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ORIGINAL ARTICLE

A 5-year follow-up in deferasirox treatment: improvement of cardiac and hepatic iron overload and amelioration in cardiac function in thalassemia major patients

E. Cassinerio · A. Roghi · N. Orofino · P. Pedrotti · L. Zanaboni · E. Poggiali · M. Giuditta · D. Consonni · M. D. Cappellini

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Abstract Deferasirox (DFX) is an oral iron chelator with established efficacy and safety. We evaluated by T2* cardiovascular magnetic resonance (CMR) the efficacy of DFX in preventing and removing cardiac and liver iron load and cardiac volume changes, along 5 years in adult thalassemia major (TM) patients. Twenty-three TM patients (9 males/14 women, mean age 36±4 years) were included in this study. Repeated CMR was performed to assess myocardial and liver iron load (baseline t0, after 2.5 years t1, after 5 years t2). Myocardial T2* values changed progressively and increased significantly between t0 and t2 (t0: 27.15±9.58 vs t2: 36.64±6.68, $p=0.0001$). At baseline evaluation, a cardiac T2* value <20 ms was detected in six patients (26 %): they showed an improvement of cardiac T2* values between t0 and t1, with normal T2* levels reached in all patients at t2. In the overall population, a significant reduction of both end-diastolic and end-systolic left ventricular volumes (EDV, ESV) were detected between t0 and t2 (EDV, t0: 132±31 ml vs t2: 124±22 ml, $p=0.033$; ESV, t0: 48±14 ml vs t2: 41±10 ml, $p=0.0007$). A significant reduction in liver iron concentration (LIC) was detected at t1 (5.36±3.58 mg/g dw at baseline vs 3.35±2.68 mg/g dw at t1, $p=0.004$). In patients with cardiac iron overload at baseline (n.6), mean cardiac T2* values doubled at t2, and mean LIC value is reduced of 29 %. After 5 years of treatment, DFX continually and significantly reduced myocardial and liver iron overload, and it prevented further iron deposition.

Keywords Thalassemia major · Cardiac iron overload · Liver iron overload · Deferasirox · Chelation therapy

E. Cassinerio (✉) · N. Orofino · L. Zanaboni · M. Giuditta · M. D. Cappellini
Rare Diseases Center, Department of Medicine and Medical Specialities, "Ca' Granda" Ospedale Maggiore Policlinico Foundation IRCCS, Milan, Italy
e-mail: elena.cassinerio@virgilio.it

A. Roghi · P. Pedrotti
CMR Unit, Department of Cardiology, Niguarda Ca'Granda Hospital, Milan, Italy

E. Poggiali · M. D. Cappellini
Department of Clinical Science and Community Health, University of Milan, Milan, Italy

D. Consonni
Epidemiology Unit, "Ca' Granda" Foundation IRCCS Ospedale Maggiore Policlinico, Milan, Italy

Introduction

Chronic iron overload is a serious complication of repeated blood transfusions required for the treatment of patients with congenital anemias such as thalassemia syndromes. Without chelation therapy, transfusional iron accumulates into the body leading to organ failure, particularly heart, liver, and endocrine glands. The introduction of chelation therapy significantly improved survival of chronically transfused thalassemia major patients (TDT); however, myocardial siderosis and the consequent cardiomyopathy remain the most common cause of morbidity and mortality [1]. In fact, patients with myocardial siderosis are at increased risk of left ventricular systolic and diastolic dysfunction, arrhythmias, and heart failure [2, 3]. Moreover, an emerging cause of death is liver disease, due to increased survival of thalassemic patients with a

