



Combination of deferasirox and deferoxamine in clinical practice: An alternative scheme of chelation in thalassemia major patients



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ABSTRACT

The availability of three iron chelators improved the scenario of chelation therapy for transfusion-dependent thalassemia (TDT) patients, allowing tailoring of drugs according to the goals expected for each patient. The use of Deferiprone/Deferoxamine (DFP/DFO) combined in different schemes has been reported since many years. Only recently data from combination of Deferasirox/Deferoxamine (DFX/DFO) have been reported showing that it can be safe and efficacious to remove iron overload, particularly in patients who do not respond adequately to a single chelating agent. We investigated the efficacy, tolerability and safety of combined DFX/DFO in thalassemia major patients. Ten TDT patients have started DFX/DFO for different reasons: 1) lack of efficacy in removing liver/cardiac iron with monotherapy; 2) agranulocytosis on DFP; and 3) adverse events with elevated doses of monotherapies. The study design included: cardiac and hepatic T2* magnetic resonance (CMR), transient elastography evaluation (Fibroscan), biochemical evaluation, and audiometric and ocular examinations. The drugs' starting doses were: DFO 32 ± 4 mg/kg/day for 3–4 days a week and DFX 20 ± 2 mg/kg/day. Seven patients completed the one-year follow-up period. At baseline the mean pre-transfusional Hb level was 9.4 ± 0.4 g/dl, the mean iron intake was 0.40 ± 0.10 mg/kg/day, the median ferritin level was 2254 ng/ml (range 644–17,681 ng/ml). Data available at 1 year showed no alteration of renal/hepatic function and no adverse events. A marked reduction in LIC (6.54 vs 11.44 mg/g dw at baseline) and in median ferritin (1346 vs 2254 ng/ml at baseline) was achieved. A concomitant reduction of non-transferrin-bound iron (NTBI) at six months was observed (2.1 ± 1.0 vs 1.7 ± 1.2 μM). An improvement in cardiac T2* values was detected (26.34 ± 15.85 vs 19.85 ± 12.06 at baseline). At 1 year an increased dose of DFX was administered (27 ± 6 mg/kg/day vs 20 ± 2 mg/kg/day at baseline, *p* = 0.01) with a stable dose of DFO (32 ± 4 mg/kg/day). Combined or alternated DFX/DFO can be considered when monotherapy is not able to remove the iron overload or in the presence of adverse events.

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Introduction

The availability of three iron chelators improved the scenario of chelation therapy for thalassemia major (TM) patients, allowing tailoring of drugs according to the goals expected for each patient. Deferoxamine (DFO) has markedly improved the survival and life-expectancy of transfusion-dependent thalassemia patients (TDT), despite the difficult compliance to treatment for its different side-effects (local side infiltration, long-term infusional therapy) [1]. Deferasirox (DFX) is a once-daily oral iron chelator with established efficacy and safety in removing iron from the liver and from the heart in pediatric and adult patients [2].

DFX is well tolerated and the most common treatment-related adverse events (gastrointestinal discomfort, liver transaminases increase and renal impairment) rarely lead to stop the drug assumption [3,4]. Deferiprone (DFP) in combination with DFO has been proven to be efficacious in removing iron overload from the heart in patients with moderate–severe cardiac iron load [5]. At present new drug combinations, Deferasirox/Deferoxamine [DFX/DFO] or Deferasirox/Deferiprone [DFX/DFP], have been reported as applicable in clinical practice. Recent papers showed that the combination of DFX/DFO can be safe and efficacious to remove iron overload, in particular in patients with resistant iron load to different monotherapies [6–10]. The need to combine different chelating agents derives from the inefficacy of monotherapies in some patients and the presence of adverse events with the standard/high doses of single drugs [6]. Moreover, DFX and DFP are low molecular weight drugs and they can have a quite rapid

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access to the intracellular iron pool and they can have a synergic effect in association with DFO [11,12]. The aim of this study is to evaluate in clinical practice the efficacy, tolerability and safety of DFX/DFO in 10 out of 150 patients (pts) affected by TM treated at our Center, who have started DFX/DFO for different reasons: 1) lack of efficacy in removing liver/cardiac iron with monotherapy (7 pts); 2) restriction to use standard combination therapy (DFO/DFP) due to agranulocytosis on DFP (2 pts); and 3) adverse events with elevated doses of monotherapies (1 pt).

Materials and methods

Study population

Ten patients (3 males, 7 females, mean age of 32 ± 6 years) have started the combination therapy DFX/DFO in 2012/2013. A female patient was withdrawn for personal reasons (lack of compliance and the timing of the follow-up); another female patient started combination therapy in May 2013. Data are analyzed for seven patients that completed the one-year follow-up period.

