original research report

Cardiac events and cardiac T2* in Egyptian children and young adults with β-thalassemia major taking deferoxamine

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BACKGROUND AND OBJECTIVES: Cardiac events and death are not uncommon in adults with β-thalassemia (β-TM) taking deferoxamine (DFO) monotherapy because of poor compliance and possibly the less effectiveness of DFO in controlling cardiac iron overload. We sought to assess compliance with DFO, the percentage of shift to other iron chelators, and the occurrence of cardiac siderosis, and cardiac events and death in β-TM patients on DFO monotherapy.

DESIGN AND SETTING: Prospective, observational, 10-year follow-up of patients attending Ain Shams Thalassemia Unit, Cairo, Egypt.

METHODS: For all β-TM patients aged 2-18 years attending the unit during January 1998 and taking DFO, we recorded all cardiac events (whether fatal or not) during January 2008. All patients still on DFO monotherapy and with a normal EKG and not showing symptoms or signs suggestive of heart failure (HF) were evaluated for cardiac siderosis by T2*.

RESULTS: Of 412 patients, only 126 (31%) were still taking DFO monotherapy (only 43% of those were compliant), 136 were taking combined DFO and deferiprone (DFP), 72 were taking DFP and 32 were taking deferasirox (DFX). Twenty-one were lost follow-up and 25 died (10 cardiac). Eight of ten cardiac deaths and 12 of 15 non-cardiac deaths were in the DFO monotherapy group. Those taking DFO monotherapy with no HF and left ventricular ejection fraction (LVEF) by T2* >56% had a median age of 19 years and 56% were males; cardiac T2* was <20 ms in 30 (22%); 10-20 ms in 20 (14.7%) and <10 ms in 10 (7.3%). LVEF ranged from 58%-76 % (median 64%). Forty percent of T2* patients <10 ms were compliant with DFO.

CONCLUSION: Fifty-eight percent of patients on DFO monotherapy were noncompliant, but even compliance did not prevent severe cardiac siderosis and most cardiac events (whether fatal or not) that occurred in the DFO monotherapy group.

Iron chelation with DFO has dramatically improved the length of life for β-TM patients.[1] However, iron-mediated cardiac toxicity remains the leading cause of death in β-TM patients starting in the second decade and increasingly thereafter.[2] This high mortality in β-TM patients on DFO monotherapy results from a number of factors. Administration of DFO is uncomfortable and lengthy and there is poor compliance.[3-5] Subcutaneously administered DFO proved to be less effective in clearing cardiac iron loading compared with DFP.[6,7] Long-term outcome studies have correlated liver iron concentrations and high ferritin values with a subsequent risk of cardiac iron toxicity and considered these parameters as surrogates for cardiac risk.[8] However, despite monitoring of the iron burden by these indices, cardiac failure and arrhythmias remain the leading cause of death in β-TM patients. Cardiac MRI measurements of the iron-sensitive relaxation time (T2*) show promise for identifying patients with preclinical myocardial iron overload.[9] The value of liver iron concentration and serum ferritin as predictors of cardiac siderosis are questionable,[10] while the value of cardiac T2* to tailor chelation is well established.[11] The aim of this prospective study was to record compliance of Egyptian β-TM children and adults on DFO monotherapy over the last decade and collect information on

the shift to other chelators, the occurrence of cardiac events and death over this period and to assess the degree of cardiac siderosis in β-TM patients with no heart failure who were still on DFO monotherapy.

PATIENTS AND METHODS

DFO therapy in β-TM patients was first introduced at the Ain Shams Thalassemia Unit in 1982, and β-TM patients have started DFO at the age of 2 to 3 years. All patients aged 2-18 years (n=412) attending two centers—the Ain Shams Thalassemia Unit (n=392) and the Zagazig Center (n=20)—were followed up prospectively from 1998 for one decade to assess compliance with DFO monotherapy and to determine the percentage of those who shifted to other chelators. All cardiac events, whether fatal or not, were also recorded. Chelation therapy consisted of deferoxamine used in a dose 20-40 mg/kg via a subcutaneous pump overnight. Compliance was considered good if DFO was received 5-6 days/week (>250 days/year), only compliant if 3-<5 days/week (150-<250 days/year), and poor if <3 days/week (<150 days/year) or irregular (<50 days/year). Deferiprone (DFP) was introduced in 2002 orally in a dose 75-100 mg/kg/day, 7 days/week. The same doses were used in combination therapy (DFP 7 days/week ±2-3 days DFO). Intensive combination therapy was DFP 100 mg/kg/d for 7 days/week and DFO 50 mg/kg/d 5-6 days/week. Deferasirox (DFX) was introduced in 2005 as a single morning oral dose 20-30 mg/kg/day, 7 days/week.

