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ORIGINAL ARTICLE

Cardiac iron removal and functional cardiac improvement by different iron chelation regimens in thalassemia major patients

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Abstract Heart failure due to myocardial iron overload remains the leading cause of morbidity and mortality in adult thalassemia major (TM) patients. We evaluated the removal of cardiac iron and the changes of cardiac function by different iron chelation in TM patients by T2* cardiac magnetic resonance (CMR). Sixty-seven TM patients (27 males/40 females; mean age, 35±6 years) on different chelation regimens underwent T2* CMR at baseline (t_0), after 6–14 months (t_1) and after 32±7 months (t_2). Patients were divided in four groups according to chelation treatment: group A (deferasirox), group B (deferoxamine), group C (combined treatment, deferoxamine plus deferiprone) and group D (deferiprone alone). Myocardial T2* at t_0 was <10 ms in 8 patients, between 10 and 20 ms in 22 patients and ≥20 ms in 37 patients. Progressive changes in T2* were observed at t_1 and t_2. Ten patients (10/36, 27.8 %) in group A, three patients (3/15, 20 %) in group B and three patients (3/12, 25 %) in group C moved from an abnormal T2* to normal values. We observed an improvement of left ventricular ejection fraction and a reduction of end-systolic and end-diastolic left ventricular volumes only in patients in group A with baseline cardiac T2* between 10 and 20 ms. Rigorous compliance to any chelation therapy at proper doses significantly improve myocardial T2*. Treatment with deferasirox significantly improves left ventricular function. Combination therapy seems to ameliorate cardiac T2* in a shorter period of time in severe siderosis.

Keywords Thalassemia major · Myocardial siderosis · Chelation therapy · Cardiac magnetic resonance T2* · Cardiac function

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Introduction

Heart failure due to myocardial iron overload still remains the leading cause of morbidity and mortality in adult transfusion-dependent beta-thalassemia major (TM) patients [1]. Iron chelation therapy with deferoxamine (DFO) has markedly improved the survival and life expectancy of these patients despite several limitations resulting in poor compliance to treatment [2, 3]. These limitation leads to the need of understanding the underlying mechanisms of iron overload organ damage and to develop new iron chelating agents and iron chelation regimen. Deferiprone (DFP), an oral chelator, administered three times daily, has been shown to be more efficacious than deferoxamine in removing myocardial iron [4]; however, its use is still limited due to the risk of adverse events as neutropenia or agranulocytosis [5]. The recently approved once-daily oral chelator deferasirox (DFX) has improved patient compliance, and in large clinical trials, it

has been shown to remove iron from the liver and from the heart [6–8]. Ferritin levels and liver iron concentration (LIC), although used as good indicators of body iron load, are insufficient to estimate myocardial iron accumulation. T2* cardiovascular magnetic resonance (CMR) is a noninvasive technique that provides rapid and direct assessment of myocardial iron content and its usefulness in monitoring iron chelation has been extensively proved [9]. The T2* relaxation values have been widely evaluated and validated, showing good reproducibility both between scanners and assessment sites [10]. CMR permits also to evaluate cardiac functional parameters such as ventricular function and morphology [9]. At present, this technique represents the gold standard to evaluate myocardial iron overload, ventricular dysfunction and efficacy of the iron chelation therapy over time. Based on T2* values, the risk of cardiac heart failure can be estimated prompting to intensify chelation therapy if necessary [11].

The usefulness of deferiprone in treating myocardial iron loading has been reported in several studies and combination treatment with DFP/DFO in severe myocardial iron overload (T2*<10 ms) is advisable [12]. More recently, the efficacy of deferasirox in removing iron from the heart with amelioration of CMR T2* values has been well documented [13, 14]. The effectiveness and the comparison of the three available iron chelators on cardiac iron removal are still missing. Only a recent paper compared retrospectively the three compounds in 115 thalassemia major patients [15]. Therefore, the aim of our study was to evaluate retrospectively the efficacy of different iron chelation therapies including combination of DFO plus DFP not only on the removal of the myocardial iron content but also on left ventricular ejection fraction (LVEF) and on ventricular volumes, assessed by CMR along 3 years in a cohort of adult TM patients, attending a single tertiary thalassemia care centre.