Study design

The study design included: at baseline (t0), T2* cardiovascular magnetic resonance (CMR) and hepatic magnetic resonance, transient elastography evaluation (Fibroscan), biochemical evaluation (liver and renal function, ferritin, non-transferrin-bound iron [NTBI], creatinine, creatinine clearance and proteinuria), and audiometric and ocular examinations. Biochemical tests were repeated at 1, 3, 6 (t1) and 12 months (t2) from baseline; Fibroscan, T2* CMR, and audiometric and ocular examinations were repeated at 6 and 12 months. Normal values of NTBI were considered $-0.71 \pm 0.70 \mu\text{M}$. The starting doses of chelation treatment were: DFO $32 \pm 4 \text{ mg/kg/day}$ for 3–4 days a week and DFX $20 \pm 2 \text{ mg/kg/day}$. Based on ferritin level and patient tolerability, doses were gradually increased.

Assessment of myocardial T2* and cardiac function by CMR

Cardiac iron load was assessed measuring myocardial T2* at 3 different time-points: basal value (t0), after a period of 6 months (t1) and after one year (t2). CMR imaging 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 post-processing software (CMR Tools, Imperial College, London). Myocardial T2* was assessed with the use of a gated gradient-echo sequence with a flip angle of 20° . A single 10-mm-thick short axis mid-ventricular slice of the LV was acquired at 8 echo times (2.6 ms 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 as $>20 \text{ ms}$; $\text{T2}^* < 10 \text{ ms}$ indicated severe cardiac siderosis and T2^* between 10 and 20 ms indicated 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) \times 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 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 liver iron concentration (LIC)

LIC was calculated from liver T2* applying the formula $[1 / (\text{T2}^* / 1000)] \times 0.0254 + 0.202$ [13].

Transient elastography

Transient elastography (FibroScan®, EchoSens) was performed in all patients. The results were expressed as a median value of the total measurements in kPascal (kPa). Only the examinations with at least 10 validated measurements and a success rate of at least 60% were considered reliable. In addition, the median value of successful measurements was considered as representative of the liver stiffness in a given patient only if the interquartile range (IQR) of all validated measurements was less than 30% of median values. The following transient elastography thresholds were considered: $>7.9 \text{ kPa}$ for $S \geq 3$; $>10.3 \text{ kPa}$ for $S \geq 4$; and $>12.0 \text{ kPa}$ for $S \geq 5$ [14].

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 were performed with Student’s paired *t*-test.

Results

We analyzed data of seven patients that completed the one-year follow-up period. Patient characteristics at baseline are summarized in Table 1. At baseline the mean pre-transfusional hemoglobin (Hb) level was $9.4 \pm 0.4 \text{ g/dl}$, the mean iron intake was $0.40 \pm 0.10 \text{ mg/kg/day}$, the median ferritin level was 2254 ng/ml (range 644–17681 ng/ml), and the mean NTBI value was $2.10 \pm 1.04 \mu\text{M}$. The median Fibroscan value was 6.3 kPa (range 4.6–75 kPa). The cardiac T2* values were $19.85 \pm 12.06 \text{ ms}$ ($<10 \text{ ms}$ in 2 pts, >10 and $<20 \text{ ms}$ in 1 pt). The median LIC (derived from CMR) was 11.44 mg/g dw (range 3.49–24.39 mg/g dw). Five patients presented at baseline LIC values above 7 mg/g dw. A marked reduction in LIC (6.54 vs 11.44 mg/g dw at baseline) and in median ferritin (1346 vs 2254 ng/ml at baseline) was achieved, as well as a significant improvement in cardiac T2* values (26.34 ± 15.85 vs 19.85 ± 12.06 at baseline) (Fig. 1). Cardiac volumes did not change during the observation period (end-diastolic volume, EDV: 139 ± 47 vs $137 \pm 44 \text{ ml}$ at baseline; end-systolic volume, ESV: 56 ± 21 vs $57 \pm 21 \text{ ml}$ at baseline). A concomitant reduction of NTBI at six months was observed (2.1 ± 1.0 vs $1.7 \pm 1.2 \mu\text{M}$). Data available at one year showed no alteration of renal and/or hepatic function and no adverse events. During the

Table 1
Main characteristics of patient population at baseline.

	All patients (n = 7)
Mean age \pm SD, years	32 ± 6
Male:female, n	4:3
Mean pre-transfusional hemoglobin \pm SD, g/dl	9.4 ± 0.4
Mean iron intake, mg/kg/day	0.40 ± 0.10
Median serum ferritin (range), ng/ml	2254 (644–17681)
Mean dosage of deferoxamine \pm SD, mg/kg/day	32 ± 4
Mean dosage of deferasirox \pm SD, mg/kg/day	20 ± 2
Median LIC (range), mg Fe/g dw	11.4 (3.49–24.39)
LIC $< 7 \text{ mg Fe/g dw}$, pts	2
LIC $> 7 \text{ mg Fe/g dw}$, pts	5
Mean cardiac T2* \pm SD, ms	19.85 ± 12.06
Cardiac T2* $< 10 \text{ ms}$, n (%)	2 (28.6)
Cardiac T2* between 10 and 20 ms, n (%)	1 (14.3)
Cardiac T2* $> 20 \text{ ms}$, n (%)	4 (57.1)

Pts: patients; SD: standard deviation.

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