long-time exposure to liver iron load and hepatitis virus (B and C) [4]. Ferritin levels and liver iron concentration (LIC), although used as markers of body iron load, do not express the real iron burden in the different organs, and particularly, they are not always predictive for myocardial siderosis and dysfunction [1]. During the last 10 years, the cardiac deaths are significantly reduced thanks to the introduction of T2* cardiovascular magnetic resonance (CMR), which allows to evaluate the cardiac iron load, and the availability of new oral iron chelators [5]. In fact, CMR has been increasingly diffused, being a rapid, direct, and highly reproducible technique to assess cardiac and hepatic iron overload. It permits also to evaluate cardiac morphology and function [6]. Based on myocardial T2* values, the risk of cardiac heart failure can be estimated prompting to intensify chelation therapy, if necessary [1]. Cardiac T2* below 10 ms, indicating very severe myocardial siderosis, is associated with reduction in left and right ventricular ejection fraction (LVEF and RVEF) and an increased risk in cardiac failure and arrhythmias [7–9]. Iron chelation therapy with deferoxamine (DFO), available since the late 1970s, has markedly improved the survival and life-expectancy of TDT patients, despite several limitations resulting in poor compliance to treatment [1]. This limitations led to develop new iron chelating agents and iron chelation regimens. Deferiprone (DFP), an oral chelator administered three times daily, has been shown to be more efficacious than DFO monotherapy in removing myocardial iron and even more in association with DFO: In several studies, it was well reported the efficacy of DFP in combination with DFO (expecially DFO ev infusions in patients with acute heart failure) in treating severe myocardial iron overload (cardiac T2* <10 ms) [10]. However, its use may be limited, due to the risk of adverse events, such as neutropenia or agranulocytosis [11]. Deferasirox (DFX) is a once-daily oral iron chelator with established dose-dependent efficacy and safety both in pediatric and adult patients, in removing iron from the liver and from the heart [12]. DFX is well tolerated, and the most common treatment-related adverse events (gastrointestinal discomfort, liver transaminase increase, and renal impairment) rarely lead to stop definitively the drug use [13]. In particular, results from the EPIC cardiac substudy have shown continued and significant reduction of cardiac iron, at mean doses of 30 to 40 mg/kg per day as assessed by T2* CMR over 3 years of DFX treatment in patients with mild-to-moderate and severe myocardial siderosis without significant variation in LVEF over the study period [14]. In our observational study, we evaluated a group of TDT patients who underwent long-term iron chelation therapy with DFX. We analyzed the safety profile of DFX and its efficacy in removing myocardial and liver iron and in remodeling heart chambers, along 5-year follow-up period.

Patients and methods

Study population

Twenty-three beta thalassemia major patients (9 males/14 women, mean age 36±4 years) followed at Rare Diseases Center in Milan were included in this observational study (Table 1). All patients were treated for at least 5 years with DFX at mean doses of 25±1 mg/kg/day, and they underwent repeated CMR to assess myocardial iron load, cardiac function, and volumes as part of their routine follow-up according to international recommendations. Liver iron load was also evaluated by CMR [15].

Assessment of myocardial T2* and cardiac function by CMR

Cardiac iron load was assessed measuring myocardial T2* at three different time points: basal value (t0), after a period of 2.5 years±6 months (t1), and after a period of 5 years (t2). CMR was performed at CMR Unit Department of Cardiology "A. De Gasperis" at Niguarda Ca' Granda Hospital in Milan, using a 1.5 Tesla MR scanner (Avanto Siemens, Erlangen). All T2* images were analyzed using 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 midventricular slice of the LV was acquired at 8 echo times (2.6 to 16.74 ms with 2.02-ms increments) with standard shimming

Table 1 Patients' characteristics at baseline

	All patients (n=23)
Mean age±SD, years	36±4
Male/female, *n*	9:14
Race (Caucasian/oriental/other), *n*	23:0:0
Mean pretransfusional hemoglobin±SD, g/dl	9.5±0.6
Mean iron intake (mg/kg/day)	0.34±0.10
Median serum ferritin, ng/ml	575 (252-2530)
History of hepatitis C, *n* (%)*	21 (91.3)*
Splenectomy, *n* (%)	15 (65.3)
History of heart failure, *n* (%)	1 (4.3)
History of relevant arrhythmias, *n* (%)	1 (4.3)
Mean dosage of deferasirox (mg/kg/day)	24.4±5.3
Mean LIC^{+}±SD at t_0 (mg/g dw)	5.36±3.58
Mean cardiac T2*±SD at t_0, ms	27.15±9.58
Cardiac T2* below 10 ms at t_0, *n* (%)	0 (0)
Cardiac T2* between 10 and 20 ms at t_0, *n* (%)	6 (26.1)
Cardiac T2* above 20 ms at t_0, *n* (%)	17 (73.9)

*Nine patients showed HCV-RNA positivity; $^{+}$ *LIC* liver iron concentration

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 contiguos 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 1000 ms)=46.35 ms, FOV (read/phase)=300–400 mm, slice thickness=7 mm, triggering=ECG/retro, views per segment=15, calculated phases=>20. Cines have been acquired in end-expiration breath-hold. Ventricular volumes were analyzed 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.