In January 2008, all β-TM patients still taking DFO monotherapy and not showing symptoms or signs suggestive of heart failure and whose echocardiogram showed LVEF >56% were evaluated for cardiac siderosis by cardiac T2* at Cairo MRI Center and interpreted at the Royal Brompton Hospital, London, UK, and liver iron (R2) performed at Misr MRI Center and interpreted at University of Western Australia, Crawley, Western Australia. Cardiac T2* and liver R2* data from the first scan for each patient are presented. Serum ferritin was assessed every 6 months and the mean values of the last 2 years were included.

Diagnostic criteria included in the evaluation were:

- Heart failure: Dyspnea on rest or exercise and or LVEF <56% by T2*
- Arrhythmia: Complaint of palpitation and a standard 12–lead ECG with 24-hour recording showing evidence of arrhythmia
- Nonfatal event: Nonfatal heart failure or arrhythmia.
- Magnetic resonance: One and half T scanner

Table 1. Demographic data for deferoxamine subgroups by values of cardiac T2*.

Total	T2* <10ms (n=10)	T2* 10-20ms (n=21)	T2* >20ms (n=95)	P1	P2	P3
Age (years)						
Range	13-21	15-30	12-28	**.0932**	.1462	.1170
Mean±SD	20.3±17.3	20.6±4.4	19.2±3.8			
Male (n)	6	11	60	.69	.69	.69
Female (n)	4	10	35			
LVEF (%)						
Range	58 – 73	60-76	58-79	.3004	.6026	.4323
Mean±SD	66.2 ± 7.9	68 ±4.6	67.4±4.8			
Liver iron concentration (mg/g)						
Range	9.8-52	12.9-59.7	5-54	.5612	**.0165**	.3027
Mean±SD	29.4±12.6	32.6±14.7	11.9±25.3			
Serum ferritin (ng/mL)						
Range	2343-9545	2139-9022	924- 9875	.5461	.1923	.0755
Mean±SD	4577±2253.6	4116.6±1815.3	3613.4±1539.3			

P1: The two-tailed *P* value of T2*<10ms versus T2*10-20ms
P2: The two-tailed *P* value of T2*10-20ms versusT2* >20ms
P3: The two-tailed *P* value of T2*<10ms versus T2* >20ms
Significant values bolded

Siemens scanner using the standard technique

- Cardiac T2*: Cardiaegated, single-breath-hold, 8-echo sequence of a single midventricular short axis slice, and data analysis was performed using CMR tools and its plug-in in thalassemia tools
- Liver SDPA R2* (FerriScan)

Excluded from the study were β-TM patients not on DFO chelation until after the age 4 years and patients missed for follow up for more than 6 months during the study period of 10 years. Those on combination therapy and those on DFO monotherapy, but with LVEF <56% as assessed by T2* echocardiogram when evaluated for cardiac siderosis were excluded. All β-TM patients with T2* <10 milliseconds were shifted to combination DFP and DFO and those <6 milliseconds received intensive combination chelation therapy.

SPSS for Windows, release 13.0 (SPSS Inc, USA) was used for data entry and analysis. All numeric variables were expressed as mean and standard deviation (SD). A comparison of different variables in various groups was done using the t test and Mann Whitney test for normal and nonparametric variables respectively. The chi-square test was used to compare frequency of qualitative variables among the different groups. The Spearman correlation test was used for correlating non-parametric variables. For all tests a probability. Less than 0.05 was considered significant.[13]

RESULTS

There were no differences in sex, age and serum ferritin by T2* level (<10, 10-20 and >20 milliseconds) (**Table 1**). Only liver iron concentration (LIC) was significantly higher in the T2* 10-20 milliseconds group, but there was a lack of correlation between LIC and cardiac siderosis as evidenced by cardiac T2* and liver R2* (**Figure 1**). Unexpectedly, LVEF was not different in the three T2* subgroups, and there was no correlation between LVEF and cardiac siderosis (**Figure 2**). Only 18 patients had good compliance and 36 were compliant (included together as the compliant group (n=54, 43%), whereas poor compliance was observed in 44 (35%) and the least compliant was the irregular group (n=28, 22%). Thirty percent of patients with T2* <10 milliseconds were either in good compliance (10%) or compliant (20%) on DFO where as 30% of patients with T2* 10-20 milliseconds were either in good compliance (10%) or compliant (20%) on DFO. Differences in iron overload (serum ferritin, LIC) were highly significant in the different compliance groups (**Table 2**). The greatest difference was in the irregular group, which showed the heaviest iron overload, while T2* was longest in the compliant groups, but the difference was statistically insignificant; unexpectedly LVEF was not significantly different in the three compliance groups; it was highest in the patients on irregular DFO, but the difference was not statistically significant.

