Brief Report

Repletion of Iron Stores With the Use of Oral Iron Supplementation in Patients With Systolic Heart Failure

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ABSTRACT

Background: Iron deficiency is associated with reduced functional capacity and increased mortality in patients with heart failure with reduced ejection fraction (HFrEF). Correction of iron deficiency in HFrEF patients with the use of intravenous iron improves symptoms, quality of life, and exercise performance. Whether oral iron improves iron stores in HFrEF patients is unknown. We conducted a retrospective study to assess the efficacy of oral iron supplementation in iron-deficient HFrEF patients.

Methods and Results: Iron-deficient HFrEF patients with a record of oral iron supplementation and iron studies before and ~180 days after supplementation were identified. Iron deficiency was defined as ferritin <100 ng/mL or as ferritin 100−300 ng/mL with transferrin saturation (Tsat) <20%. Spearman correlation was performed to assess for treatment responsiveness. In 105 patients, ferritin (from median 39 ng/mL to 75 ng/mL), Tsat (from 10% to 21%), iron (from 34 μg/dL to 69 μg/dL), and hemoglobin (from 10.4 g/dL to 11.6 g/dL) values increased ($P < .0001$), whereas total iron-binding capacity decreased (from 343 to 313 μg/dL; $P = .0007$) at 164 days after initiation of oral iron supplementation.

Conclusions: In this retrospective study, oral iron supplementation improved iron stores similarly to previously reported results with the use of intravenous iron repletion in HFrEF patients, suggesting that oral iron merits prospective evaluation as an intervention strategy in HFrEF. (*J Cardiac Fail 2015;21:694−697*)

Key Words: Heart failure, iron deficiency, anemia, iron supplementation.

Approximately 70% of patients with heart failure with reduced ejection fraction (HFrEF) have reduced bone marrow iron stores, and ~50% of patients with chronic HFrEF have iron deficiency, as defined by ferritin <100 ng/mL or by ferritin 100−300 ng/mL with transferrin saturation (Tsat) <20%.[1−3] Iron deficiency in HF predicts quality of life and survival, independently from other well established prognosticators, including anemia.[2]

Iron deficiency impairs oxygen transport and cellular oxidative capacity.[4,5] Initial single-center trials consistently demonstrated increased peak VO_2, and decreased N-terminal pro−B-type natriuretic peptide levels in iron-deficient HF patients receiving intravenous (IV) iron therapy.[6−8] Correction of iron deficiency has also been shown to have beneficial direct myocardial effects in HF patients.[5] The landmark FAIR-HF trial demonstrated hemoglobin-independent improvements in patient global assessment scores and New York Heart Association (NYHA) functional class with administration of 200 mg IV ferric carboxymaltose weekly until repletion.[9] The CONFIRM-HF trial extended those findings by demonstrating a reduction in HF hospital admissions with the use of 12 months of IV iron carboxymaltose.[10]

However, treating HF outpatients repeatedly with IV iron products is expensive and poses logistical challenges. It has been postulated that oral iron may not be effective in patients with chronic HF owing to potentially impaired absorption and delivery.[11] However, with the exception of 1 truncated study that included 7 individuals randomized to

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oral iron,[12] trials exploring the utility of oral iron supplementation in HF have not been performed. Therefore, the present retrospective study was conducted to investigate the efficacy of oral iron supplements in improving iron stores in patients with HFrEF and iron deficiency.

Methods

The Research Patient Data Registry (RPDR) was used to identify a cohort of iron-deficient HF patients with a record of oral iron supplementation and ≥2 laboratory assessments of iron stores (1 before and 1 after treatment). Iron deficiency was defined as ferritin <100 ng/mL or as ferritin <300 ng/mL with transferrin saturation (Tsat) <20%, mirroring the inclusion criteria of recent clinical trials involving IV iron repletion in HF.[9,10] Patients meeting these criteria before initiation of oral iron therapy and with left ventricular ejection fraction (LVEF) <0.45 within 1 year of iron supplementation were included in our analysis. Patients with suspected gastrointestinal bleeding, as assessed by review of endoscopic procedures and admission/discharge diagnoses, or those who had received a red blood cells transfusion or IV iron therapy within the preceding 12 months or during the observation period were excluded.