Assessment of LIC

LIC was calculated from liver T2* applying the formula [1/(T2*/1000)]×0.0254+0.202 [16].

Statistical analysis

For continuous variables, we reported mean and standard deviation (SD). For ferritin level, which had a right-skewed distribution, we presented the median (minimum-maximum). Crude comparisons of continuous variables between baseline, 2.5-, and 5-year follow-up visits were performed with Student's paired *t* test [17]. Ferritin, LIC, and hepatic T2* were $\log_{10}$-transormed before *t* tests. Statistical analyses were performed with Stata, version 12 [18].

Results

Patients' characteristics

Overall, the characteristics at baseline of 23 TDT patients (mean age 36±4 years; 9 males and 14 women) treated with deferasirox are shown in Table 1. The mean iron intake was 0.34±0.10 mg/kg/day, and the pretransfusional mean hemoglobin (Hb) was 9.7±0.5 g/dl. The median ferritin value was 575 ng/ml (range 252–2530 ng/ml). The mean dosage of deferasirox at the beginning of the observation period was 24.4±5.3 mg/kg/day; the mean dose of DFX along the 5-year follow-up was 25.3±1.2 mg/kg/day. In the overall population, the mean T2* value was 27.15±9.58 ms at baseline. None of the patients had a baseline myocardial T2* below 10 ms, 6 patients (26.1 %) showed a myocardial T2* between 10 and 20 ms and 17 patients (73.9 %) above 20 ms. A male patient showed a previous history of symptomatic heart failure, and one patient had an history of arrhythmia (treated with amiodarone). At baseline, nine patients were HCV-RNA positive.

Myocardial and liver iron overload

In the overall population, myocardial T2* values progressively changed and increased significantly between t0 and t1 (27.15±9.58 vs 34.79±10.52, p=0.008) and between t0 and t2 (27.15±9.58 vs 36.64±6.68, p=0.0001) (Fig. 1). An initial reduction of mean ferritin levels was observed in the first 2.5 years of observation reaching a statistical significance only after 5 years (1055±563 ng/ml at baseline vs 960±568 ng/ml at t1 vs 751±627 ng/ml at t2, p=0.009 between t1 and t2)

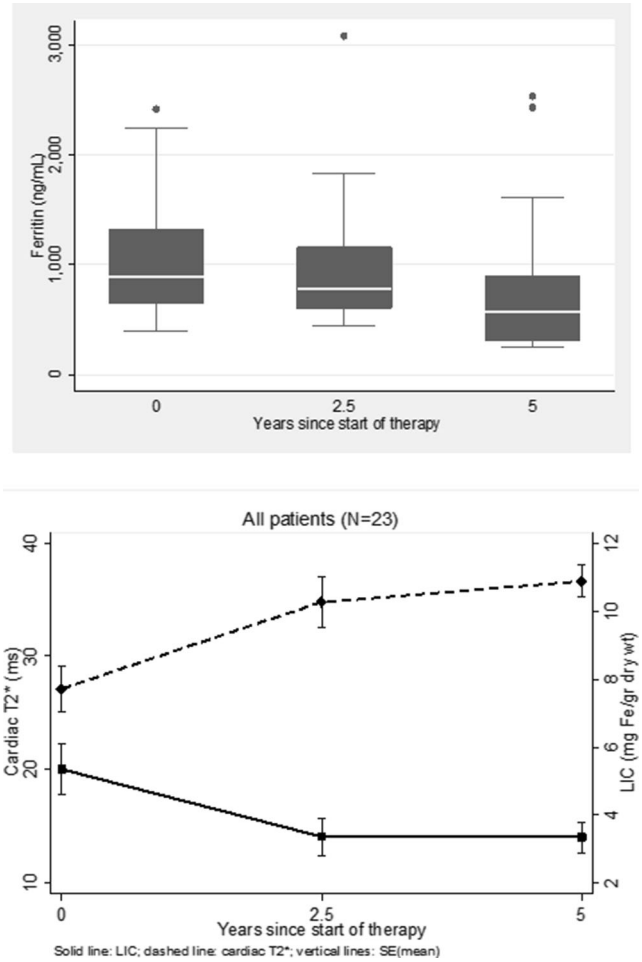

Fig. 1 Median ferritin levels, mean cardiac T2* and LIC during the period of follow-up

