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ORIGINAL SCIENTIFIC PAPER

Iron deficiency in pulmonary arterial hypertension: prevalence and potential usefulness of oral supplementation

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ABSTRACT

Background: The aim of this study was to evaluate the prevalence of iron depletion in a prevalent population of patients with pulmonary arterial hypertension (PAH) and to gain preliminary insights on the possibility of its treatment with oral drugs.

Methods: Iron status was determined in 31 consecutive prevalent idiopathic patients with PAH. Iron depletion was defined as serum iron <10 mmol/L and decreased transferrin saturation irrespective of the coexistence of anaemia. Patients underwent laboratory examinations, 6-min walking test and echocardiography in the same day. A subgroup of iron depleted patients received one oral capsule/day containing 30 mg of pyrophosphate liposomal iron for 16 weeks. After this period all patients were re-evaluated.

Results: Iron depletion was observed in 22 patients (71%), of whom 6 were also anaemic and 16 were not anaemic. Iron depletion was associated with higher systolic pulmonary artery pressure (60 [50–90] vs. 45 [40–50] mmHg, $p = .007$), greater prevalence of moderate to severe tricuspid regurgitation (36% vs. 0%, $p = .039$), lower tricuspid annular plane systolic excursion (23 [21–24] vs. 19 [18–20] mm; $p = .025$]) and higher left ventricular eccentricity index (1.35 vs. 1, $p = .042$). After 16 weeks of treatment, 6-min walking distance significantly improved (500 [390–500] vs. 530 [410–550] metres; $p = .043$).

Conclusions: Iron deficiency is highly prevalent in patients with PAH and is associated with worse clinical conditions. Treatment with oral liposomal iron is a therapeutic option which should be further investigated in future trials.

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KEYWORDS
Pulmonary arterial hypertension; iron deficiency; iron supplementation

Introduction

There is growing evidence that iron deficiency is a clinically relevant issue in pulmonary hypertension. Several studies in the literature demonstrated a high prevalence of iron deficiency in patients with different forms of pulmonary hypertension, ranging from as high as 63% to a minimum of 27% [1–5]. Much of this variability is likely due to the method used to define iron deficiency. In addition, variability also depends on the fact that iron deficiency is typical in patients with pulmonary arterial hypertension (PAH): as a matter of fact, it has been observed only in 4.9% of patients with chronic thromboembolic disease [2] and only in 16% of patients with systemic sclerosis without pulmonary hypertension [6]. The clinical relevance of iron deficiency lies in the fact that it is associated with reduced exercise capacity and increased mortality [1–3]. It has to be noted that when the iron deficient patients with PAH were split into anaemic and non-anaemic groups, there was no significant difference in functional capacity, which would suggest that poor functional status is related more to defects triggered by low systemic iron than to anaemia [2].

Overall, the data in PAH are very similar to those observed in chronic heart failure, another chronic illness in which anaemia and iron deficiency are common and both are associated with advanced symptoms and poor prognosis and in which treatment with erythropoietin-stimulating agents did not improve clinical outcomes whereas i.v. iron over up to 52 weeks was associated with reduced hospitalisation rates and improved symptoms, exercise capacity and quality of life [7–10].

The aim of this study was to evaluate the prevalence of iron deficiency in a prevalent PAH population attending a single referral centre and to gain preliminary insights on the possibility to treat iron deficiency with a new formulation of oral iron, i.e. pyrophosphate liposomal iron.

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Methods

Patients

In this observational longitudinal study, iron status was determined for 31 consecutive prevalent idiopathic patients with PAH attending a single referral centre for PAH in Italy. Patients were included if age was more than 18 years. Exclusion criteria were: chronic renal disease with glomerular filtration rate lower than 30 mL/min, unable to provide informed consent, haemoglobin concentration <10 g/dL, known haemoglobinopathy, admission to hospital related to PAH or change in PAH therapy within 3 months prior to screening.

Patients underwent clinical evaluation, laboratory examinations, 6 min walking test and echocardiography within few hours. The hemodynamic evaluation was performed < 1 year before enrolment.

In cases of iron deficiency, patients were questioned about pathological blood loss (gastrointestinal or menstrual), known haematological comorbidities and previous anaemia to obtain information about possible causes for iron deficiency. A subgroup of iron deficient patients received oral liposomal iron treatment: one oral capsule/day containing 30 mg of pyrophosphate liposomal iron and 70 mg of ascorbic acid (Sideral® Forte, Pharmanutra Spa) for 16 weeks. After this period, iron parameters were measured again in all patients and standard iron treatment was prescribed in all iron deficient patients.

The investigation conforms to the principles outlined in the Declaration of Helsinki. The local Ethical Committee approved this study (Protocol no.44784/2011, EC Pavia). All patients signed an informed consent agreement approved by the Institutional Review Board of Fondazione IRCCS Policlinico S. Matteo for observational, non-pharmacological, non-sponsored studies which complies with the Italian legislation on the privacy (Codex on the Privacy, D. Lgs. 30 giugno 2003, n. 196).