Patients and methods

Study population

Sixty-seven beta-thalassemia major patients (27 males/40 females, mean age 35±6 years) followed up at the Hereditary Anemia Centre in Milan were included in this observational study. They were treated with different iron chelators and they underwent repeated cardiac CMR to assess myocardial iron load as part of their routine follow-up according to international recommendations [16]. Patients were divided based on their chelation therapy in four groups: group A (n=36, 53.7 %)—patients chelated with DFX (mean actual dose 27±7 mg/kg/die), group B (n=15, 22.4 %)—DFO (mean actual dose 48±9 mg/kg for a median of 6 days/week), group C (n=12, 17.9 %)—DFO plus deferiprone (DFO mean actual dose 46±7 mg/kg for a median of 4 days/week, DFP mean actual dose 73±7 mg/kg/day) and group D (n=4, 6 %)—DFP alone (mean actual dose 75±3 mg/kg/day). The evaluated patients had to be chelated with the same iron chelation therapy at least for 1 year before the baseline CMR evaluation. All data were collected during their regular follow-up. A written informed consent to use clinical data was obtained from each patient. The study was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki.

Assessment of myocardial T2* and cardiac function by CMR

Myocardial T2* was assessed at baseline (t_0), after 6–14 months (t_1) (according to clinical conditions and to T2* at baseline) and as second control (t_2) after a mean of 32±7 months from baseline. CMR was performed at the CMR Unit Department of Cardiology "A. De Gasperis" at Niguarda Ca' Granda Hospital in Milan, using a 1.5-T MR scanner (Avanto Siemens, Erlangen). All T2* images were analysed using a postprocessing software (CMR Tools, Imperial College, London). Myocardial T2* was assessed with the use of a gated gradient-echo sequence with flip angle of 20°. A single 10-mm-thick short axis mid-ventricular slice of the left ventricle (LV) was acquired at eight echo times (2.6 to 16.74 ms with 2.02 ms increments) with standard shimming with a single breath-hold. For analysis, a full-thickness region of interest was chosen in the LV septum. CMR evaluation was performed blind to patients' clinical data and the calculation was performed by a single operator. Normal cardiac T2* was defined >20 ms; T2* <10 ms indicated severe cardiac siderosis and T2* between 10 and 20 ms moderate-to-mild cardiac siderosis). Ventricular volumes were determined with the use of steady-state free precession cines, with contiguous short axis slices of 7 mm from base to apex with a 3-mm interslice gap. Typical parameters of acquisition were the following: bandwidth=977 Hz/pixel, base matrix=128 (phase encoding steps) × 256 (read-out points), TE=1.55 ms, TR (assuming R–R interval of 1,000 ms)=46.35 ms, FOV (read/phase)=300–400 mm, slice thickness=7 mm, triggering=ECG/retro, views per segment=15 and calculated phases ≥20. Cines have been acquired in end-expiration breath-hold. Patients have been examined in supine position by using a phased-array coil for signal detection using a single frame scouts to localise the heart within the thorax. Following the vertical long axis (VLA) and horizontal long axis (HLA) acquisition, eight short axis (SA) perpendicular to the HLA have been obtained. The cine 4 chamber view has been obtained by lining up the mid-ventricular SA scout through the acute angle between the anterior and diaphragmatic wall of the right ventricle and through the anterior papillary muscle of the left ventricle. The cine 2 chamber (2 CH) view has been

obtained by lining up the 4 CH view through the centre of the mitral valve and through the apex. The left ventricular outflow tract view has been obtained by lining up the scan SA plane through the centre of the outflow tract and through the apex. The first short axis cine has been placed using the end-diastolic frame of the 4 CH and 2 CH cine views, on the line joining the basal portion of the left and right ventricle. Successive cines are then acquired moving towards the apex and including apical tip. Ventricular volumes were analysed with the use of a commercial software (CMRtools, Cardiovascular Imaging Solutions, London, UK), and stroke volume and ejection fraction have been calculated from end-diastolic and end-systolic ventricular volumes.