Measurements of iron stores before oral iron treatment were compared with values obtained within 1 year of initiation of oral iron supplementation. Electronic medication reconciliation records were reviewed to assess exposure to oral iron during the follow-up period, although medication compliance was not formally assessed.

Paired analysis with the use of Wilcoxon signed rank test was performed on laboratory measures before and after iron supplementation. Spearman correlation was performed to identify predictors of positive changes in iron indices. $P < .05$ was considered to be significant.

Results

Characteristics of the patient population are summarized in Table 1. The median daily dose of elemental iron was 130 mg in the form of ferrous sulfate (82%), iron polysaccharide (11%), or ferrous gluconate (7%).

Table 1. Baseline Patient Characteristics (n = 105)

Characteristic	Value
Age (y)	69 ± 14
Sex: male	65%
Race: white	71%
BMI (kg/m^2)	27 (23−30)
LVEF (%)	34 (25−40)
NYHA (1, 2, 3, 4)	7%, 38%, 49%, 6%
Creatinine (mg/dL)	1.3 (1.0−1.6)
Ischemic cardiomyopathy	46%
Diabetes	48%
Atrial fibrillation	25%
Anticoagulation therapy	35%
Antiplatelet therapy	75%
Average daily dose of elemental Fe (mg)	130 (65−150)

BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class.

Data are presented as mean ± SD, median (interquartile range), or %.

When laboratory values within 30 days before iron supplementation were compared with laboratory values a median 164 (interquartile range [IQR] 114−224) days after the initiation of iron, significant increases in iron, Tsat, ferritin, and hemoglobin levels were observed, as well as a decrease in total iron-binding capacity levels (Table 2). Change in Tsat was not related to change in ferritin levels over the treatment period ($\rho = 0.04$, $P = .69$). Changes in hemoglobin and Tsat over the course of the study were positively correlated ($\rho = 0.32$; $P = .004$). Fifty of the 105 patients (48%) were hospitalized when the laboratory tests that immediately preceded oral supplementation were performed, and 26 of those hospitalizations were attributed to acute decompensated HF. The median numbers of hospitalizations (1 vs 1; $P = .16$) and the percentages of patients having ≥1 hospitalization (50% vs 47%) were no different between the year before treatment and the year after treatment initiation. There were no deaths during the observation period, in keeping with the study design.

Changes in iron indices over the study period were unrelated to clinical characteristics (ie, age, body mass index, LVEF, and NYHA functional class) or the daily dose of elemental iron.

Comparison With the FAIR-HF Trial

In our study, median Tsat increased from 10% before treatment to 21% after a median 164 days of receiving oral iron. In the FAIR-HF trial, mean Tsat increased from 17.9% to 29% over 180 days, closely resembling the amount of change observed in our cohort (Fig. 1A). Although mean ferritin levels increased significantly in our cohort, from 40 to 72 ng/mL, with oral iron supplementation, mean ferritin levels increased to a greater extent in patients treated with IV iron in the FAIR-HF trial (eg, from 53 to 312 ng/mL; Fig. 1B).

Discussion

In this retrospective study of 105 patients, we observed significant increases in markers of iron stores with the initiation of oral iron supplementation. The degree of change in Tsat over the course of this study was similar to the change in Tsat observed in the FAIR-HF trial with the administration of IV iron. Our results suggest that oral iron therapy may have utility in repleting iron stores, which has been recently associated with improvements in functional capacity, quality of life, and reduction in hospital readmissions among patients with HFrEF.

Despite growing recognition of the functional and prognostic significance of iron deficiency, current HF guidelines in the United States do not specify when or if to assess for and treat iron deficiency. Our findings suggest that oral iron supplementation may be an appropriate way to address this unmet need for selected HF patients.