

Long-term use of deferiprone significantly enhances left-ventricular ejection function in thalassemia major patients

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A multicenter randomized open-label long-term sequential deferiprone–deferoxamine (DFP-DFO) versus DFP alone trial (sequential DFP-DFO) performed in patients with thalassemia major (TM) was retrospectively reanalyzed to assess the variation in the left ventricular ejection fraction (LVEF) [1].

Serial observations of LVEF over 3 years, in the same patient, were retrospectively assessed in 99 patients with TM during the sequential DFP-DFO multicenter randomized open-label trial [1]. A generalized estimating equation (GEE) model was used to demonstrate changes in mean LVEF over time [2].

The regression coefficient of treatment suggested that the DFP-alone group showed a statistically significant increase in mean LVEF over time (coefficient 0.97, 95% CI (0.51; 1.44), *P*-value <0.0001).

These findings suggest that long-term treatment with DFP-alone can significantly enhance LVEF over time. These findings agree with a survival analysis reporting a substantial decline in cardiac deaths during recent years, related to the switching of high-risk patients from DFO to chelation regimens that include the oral chelator DFP [3–5].

Oral chelation treatment has improved greatly adherence and management of patients with TM [6,7].

The improvement of the LVEF after 1-year DFP treatment has been reported [8–11].

However, the effects of DFP on LVEF after long-term treatment have not been fully investigated.

This letter reports a retrospective survey performed on patients with TM, previously enrolled in a long-term randomized open-label trial carrying ahead in Italy on the behalf of the Italian Society for the Study of Thalassemia and Haemoglobinopathies (SoSTE) [1]. Ninety-nine out of 213 patients enrolled in the sequential DFP-DFO trial underwent long-term echocardiographic study of LVEF measured at baseline and every 12 months over three consecutive years (Fig. 1). Among these, 39 and 60 received sequential DFP (75 mg/kg for 4 days/week)–DFO (50 mg/kg for 3 days/week) or DFP-alone (75 mg/kg for 7 days/week) treatment, respectively (Table I).

The hematological and clinical findings at enrollment are shown in Table I. No differences were observed at baseline between the two randomized groups. Particularly, the main findings of body iron overloading, expressed as serum ferritin at baseline, liver iron concentration (LIC), baseline LVEF <55%, and total number of blood transfusions were not statistically significantly different (Table I). Moreover, although baseline LVEF appears unlike between the two groups (Fig. 1), this was not statistically significantly different (*P*-value = 0.10, Table I).

The DFP-alone group showed statistically significant increase over time in mean LVEF in comparison with sequential DFO-FP treatment (coefficient 0.97, 95% CI (0.51; 1.44), *P*-value <0.0001).

Furthermore, the regression coefficient of treatment suggested that there was a statistically significant difference in mean LVEF between the two treated groups favoring the sequential group (coefficient 2.36, 95% CI (0.02; 4.71), *P*-value = 0.047, but this last treatment did not show a statistically significant variation of mean LVEF over time (coefficient –0.34, 95% CI (–1.09; 0.39), *P*-value = 0.359). These findings suggest that DFP-alone treatment significantly improves LVEF over time.

As it is well known, the main cause of death in patients with TM remains mechanical and electrophysiological myocardial dysfunction, the incidence of which ranges from 11.4% to 15.1% [12].

Several survival analyses have suggested a substantial decline in cardiac deaths over recent years, which are related to the tendency to switch high-risk patients from subcutaneous DFO to chelation regimens that include the oral chelator DFP [3,4].

Pennell et al. [9] suggested that, during an RCT of over 1 year, in a comparison of DFO to DFP, LVEF increased significantly in the DFP-treated group (3.1% vs. 0.3% absolute units; *P* = 0.003) whilst DFP in combination with DFO raised absolute LVEF by 2.6% [10]. Moreover, Pennell et al. [11] showed that these changes in LVEF (3.1% vs. 2.6%), measured by cardiac magnetic resonance (CMR) during DFP-alone or combination, were associated with risk reduction for development of heart failure over 12 months of 46.4% or 25.5%, respectively.