Statistical analysis

Statistical analysis was performed using Student's *t* test. Data are presented as mean ± standard deviation (SD) except for ferritin levels that are presented as median with range in brackets. A *p* value of 0.05 (confidence interval 95 %, double-tailed) was the threshold used for statistical significance.

Results

Patients' characteristics

Overall, the characteristics at baseline of 67 TM patients treated with the different iron chelators are shown in Table 1.

Table 1 Patients' characteristics at baseline

	All patients (*n*=67)
Mean age ± SD, years	35±6
Male/female, *n*	27:40
Race (Caucasian/oriental/other), *n*	67:0:0
Mean pre-transfusional hemoglobin ± SD, g/dl	9.7±0.5
Mean iron intake (mg/kg/day)	0.41±0.12
Median serum ferritin, ng/ml	913 (229–5934)
History of hepatitis B and/or C, *n* (%)[a]	56 (83.6)[a]
Splenectomy, *n* (%)	23 (34.3)
Diabetes, *n* (%)	12 (17.9)
Hypothyroidism, *n* (%)	15 (22.4)
Hypogonadism, *n* (%)	58 (86.6)
History of heart failure, *n* (%)	8 (11.9)
History of relevant arrhythmias, *n* (%)	5 (7.5)
Cardiac T2* under 10 ms at t_0, *n* (%)	8 (11.9)
Cardiac T2* between 10 and 20 ms at t_0, *n* (%)	22 (32.8)
Cardiac T2* above 20 ms at t_0, *n* (%)	37 (55.2)
Mean cardiac T2*±SD at t_0, ms	24.5±12.7

[a] Patients still HCV-RNA positive: *n*=28

The pre-transfusional mean haemoglobin (Hb) was 9.7± 0.5 g/dl, the median ferritin value was 913 ng/ml (range 229–5934 ng/ml) and the mean iron intake was 0.41± 0.12 mg/kg/day. In the overall population, the baseline myocardial T2* was <10 ms in 8 patients (11.9 %), between 10 and 20 ms in 22 patients (32.8 %) and ≥20 ms in 37 patients (55.2 %); the mean T2* value was 24.5±12.7 ms. Eight patients showed a history of symptomatic heart failure and five patients had a relevant arrhythmia (four atrial fibrillation, one supraventricular tachycardia) in the past 10 years. Twelve patients were taking cardiac therapies (ACE inhibitors, diuretics or antiarrhythmic drugs) and two patients were assuming oral anticoagulant drugs. Hypothyroidism was present in 15 patients, diabetes in 12 patients and hypogonadism in 58 patients. All patients were divided into four groups on the basis of their chelation therapy (group A on DFX, group B on DFO, group C on DFO plus DFP and group D only on DFP). The patients' characteristics in the different groups are reported in Table 2. No statistical differences in mean age, Hb levels or ferritin levels were found between the different groups. Iron intake was significantly lower in group A (p= 0.0009, group A vs group B). Group B and C included patients with more severe iron overload, based on ferritin levels.

Myocardial iron overload

At baseline evaluation, T2* <10 ms was detected only in one patient (1/36, 2.8 %) in group A, in four patients (4/15, 26.7 %) in group B and in three patients (3/12, 25 %) in group C. Group D included only four patients, all showing a myocardial T2* above 20 ms at baseline. Progressive changes in T2* values were observed at t_1 and t_2 for all the groups. Ten patients (10/36, 27.8 %) in group A, three patients (3/15, 20 %) in group B and three patients (3/12, 25 %) in group C moved from an abnormal T2* (<20 ms) to normal values, in 32±7 months (Table 3). Significant increases in myocardial T2* were observed in patients with baseline T2* <10 ms and between 10 and 20 ms. T2* values at t_2 improved significantly compared to baseline in patients treated with DFX (group A) and with DFO (group B). In group C, myocardial T2* values increased but without statistical significance (Table 4). In patients with T2* <10 ms treated with combination therapy (DFO and DFP), T2* apparently increased in a shorter period of time than with other regimens. No statistically significant reduction in ferritin levels was associated with ameliorating myocardial T2* values.