DISCUSSION

Since DFO was licensed in Egypt in 1982, a new era of thalassemia management began in our center. However, compliance after a few years was declining, with a good percentage noncompliant or irregular. About two decades later DFP was licensed in Egypt in 2000. A good percentage of β-TM patients shifted to the newly introduced oral chelator, but after publication of results of

Table 2. Age, iron overload and LVEF by deferoxamine compliance.

	Good compliance and compliant (n=54)	Poor compliance (n=44)	Irregular compliance (n=28)	P1	P2	P3
Age (years) mean±SD	19.4±3.2	18.9±4.1	19.3±4.1	.4994	.6878	.9035
T2* (ms) mean±SD	28.9±11.3	25.3±9.8	26.1±10.9	.0994	.7475	.2848
LVEF (%) mean±SD	67.1±4.8	66.3±5.5	68.7±4.7	.4440	.0606	.1534
Liver iron concentration (mg/g) mean±SD	17.1±7.6	31.2±8.7	37.6±11.2	.0001	.0077	.0001
Serum ferritin (ngml) mean±SD	3080.6±890.8	3750.9±.1367.8	5114.3±2144.2	.0043	.0015	.0001

P1: The two-tailed P value for compliant versus poor compliance
P2: The two-tailed P value for poor compliance versus irregular compliance
P3: The two-tailed P value of compliant versus irregular compliance
Significant values bolded

better chelation with combination therapy, more patients shifted to combination therapy. In 2005, DFX was introduced to our patients and some patients shifted to the newer iron oral chelator.

In this prospective study, after a decade of follow up, slightly less than 1/3 of the studied patients were still on DFO monotherapy, even though it is cheaper and there is more experience with it. Another one-third of this cohort shifted to combination (DFO and DFP) and almost one-third shifted to either DFP or DFX monotherapy. However, most of them (58%) taking DFO were either noncompliant or using irregularly because of its uncomfortable, painful administration by lengthy subcutaneous pump infusion.

Contrary to most reports,[12,14] heavy liver iron overload occurred in most of our patients taking DFO monotherapy, and almost 60% of the patients were poorly compliant or irregularly compliant therapy and LICs were significantly higher. Even compliant patients appeared to have high median LIC (>14 mg/g), which is toxic to the liver. Patients who were in good compliance to DFO treatment had the best LIC; however, none had an LIC <2mg/g and only 20% had an LIC between 2-7 mg/g. There was also a lack of correlation between cardiac siderosis and LIC.

The three available iron chelators have a different mode of action, efficacy and route of administration. Dosage and compliance are essential for optimum chelation. The recommended initial dose for DFX was 20 mg/kg/day for patients receiving 2 packed red blood cell units/month and 10 or 30 mg/kg/day was recommended for patients receiving less or more frequent transfusions, respectively,[15] while DFP was used in a dose of 75-100 mg/kg. According to the degree of hemosiderosis, DFO was used in a dose 20-40 mg/kg/dose, using the subcutaneous pump overnight. Most patients in this study were following the same doses, while those with suboptimal chelation, increased transfusional requirements, or who had initiated transfusions earlier in life should be tested more frequently and have more intensive chelation.[16]

Over the decade, both cardiac events and death[2, 12,15] were commoner in the DFO monotherapy group compared to the DFP group. In this prospective study, most cardiac events and death were recorded in the DFO monotherapy group, which may be explained by poor clearance of iron from the heart in patients with severe cardiac siderosis. Severe cardiac siderosis cannot be corrected easily by subcutaneous DFO infusion. Cardiac T2* magnetic resonance identifies patients at high risk of heart failure and arrhythmia from myocardial siderosis in thalassemia major and is superior to serum ferritin and LIC. Using cardiac T2* for the early identification and

