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 Thalassaemia 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).

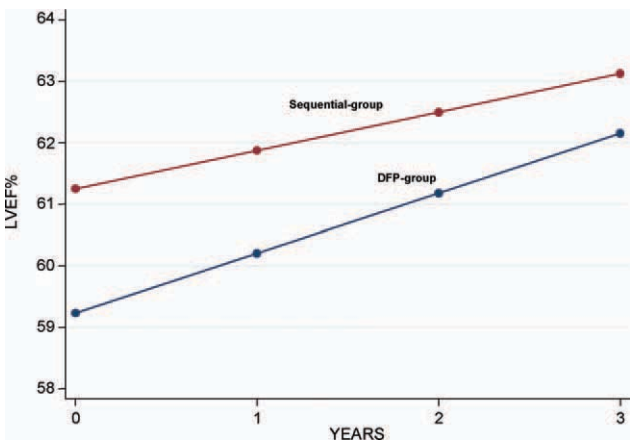

Figure 1. Estimated profiles from the fitted GEE model for the DFP-alone group and the sequential DFP-DFO group. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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, Pennel 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

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

Findings	DFP group	Sequential group	*P*-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

Ecocardiographic 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 (StataCorp, 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 Thalassaemia 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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References

1. Maggio A, Vitrano A, Capra M, et al. Long-term sequential deferiprone-deferoxamine versus deferiprone alone for thalassaemia major patients: A randomized clinical trial. Br J Haematol 2009;145:245–254.
2. Hedeker D, Gibbons RD. Longitudinal data analysis. Hoboken, New Jersey: Wiley; 2006.
3. Borgna-Pignatti C, Cappellini MD, De Stefano P, et al. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. Blood 2006;107:3733–3737.
4. Telfer P, Coen PG, Christou S, et al. Survival of medically treated thalassemia patients in Cyprus. Trends and risk factors over the period 1980–2004. Haematologica 2006;91:1187–1192.
5. Maggio A, Vitrano A, Capra M, et al. Improving survival with deferiprone treatment in patients with thalassemia major: A prospective multicenter randomised clinical trial under the auspices of the Italian Society for Thalassemia and Hemoglobinopathies. Blood Cells Mol Dis 2009;42:247–251.
6. Trachtenberg F, Vichinsky E, Haines D, et al. Iron chelation adherence to deferoxamine and deferasirox in thalassemia. Clinical Research Network. Am J Hematol 2011;86:433–436.
7. Wood JC, Glynos T, Thompson A, et al. Follow-up report on the 2-year cardiac data from a deferasirox monotherapy trial. Am J Hematol 2010;85: 818–819.
8. Pepe A, Lombardi M, Positano V, et al. Evaluation of the efficacy of oral deferiprone in β-thalassemia major by multislice multiecho T2*. Eur J Haematol 2006;76:183–192.
9. Pennell DJ, Berdoukas V, Karagiorga M, et al. Randomized controlled trial of deferiprone or deferoxamine in β-thalassemia major patients with asymptomatic myocardial siderosis. Blood 2006;107:3738–3744.
10. Tanner MA, Galanello R, Dessi C, et al. A randomized, placebo controlled, double blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. Circulation 2007;115:1876–1884.
11. Pennell DJ, Carpenter JP, Roughton M, Cabantchik ZI. On improvement in ejection fraction with iron chelation in thalassemia major and the risk of future heart failure. J Cardiovasc Magn Reson 2011;12:13–45.
12. Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica 2004;89:1187–1189.
13. Wood JC. Diagnosis and management of transfusion iron overload: The role of imaging. Am J Hematol 2007;82(12 Suppl.):1132–1135.
14. Ademola AA. An appraisal of the cost benefit of magnetic resonance imaging in Nigeria Niger. Postgrad Med J 2003;10:251–253.
15. Shahgaldi K, Gudmudson P, Manouras A, et al. Visually estimated ejection fraction by two dimensional and triplane echocardiography is closely correlated with quantitative ejection fraction by real-time three dimensional echocardiography. Cardiovasc Ultrasound 2009;25:41.
16. Blondheim DS, Beeri R, Feinberg MS, et al. Reliability of visual assessment of global and segmental left ventricular function: A multicenter study by the Israeli Echocardiography Research Group. J Am Soc Echocardiogr 2010;23: 258–264.
17. Giakoumis A, Berdoukas V, Gorsis E, Aessopos A. Comparison of echocardiographic (US) volumetry with cardiac magnetic resonance (CMR) imaging in transfusion dependent thalassemia major (TM). Cardiovasc Ultrasound 2007;5:24.
18. Otterstad JE, Froeland G, St John Sutton M, Holme I. Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. Eur Heart J 1997;18: 507–513.
19. Link G, Konijn AM, Hershko C. Cardioprotective effect of α-tocopherol, ascorbate, deferoxamine, and deferiprone: Mitochondrial function in cultured, iron-loaded heart cells. J Lab Clin Med 1999;133:179–188.