Myocardial function and left ventricular volumes

We observed an improvement of LVEF and a reduction of both end-systolic and end-diastolic left ventricular volumes [end-diastolic volume (EDV), end-diastolic volume index (EDVI), end-systolic volume (ESV) and end-systolic volume

Table 2 Patients' characteristics at baseline, in the groups of patients with different iron chelation therapy

Characteristics at baseline	Group A n=36	Group B n=15	Group C n=12	Group D n=4	Total n=67
Mean age ± SD, years	35±7	38±6	33±5	33±9	35±6
Male/female, n	18:18	1:14	5:7	3:1	27:40
Hb levels ± SD, g/dl	9.6±0.5	9.8±0.7	9.7±0.3	9.6±0.6	9.7±0.5
Ferritin levels, ng/ml[a]	921	1,158	882	891	913
Iron intake ± SD, mg/kg/die	0.35±0.10*	0.44±0.07	0.52±0.12	0.47±0.08	0.41±0.12
Values of T2*					
T2* <10 ms, n (%)	1 (2.8)	4 (26.7)	3 (25)	0 (0)	8 (11.9)
T2* 10–20 ms, n (%)	13 (36.1)	4 (26.7)	5 (41.7)	0 (0)	22 (32.8)
T* >20 ms, n (%)	22 (61.1)	7 (46.7)	4 (33.3)	4 (100)	37 (55.2)

*p=0.0009 group A vs group B

[a]Median values

index (ESVI)] only in patients in group A with baseline cardiac T2* between 10 and 20 ms (Table 4).

Adverse events and safety

During the observation period, no serious adverse events related to drugs were detected. One patient (female) died of hepatocarcinoma during the study period. In group A, some patients showed creatinine levels fluctuating within the normal range or near borderline upper limit. Two patients in group A showed a mild skin rash, solved after the administration of an antihistaminic drug, without DFX interruption. In groups C and D, no episodes of neutropenia or agranulocytosis were recorded.

Discussion

Heart failure due to myocardial iron overload secondary to regular blood transfusions still remains the most important cause of morbidity and mortality in patients affected by TM [17, 18]. Therefore, the early assessment and consequently the adequate chelation treatment of cardiac iron overload are mandatory to prevent severe cardiac siderosis and symptomatic heart failure which are difficult to treat and with poor prognosis. The iron chelation therapy has a major role in preventing iron deposition in different organs and in removing iron from a different tissue [2, 19]. The standard use of DFO leads to an improvement of the survival of patients affected by TM although it was not sufficient to reduce cardiac morbidity and mortality [17]. The major issues limiting the efficacy of this drug are the lack of compliance to subcutaneous infusion by pump. Nowadays, the availability of three different iron chelators permits to tailor the chelation therapy and to adapt the administration of each drug to a single patient. The tailored therapy has to be adapted considering different factors such as the distribution of iron overload in the different target organs, the iron intake, the effective doses, the adverse events and the patients' quality of life. It has been demonstrated that intensive, continuous DFO infusion can ameliorate and reverse myocardial iron overload in many cases [2, 19]. Since 1995, the introduction of DFP and the use of the combination therapy (DFO plus DFP) lead to a reduction in the prevalence of cardiac events [4, 12, 15, 17]. The combination therapy has been demonstrated to be effective in severe cardiac siderosis [17, 20]. Recently, it has been shown that a new oral iron chelator, deferasirox, can significantly reduce myocardial iron content over a 2-year treatment period at a mean dose of 30 mg/kg/day [8]. The evaluation of the effectiveness of these different drugs on cardiac and hepatic iron load has been changed during the last few years. The markers of iron loading such as ferritin levels and LIC are not completely sufficient to express the real iron burden in the different target organs and they are not always predictive for myocardial siderosis and dysfunction [21]. Over the last 10 years, T2* CMR has been increasingly diffused, being a rapid, direct and highly reproducible method to assess myocardial and hepatic iron overload; moreover, this technique