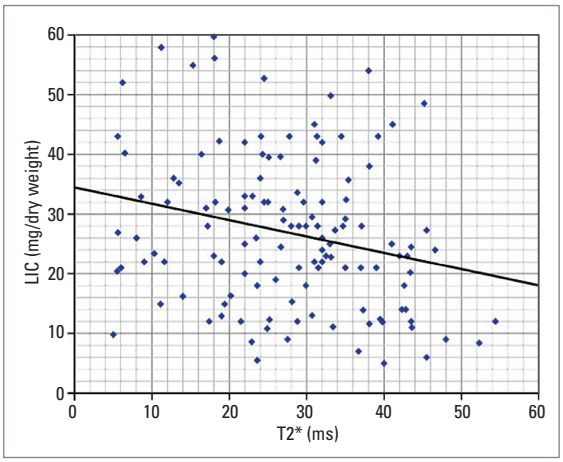

Figure 1. Lack of correlation between T2* and liver iron concentration (r=0.23, *P*>.05).

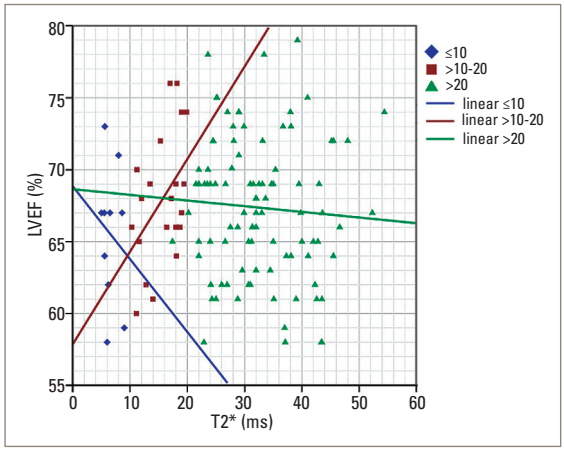

Figure 2. No significant correlation between LVEF and T2* ≤10 ms (r=0.15), >10-20 ms (r= 0.42), ≥20 ms (r=-0.92).

treatment of patients at risk is a logical means of reducing the high burden of cardiac mortality in myocardial siderosis. Since 1999, there has been a marked improvement in survival in thalassaemia major in the UK, which has been mainly driven by a reduction in deaths due to cardiac iron overload. The most likely causes for this include the introduction of T2* CMR to identify myocardial siderosis and appropriate intensification of iron chelation treatment, alongside other improvements.[18]

Cardiac and endocrine disorders are common sequelae of iron overload in transfused thalassaemia patients. Combined chelation with DFO and DFP is well tolerated and produces an additive/synergistic effect superior to either drug alone.[19] Patients on combination therapy were less affected by cardiac problems.

This prospective study showed that in the cohort

on DFO monotherapy with no evidence of heart failure (their upper age limit was less than 30 years with a median of 19 years), less than one-third had cardiac T2* <20 milliseconds and 37.5% were compliant with DFO monotherapy. One-third of those with cardiac siderosis had T2*<10 milliseconds, which indicates moderately severe siderosis. Serum ferritin and LIC were higher in β-TM with T2* <20 milliseconds, but there was no correlation between these variables. Tanner et al showed a prevalence of myocardial iron overload (T2*<20 milliseconds) in 65% of thalassemia major in an age group ranging from (18-42 years, mean=30±5.3).[20] In contrast to our study, only 28.9% were < 20 milliseconds, which may be attributed to the younger age group of median age 10 years and the inclusion of patients with compensated heart.

As determined by T2*, LVEF was not different in the three groups (T2* <10, 10-<20 and ≥ 20 milliseconds). However, since all enrolled patients had LVEF >56% as checked by ECHO (data not shown), nonsignificant differences were expected. Patients with T2*<10 milliseconds were considered to have severe iron overload and this category included most patients with nonsignificantly reduced LVEF.

The availability of two oral chelators, DFP and DFX, has reduced the need for the injectable chelator DFO and an additional benefit has been that DFP has been shown to be more cardioprotective than DFO.[21,22] Recently, alternate daily DFP and DFX was introduced.[23] In another study, satisfaction was significantly better with DFX compared to DFO.[24]

Author Contributions

Mohsen Elalfy are main investigators at Ain Shams University, Iman Abdin is subinvestigator at Ain Shams University, Usama El Safy is main investigator of Zagazig University, Fatma S. Ebeid is investigator Ain Shams University, Ahmed S. Ibrahim-Radiology, Doria Salem-Radiology

Conflict of interest

None declared.

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