(Fig. 1). A significant reduction in LIC levels from baseline was detected at t1 (5.36±3.58 mg/g dw vs 3.35±2.68 mg/g dw, p=0.004) remaining stable till the end (LIC at t2 3.34±2.17 mg/g dw) (Fig. 1). At baseline evaluation, six patients (26 %) had a T2*<20 ms, and five of them showed an improvement at t1 and all achieved a normal value at t2 (31.33±8.37 ms) (Fig. 2). In this group of patients, LIC was 5.98±2.72 mg/g dw and decreased to 4.27±2.57 mg/g dw at t2 (Fig. 2). Moreover, in patients with cardiac iron overload at baseline, mean cardiac T2* values doubled at t2 (14.03±2, 53 ms at t0 vs 31.33±8.37 ms at t2), and mean LIC value is reduced of 29 % (5.98±2.72 ms at t0 vs 4.27±2.57 ms at t2) (Fig. 2). In patients with LIC>7 at baseline (n. 7), the mean LIC values is reduced of 60 % (9.92±2.67 ms at t0 vs 3.99±2.70 ms at t2) and the same percentage of amelioration of mean cardiac T2* was detected (24.70±8.39 ms at t0 vs 38.77±7.31 ms at t2) (Fig. 2).

Myocardial function and left ventricular volumes

In the overall population, no significant changes in LVEF were observed, and the mean LVEF was maintained into the normal range (64±6 vs 66±6 % at t0 and t2, respectively). Progressive changes in left ventricular volumes were observed at t2: A significant reduction of both end-diastolic and end-systolic left ventricular volumes (EDV, ESV) was detected between t0 and t2 (EDV: 132±31 ml vs 124±22 ml at t0 and t2, respectively, p=0.033; ESV: 48±14 ml vs 41±10 ml at t0 and t2, respectively, p=0.0007) (Table 2). The same parameters have been evaluated in the six patients with cardiac T2* below 20 ms at baseline, and they showed a significant improvement of EDV and ESV (EDV: 139±33 ml vs 121±22 ml at t0 and t2, respectively, p=0.03; ESV: 54±14 ml vs 44±10 ml at t0 and t2, respectively, p=0.02) (Table 2).

Adverse events and safety

During the observation period, no serious adverse events related to drugs were detected. Some patients showed creatinine levels fluctuating within the normal range or near borderline upper limit. No deaths were reported in this group of patients.

Other events or concomitant treatment during observation period

During the follow-up period, two patients became pregnant, and they stopped chelation therapy with deferasirox for the duration of the pregnancy: They restarted oral iron chelation therapy with DFX after the delivery without any adverse event. Six patients underwent treatment with interferon and ribavirin with the aim to treat their hepatitis C: The dose of DFX was modulated based on increased iron intake during the treatment period. Female patients were advised not to start pregnancy if CMR T2* showed cardiac iron overload, and no patients starting antiviral therapy showed myocardial iron overload.