Table 3 Changes in myocardial iron overload in patients with different iron chelation therapy

	t_0		t_1 (6–14 months)		t_2 (32±7 months)	
Group A (n=36)	n	T2* (ms)	n	T2* (ms)	n	T2* (ms)
T2* <10 ms	1	8.7	0	–	0	–
T2* 10–20 ms	13	15.3±2.9	12	15.8±2.8	4	15.8±1.9
T* >20 ms	22	32.3±6.5	24	34.6±6.8	32	33.8±8.0
Group B (n=15)						
T2* <10 ms	4	8.5±1.1	3	7.2±1.7	0	–
T2* 10–20 ms	4	14.1±3.8	6	13.5±3.1	5	12.3±1.5
T* >20 ms	7	31.5±7.8	6	32.9±10.0	10	30.4±9.8
Group C (n=12)						
T2* <10 ms	3	5.9±1.3	3	7.9±1.2	2	6.9±0.6
T2* 10–20 ms	5	13.7±3.0	5	13.4±1.9	3	16.9±3.3
T* >20 ms	4	38.4±17.0	4	38.0±10.7	7	39.8±6.4

Table 4 Changes in T2* values and cardiac function parameters in patients with T2* at baseline ≤20 ms and treated with different iron chelation therapy

Group A (patients treated with DFX)						
	Baseline T2* <10 ms (n=1)			Baseline T2* 10–20 ms (n=13)		
	t_0	t_2	p value	t_0	t_2	p value
T2* heart (ms)	8.81	13.04	NA	15.32±2.87	27.61±10.85	0.0008
LVEF (%)	51	30	NA	59.8±6.4	63.9±3.4	0.035
EDV (ml)	213	211	NA	141.1±24.4	125.8±25.4	0.025
EDVI (ml/m^2)	130	132	NA	86.6±11.0	75.1±13.2	0.01
ESV (ml)	105	148	NA	57.4±13.3	45.5±9.3	0.001
ESVI (ml/m^2)	64	93	NA	35.1±6.1	27.4±5.2	0.0006
Group B (patients treated with DFO)						
	Baseline T2* <10 ms (n=4)			Baseline T2* 10–20 ms (n=4)		
	t_0	t_2	p value	t_0	t_2	p value
T2* heart (ms)	8.56±1.14	11.74±1.05	0.006	14.09±3.77	25.35±5.93	0.02
LVEF (%)	50.5±8.5	50.7±5.7	ns	59.2±1.5	67.2±4.3	ns
EDV (ml)	144.2±11.6	117.3±20.0	ns	128.5±28.2	105.8±15.5	ns
EDVI (ml/m^2)	95.5±6.3	78±17.6	ns	76.2±22.4	66.0±3.6	ns
ESV (ml)	70.5±6.6	58±13.1	0.05	51.7±12.1	35.0±8.4	0.05
ESVI (ml/m^2)	47±8.2	39±11.7	0.05	30.5±10.4	21.7±2.2	ns
Group C (patients treated with DFO plus DFP)						
	Baseline T2*<10 ms (n=3)			Baseline T2* 10–20 ms (n=5)		
	t_0	t_2	p value	t_0	t_2	p value
T2* heart (ms)	5.87±1.33	10.70±6.58	ns	13.70±3.02	27.07±10.61	0.03
LVEF (%)	52.00±6.56	53.3±7.5	ns	57.6±13.8	60.2±8.2	ns
EDV (ml)	136.0±10.6	117.3±9.9	ns	155.5±50.5	125.0±26.9	ns
EDVI (ml/m^2)	94.0±5.0	80.3±9.0	ns	105.4±35.9	83.8±19.7	ns
ESV (ml)	64.7±4.5	54.7±9.9	ns	72.0±43.6	44.4±17.4	ns
ESVI (ml/m^2)	44.7±4.2	37.0±7.8	ns	49.4±30.4	31.2±14.0	ns