However, although the use of CMR is spreading [13], its availability is so far limited, constituting worldwide for many centers, where thalassemia is common, one of the main crucial issue for the right management of patients

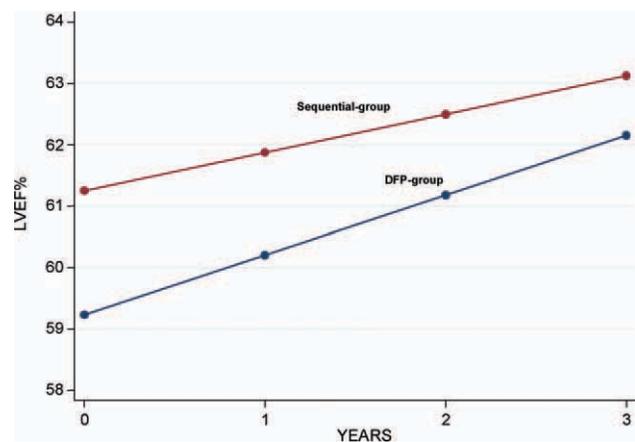


Figure 1. Estimated profiles from the fitted GEE model for the DFP-alone group and the sequential DFP-DFO group. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE I. Baseline Findings in the 99 Patients Included in the Retrospective Cohort Study

Findings	DFP group	Sequential group	<i>P</i> -value
No. patients (99)	60	39	
Females (%)	22 (36.66)	21 (53.84)	0.25
Age in years	31 ± 7.52	31 ± 8.66	0.96
Hgb, (g/L)	9.24 ± 0.87	9.32 ± 0.68	0.78
ALT, (IU/L)	49.73 ± 37.88	38.27 ± 45.97	0.43
LIC, mg/g/dw	2946.03 ± 2026.56	2351.08 ± 2234.03	0.38
Total blood transfusion, mL/kg/year	8716.172 ± 2111.04	8268.02 ± 2561.87	0.34
Mean ferritin, µg/L	1664.21 ± 846.62	1717.54 ± 497.79	0.84
Baseline LVEF <55% (n)	52 ± 2.19 (6)	50.66 ± 3.05 (3)	0.47
Baseline LVEF	59.25 ± 4.25	60.89 ± 5.78	0.10
Mean starting age of DFO, years	5.75 ± 4.34	5.03 ± 4.61	0.46
Splenectomy (%)	33(55)	27 (69.23)	0.26
Cirrhosis (%)	54 (90.00)	38 (97.43)	0.16
Arrhythmia (%)	49 (81.66)	35 (89.74)	0.31
HCV-RNA positive (%)	42 (70.00)	30 (76.92)	0.51

with TM [14]. Instead, worldwide availability of echocardiography is surely greater. Furthermore, several recent studies have shown the excellent inter-observer and intraobserver reproducibility of echocardiographic evaluation on LVEF [15,16]. This has been evaluated as similar to that of cardiac magnetic resonance (CMR), even in patients with TM [17]. Finally, Otterstad et al. [18] suggested that 2-D echocardiography measurements of LVEF is more accurate and reproducible if the determination is performed, as in our study, by single operator.

The most likely explanation for the improvement in LVEF function using DFP could be due to its cardioprotective effect on mitochondrial function as it was suggested in cultured, iron-loaded heart cells, even at concentrations below the iron-mobilizing effect [19], although, the exact mechanism of this effect remains unknown [11].

In conclusion, this retrospective survey of the sequential DFP-DFO trial data suggests that the long-term administration of DFP significantly enhances LVEF over time, as determined by echocardiography. However, because of limitations related to the design of this study, these findings should be confirmed in a prospective randomized clinical trial.

Methods

Echocardiographic measurement of LVEF. LVEF was measured by single operator with echocardiography by dividing the stroke volume by the end-diastolic volume in each patient (Vivid S5, Gems Ultrasound, Tirat Carmel, Israel).

Statistical analysis. The GEEs [2] model was used to evaluate possible changes in mean LVEF over time between the sequential DFP-DFO treatment and the treatment with DFP alone. This approach was implemented in the "xtgee" procedure presented as part of the Stata 11 software (Stata-Corp, College Station, TX). All of the statistical analyses were performed at the Department of Mathematical and Statistical Science 'S. Vianelli', University of Palermo (Italy).

Authors Contributions

AM was the principal investigator and takes primary responsibility for this paper. Patients were recruited and treated in 25 centers of the Italian Society for the Study of Thalassemia and Haemoglobinopathies (SosTE). AM, AV, and GL wrote the paper. AV performed the statistical analysis. The author reported no potential conflict of interest.

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