8.4% improvement in T2* (although both these value were not statistically significant).

DISCUSSION

The outcome of patients with cardiac siderosis cannot be predicted on the basis of serum ferritin as ferritin is not a suitable predictor of subclinical cardiac disease and cardiac decompensation can occur with serum ferritin level <2500 ng/mL [8,9]. This may be due to the fact that iron chelators (including deferasirox) remove iron from liver more rapidly than from the heart, and also the possible genetic variations of various cardiac ion transport channels [7]. Measurement of cardiac function by echocardiography is not accurate in predicting cardiac dysfunction as in thalassemia, cardiac function is supra normal and decline in systolic function is a late sign of cardiac siderosis**.** Once cardiac dysfunction occurs, there is high risk of death, unless chelation is dramatically intensified [13]. Cardiac T2* is the best predictor of congestive heart failure (CHF) and of arrhythmias in patients with cardiac siderosis. With T2* <6 ms, approximately 50% of patients develop CHF within 1 year. The cardiac T2* is also a good predictor of arrhythmia as well as of CHF as approximately 90% of CHF patients have T2* <10 ms whereas about 83% of patients with arrhythmia have cardiac T2*<20 ms [7,17,18].

In our study DFX not only decreased total body iron, *i.e.* decrease in serum ferritin, but also effectively chelated cardiac iron, particularly in children with T2* <10 ms. The current dose of DFX approved by most authorities is 30mg/kg/day [14,15]. Although the optimal dose for cardiac iron chelation has not been fully defined, FDA and other health authorities recently approved doses up to 40mg/kg/day in those patients whose cardiac iron overload is not controlled on standard recommended doses [8,15]. However, even with good compliance, some patients are known to respond poorly to DFX therapy due to decrease in drug bioavailability at higher dose [12].

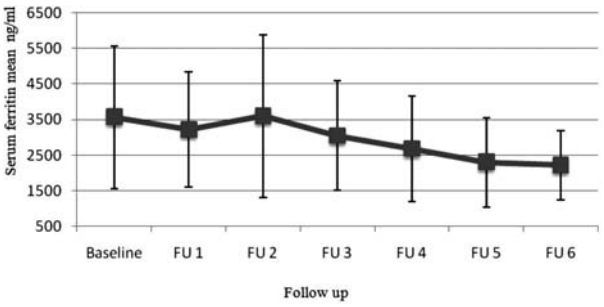

Fig. 1 *Mean value of serum ferritin on follow-up in patients treated with deferasirox.*

Although there was an improvement in cardiac T2* after 12-18 month of therapy, this was statistically not significant. This could be due to small sample size and the fact that we started DFX at 20mg/kg/dose initially and increased gradually up to max of 35mg/kg/day depending on the need and tolerance; hence the patient's exposure to optimum dose was short. A clear demarcation between the good responders (*i.e.* those with T2* <20 ms) and not so good responder was oberved. None of our patient with low risk *i.e.* T2*>20 ms progressed to moderate or high risk category (*i.e.* T2*<20 ms) indicating that deferasirox not only chelates the cardiac iron from iron overloaded myocardium but also prevents further cardiac siderosis by continuing to remove total body iron [2]. LVEF showed decline of 4.8% after therapy (P=0.061) but remained well within normal range. In thalassemia, EF is supranormal in the beginning due to anemia and hyperdynamic circulation which actually normalizes with transfusion therapy thereby explaining this apparent paradox. Increase in ESV and EDV value, which remained within normal range, can also be explained similarly.

Although the sample size of this study was small, observational bias was tempered as the radiologists reporting MRI T2* were blinded to therapy. This study sample size was not adequately powered to evaluate the

TABLE II CHANGE IN SERUM FERRITIN AND CARDIAC T2* BEFORE AND AFTER TREATMENT WITH DEFERASIROX (DFX)

Cardiac T2* (ms)	Pre treatment Mean ± SD	Post treatment Mean ± SD	Mean change and (% change)	*P* value	Serum Ferritin Pre treatment Mean± SD	Serum Ferritin Post treatment Mean± SD	Mean and (% change) after treatment	*P* value
<10ms (*n*=6)	8.3±1.3	10.4±2.8	2.1 (24.8%)	0.053	4568.8±1867.6	2402.0±354.5	1027.3 (22.5)	0.008
10-20ms (*n*=9)	14.5±3.5	19.3±8.3	4.8 (33.4%)	0.058	4271.1±1584.1	2505.8±1434.0	1765.3 (41.3)	0.0001
>20ms (*n*=15)	35.6±12.7	32.6±11.3	3.0 (8.4%)	0.493	3329.4±1617.4	2466.7±1823.9	862.7 (25.9)	0.002
Total (*n*=30)	23.8±15.2	24.2±12.9	0.4 (1.6%)	0.870	3859.8±1690.7	2693.4±183.4	1166.4 (30.2)	0.001

WHAT IS ALREADY KNOWN?

- Deferasirox is an effective total body and myocardial iron chelator.

WHAT THIS STUDY ADDS?

- Deferasirox is a safe and efficacious iron chelator in Indian population.

relationship between transfusion load and chelator response. The improvement in the cardiac iron load in our patients was associated with maintained EF/ESV/EDV within the normal range; hence we did not observe any significant improve-ment in overall cardiac function. Similar findings have also been reported by other researchers [2,3,8,14]. LVEF was maintained at approximately 67% in the EPIC sub study [19] and improved from 65.1% to 66.8% (P=0.0002) in one year reported by the ESCALATOR study [16].

Adverse events reported with DFX are generally mild and include mainly gastrointestinal disturbance and rash but 11-38% patients may have dose-dependent increase in serum creatinine, and 2% may have increase in liver transaminases [20]. In the present study, there were no significant adverse effects even after doses of DFX were escalated to >30 mg/kg/day. Two patients developed transient maculopapular rash, 2 developed diarrhea, while 3 developed transient albuminuria (+2). In all these patients, the problem disappeared when medications were temporarily stopped and did not recur on restarting therapy. Creatinine elevation was not seen in any case, although 6 patients (20%) had elevation of ALT twice above normal levels needing dose reduction. This indicates that DFX is well tolerated by Indian population.

Overall these initial observations are encouraging; however, long term multicentric studies with larger patients sample size will help contribute to better understanding of DFX therapy as an iron chelator. The goal of thalassemia therapy should be regular transfusion with optimum iron chelation in proper doses to maintain SF and cardiac iron level within the normal range. As iron chelation is needed for a life time, long term safety of any iron chelator is important and needs constant vigilance. Our results should serve as a benchmark for evaluating DFX chelation therapy in heavily iron overloaded Indian TM cases, using serum ferritin, cardiac T2* and safety profile measures for tailoring continued therapy.

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Contributors: RM conceptualized the study and was responsible for care of the patients, analyzing data and finalizing the script; JA entered and analyzed data, drafted manuscript; PK and BJ did radiological reporting of cardiac MRI and T2* and also contributed to final manuscript.

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