Data represent mean ± SD

ns nonsignificant, *NA* not applicable

permits to evaluate cardiac morphology and function [9]. The efficacy of the different chelation regimen can be evaluated monitoring T2* CMR along time. In our study, we analysed retrospectively, based on repeated T2* CMR evaluations, in a mean period of time of 32±7 months, the efficacy of four different chelation regimens in removing iron from the heart, in TM patients treated with the same chelation therapy for at least 1 year. In literature, only one recent study compared the myocardial T2* values in 115 TM patients from different centres treated with one chelator alone (DFO or DFP or DFX), using only a single T2* CMR measurement [15]. We enclosed in this study 67 TM patients treated in a single centre, comparable for age, gender and pre-transfusional haemoglobin. Ferritin levels were slightly higher in patients treated with combination treatment, as expected, because this is the standard treatment in those patients with more severe iron overload. Overall, at baseline, a severe cardiac siderosis was present in 12 % of the patients and a mild–moderate myocardial siderosis in 33 % of the study population. Only one patient in the DFX treatment group had a myocardial T2* value under 10 ms. More patients with T2* <10 ms were either on DFO or in combination (DFO plus DFP). At present, an intensive chelation therapy (24 h DFO or combination DFO/DFP) is the advisable chelation regimen in patients with severe iron overload [16]. Our patients were allocated to combination therapy before T2* availability on the basis of persistent high level of ferritin or of abnormal cardiac function estimated by echocardiography. Our study suggests the effectiveness of each chelator on myocardial iron removal. As described in Table 3, many patients ameliorate cardiac T2* value after the observational period, moving from an abnormal T2* (<20 ms) to normal values under any chelation regimen (at least 20 % of patient in each group). The amelioration of cardiac T2* that we observed in all groups during the follow-up could be related to an improved compliance to any chelation regimen, although these patients were out of any clinical trials. The observed improved compliance could be related to the following explanations: (a) the availability of T2* that directly shows the cardiac iron load and the related risk of cardiac failure makes the patients more responsible and more conscious of their risk thus they better adhere to therapy and (b) the caregivers in a dedicated thalassemia centre pay more attention to patients' compliance and to improve trusted relationship with patients. Continued treatment with deferasirox significantly increase myocardial

T2* over time, showing its efficacy in removing iron from the heart; DFO and DFP combination therapy, that in our cases was simultaneous for 4 days a week plus 3 days with DFP alone, seems to ameliorate cardiac T2* more rapidly in patients with T2* <10 ms at baseline. DFO at proper doses (>40 mg/kg/day) for at least 6 days weekly was also effective. Interestingly, we observed improvement of cardiac function mainly in patients treated with DFX. Previous studies had shown a relationship between cardiac T2* and CMR-derived LVEF [22]. In our cohort, a significant increase in LVEF with an improvement of T2* was observed in patients treated with DFX, whereas no differences were detected in DFO group and in the group treated with combined therapy, even if LVEF was never less than 50 % in those groups. As suggested, the LVEF may improve when there is a reduction in cardiac iron burden. However, in our study, such relationship was not significant in the DFO group and in the combined therapy group: this observation requires further investigation in iron-related cardiac functions. An additional relevant finding of our study, supporting the relevance of volume reduction as myocardial improvement indicator, was the significant reduction in both end-systolic and end-diastolic left ventricular volumes (EDV, EDVI, ESV and ESVI) in patients treated with DFX (group A) with baseline cardiac T2* between 10 and 20 ms (Table 4). It could be hypothesised that the amelioration of LVEF was related to improved contractility, mediated by a reduction in end-systolic and end-diastolic volumes. This observation allows to speculate that DFX has an important effect on cardiac function [7, 8]. Pepe et al. reported no differences in EDVI and ESVI between the analysed groups of chelation therapy but they have a single evaluation without any follow-up [15]. No patients died of cardiac disease but one patient (female, aged 52 years, HCV-positive) in group B died of hepatocellular carcinoma during the study period. No serious adverse events were experienced by patients treated with any of the chelation regimen. This study is limited by the relatively small number of patients in the different groups mainly for patients with T2* <10 ms; however, the group with T2* between 10 and 20 ms was similar and showed some differences that require further investigations. In conclusion, our data showed that compliance to any chelation therapy at proper doses significantly improves myocardial T2* over the 3-year treatment period. Continued treatment with deferasirox significantly increase myocardial T2* over time and improve left ventricular function. Simultaneous combination of DFO and DFP considered a more intensive regimen seems to ameliorate cardiac T2* more rapidly particularly in patients with T2* <10 ms at baseline. Data on possible other iron chelation regimens such as DFO/DFX or DFX/DFP combination are warranted in order to achieve several options for tailoring iron chelation not only in thalassemia patients but in any other patient at risk for organ damage due to transfusional iron overload.

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