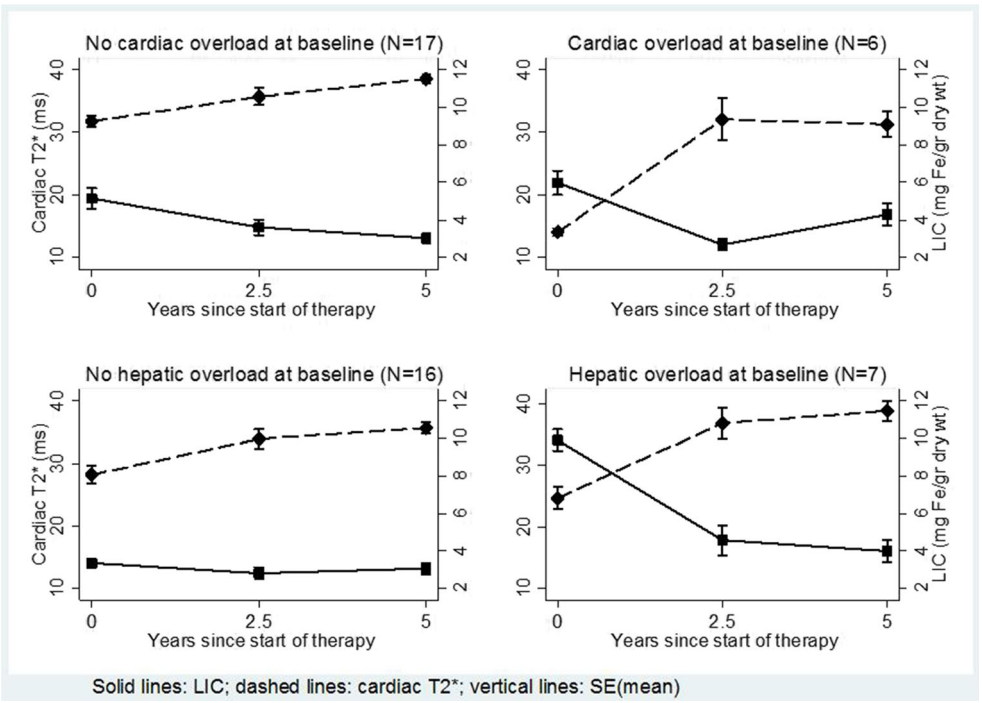

Fig. 2 Cardiac T2* and LIC from baseline to 5-year treatment

Table 2 Left ventricular ejection fraction and cardiac volumes during the period of follow-up

	Overall patients			Patients with baseline T2* 10–20 ms		
	t0	t2	*p* Value	t0	t2	*p* Value
LVEF (%, mean±SD)	64±6	66±6	*ns*	61±7	63±6	*ns*
EDV (ml, mean±SD) (nv: 52–141 ml)	132±31	124±22	*0,033*	139±33	121±22	*0.03*
ESV (ml, mean±SD) (nv: 13–51 ml)	48±14	41±10	*0,0007*	54±14	44±10	*0.02*

LVEF left ventricular ejection fraction, *EDV* end-diastolic left ventricular volume, *nv* normal value, *ESV* end-systolic left ventricular volume, *SD* standard deviation, *ns* not significative

Discussion

In TDT, the early assessment and consequently the adequate chelation treatment of cardiac and hepatic iron overload is mandatory. Nowaday, the availability of three different iron chelators permits to tailor the chelation therapy on each patient, analyzing strictly the efficacy, safety, and compliance. Recently, it has been shown that a new oral iron chelator, deferasirox, can significantly reduce myocardial and liver iron content [12, 19]. Cappellini et al. confirmed a sustain reduction in iron burden in adult and pediatric patients with long-term DFX treatment in a 5-year period [13]. In the EPIC cardiac substudy, study of Pennel et al. [12] demonstrated that DFX is able to reduce progressively and significantly cardiac iron overload and to decrease LIC in a period of 3 years. In those studies, DFX showed a good profile of tolerability; no serious adverse event were registered, and good patients' compliance was demonstrated [20]. ESCALATOR study showed that DFX is successful to reduce LIC value in a large cohort of patient in a 2.7-year follow-up period, at adequate doses, related to iron intake [21]. In our cohort of patients, we evaluated, in an observational study, the efficacy of DFX in preventing and removing cardiac and hepatic iron overload. We also evaluated cardiac volume changes assessed by CMR in a long period of follow-up (5 years). Twenty-three thalassemia major patients were treated with DFX for at least 5 years, and they repeated T2* CMR evaluations periodically. The observation period started from 2007 because of first availability of CMR in our center. Only six patients showed moderate cardiac siderosis at baseline (T2* value between 10 and 20 ms), and all of them improved significantly after 2.5 years. Concomitantly, a reduction in ferritin level and in LIC was observed. Interestingly, there is an association between the significant increase of myocardial T2* and the significant reduction of the LIC. In patients with baseline cardiac T2* below 20 ms, the values doubled in 5 years, and the reduction of LIC was of 29 %. If we considered patients with hepatic iron overload (LIC>7 mg/g dry weight), we observed a marked reduction in LIC in 2.5 years (60 % of reduction) with a slow amelioration of cardiac T2* values (Fig. 2). We can presume that patients with cardiac and hepatic iron overload remove iron along time from the two districts with two different pathways, according to the levels of iron load prevalent in one or in the other organ. In patients with iron overload located only in one district, the amelioration is more marked (Fig. 2). Moreover, in our patients, ferritin levels decreased significantly during the observational period of time. The functional analysis of CMR showed no significant variation in LVEF confirming the EPIC cardiac substudy. However, a significant reduction of end-systolic and end-diastolic left ventricular volumes during the 5-year follow up was observed in our cohort of patients, although within a normal range. There are evidence that DFX treatment lead to a significant reduction in both end-systolic and end-diastolic left ventricular volumes as myocardial improvement indicator [22]. A recent paper [23] showed an increase of EDV and ESV in 30 pediatric patients treated with DFX in a follow-up period of 18 months. The authors concluded that in thalassemia patients, anemia and hyperdinamic circulation can explain these data. In our experience, in 41 TDT patients other than those considered for this long-term follow-up study, with or without myocardial overload, both end-systolic and end-diastolic ventricular volumes in a median period of 12 months (range 6–19 months) showed a significant improvement during deferasirox treatment (unpublished data). The improvement of EDV and ESV during DFX treatment in patients without significant cardiac iron overload remains an interesting issue to be explored in a large cohort of patients. The evidence of LV volumes reduction in our study represents the positive LV remodeling induced by iron chelation therapy even in patients with normal regional wall motion and

LV ejection fraction. The early normalization of regional wall motion and LV ejection fraction is probably due to the rapid neutralization of NTBI cardiotoxic effects induced by iron chelation therapy, while volume reduction, affected by complex interactions with multiple variables such as chronic anemia, needs longer times. Our findings are suggesting the accurate assessment of LV function during follow-up, continuing the intensive iron chelation therapy to allow the complete resume of LV function. The simultaneous evaluation of cardiac T2* values and LIC in our patients permits to show an amelioration along time of the overall iron burden (the heart and liver) that lead all patients to have a myocardial T2* above 20 ms and all, except two, a LIC under 5 ms. The two patients were not compliant to deferasirox during interferon and ribavirin treatment for the HCV infection. It seems that the improvement of cardiac and liver iron overload in our patients was achieved with a mean dose of DFX of 25 mg/kg/day considering that majority had a moderate iron overload. For each patients, the dosage was personalized, and the maintenance of a low iron burden or the amelioration of iron overload was the criteria to adjust the dosage. Deferasirox treatment for up to 5 years seems to be efficacy in preventing or in removing iron overload with a good tolerability profile. In all patients considered, there were no drug interruption due to serious AE. Some patients experienced a mild, nonprogressive fluctuation in creatinine levels. No gastrointestinal AE were observed. During the observation period, two patients became pregnant: Both patients underwent hormonal stimulation therapy, and they interrupted DFX during the period they were supposed to be fertile. They did not assume chelation therapy during pregnancy, and in a month after delivery, they restarted chelation with DFX without adverse events. In both patients at the CMR after delivery, there was no cardiac iron overload but only a mild increased liver iron overload. The liver iron overload was efficiently removed with the restart of chelation treatment with DFX. Moreover, six patients started antiviral treatment for hepatitis C with interferon and ribavirin during the 5 years of observation. During the period of antiviral treatment, we observed an increase of iron intake due to ribavirin, and the dosage of DFX had to be adjusted. All patients well tolerated the dose adjustment, and no AE were reported.

This is an observational study with a variable period of time between CMR controls; thus, it has some limitations. Nevertheless, we can conclude that DFX, at a personalized dose, progressively and significantly reduces myocardial and liver iron overload, and it prevented the iron deposition along 5 years of continuous treatment. All the patients with myocardial iron load at baseline reached normal T2* values within 3 years of treatment.

Conflict of interest The authors declare that they have no conflict of interest.

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