Blood samples and analysis

Whole blood samples were collected through peripheral venipuncture in fasting subjects and analysed for haemoglobin (Hb), haematocrit, mean corpuscular volume (MCV), kidney function, brain natriuretic peptide (BNP), serum iron, transferrin saturation, total iron binding capacity (TIBC) and serum ferritin levels; transferrin saturation was calculated from serum iron divided by TIBC. Iron deficiency was defined as serum iron <10 mmol/L and decreased transferrin saturation (<15% in women and <20% in men) irrespective of the coexistence of anaemia (Hb <12 g/dL in women and <13 g/dL in men).

Echocardiographic examination

A standard M-mode, two-dimensional and Doppler study was performed using a commercially available equipment (GE Healthcare). The examination included the following parameters: right ventricular (RV) end-diastolic diameter (RVEDD); tricuspid annular plane systolic excursion (TAPSE); RV areas and fractional area change (FAC); end-diastolic eccentricity index of the left ventricle (LVEI-d); systolic pulmonary artery pressure (sPAP); degree of tricuspid regurgitation; right atrial pressure (RAP) estimated on the basis of inferior vena cava diameter and its respiratory variation.

Six-minute walk test

A non-encouraged test was performed according to the American Thoracic Society guidelines. Total walking distance (metres) and oxygen saturation were recorded.

Statistical analysis

Continuous variables were expressed as median and interquartile range [IQ range] and categorical variables as absolute and relative frequencies. Comparisons between clinically defined groups of patients were performed using non-parametric test (Mann–Whitney *U* test for independent samples and Wilcoxon signed-rank test for dependent samples as appropriate). Chi-square test was used to analyse independent categorical variables while paired categorical variables were analysed with McNemar's test.

Statistical analyses were performed using Statistical Package for the Social Sciences software, version 21.0 (IBM, Armonk, NY, USA) and GraphPad Prism version 7 for Windows (GraphPad software, La Jolla, CA, USA). A value of $p < .05$ was considered statistically significant.

Results

Clinical characteristics

Overall, there were 24 women and 7 men, median age [IQ range] was 53 [41–65] years, and they were mainly in WHO functional class II. Anaemia was observed in 6 patients (19%) and iron depletion in 22 patients (71%), of whom 6 were also anaemic and 16 were not anaemic.

Table 1. Clinical characteristics at baseline, stratified by iron deficiency.

	All patients ($n = 31$)	Patients with normal iron level ($n = 9$)	Iron depleted patients ($n = 22$)	p
Age (years)	53 [41–65]	60 [48–64]	51 [34–65]	.306
Female gender *n*, (%)	24 (77%)	5 (56%)	19 (86.4%)	.063
WHO class III/IV *n*, (%)	19 (61%)	5 (56%)	14 (64%)	.456
SBP (mmHg)	120 [110–120]	120 [120–130]	120 [110–120]	.283
HR (bpm)	70 [62–76]	69 [60–75]	71 [62–76]	.663
6MWD (m)	470 [385–508]	450 [425–515]	475 [370–500]	.767
LVEDV (mL)	70 [60–86]	88 [61–108]	69 [57–83]	.110
LVEF (%)	60 [60–65]	60 [55–63]	60 [60–65]	.178
RVEDD (mm)	32 [28–36]	34 [30–37]	32 [28–36]	.660
RVEDA (mm^2)	24 [21–28]	24 [19–27]	24 [22–30]	.525
FAC (%)	30 [27–38]	32 [28–40]	30 [27–36]	.676
TAPSE (mm)	20 [18–22]	23 [21–24]	19 [18–20]	.025
sPAP (mmHg)	50 [45–80]	45 [40–50]	60 [50–90]	.007
TR moderate to severe (n %)	8 (36%)	0	8 (36%)	.039
LV EI–d	1.1 [1–1.5]	1 [1–1]	1.35 [1.0–1.5]	.042
RBC (*10^6/mL)	4.7 [4.4–5.1]	5.0 [4.5–5.1]	4.7 [4.4–5.1]	.744
Hb (g/dL)	14 [12.8–14.9]	14.8 [14.2–15.0]	13.7 [11.9–14.4]	.026
HCT (%)	43.6 [39.2–46.7]	44.6 [43.6–46.8]	42.3 [38.3–44.5]	.086
MCV (fl)	91.9 [84.9–96.4]	93.5 [91.3–95.3]	88.9 [79.4–96.4]	.286
MCH (pg)	29.8 [27.0–31.1]	30.1 [29.6–31.4]	28.9 [25.4–31.0]	.192
MCHC (%)	32.0 [31.4–32.6]	32.3 [31.5–32.6]	32.0 [31.2–32.6]	.556
Serum Iron (mmol/L)	63 [44–94]	94 [78–115]	55 [40–71]	.002
Transferrin (mg/dL)	273 [234–308]	243 [220–273]	295 [241–311]	.098
TIBC (μg/dL)	388 [332–437]	342 [312–388]	418 [342–442]	.094
Ferritin (ng/mL)	29 [14–66]	60 [46–70]	17 [12–50]	.006
TS (%)	18.0 [9.6–22.0]	22 [20–31]	12.5 [8–18]	.001
eGFR (mL/min)	92 [73–106]	90 [73–95]	98 [77–108]	.223
Uric Acid (mg/dL)	5.4 [4.7–6.0]	5.9 [5.0–6.4]	5.4 [4.7–6.0]	.408
BNP (pg/mL)	40 [17–94]	34 [18–54]	41 [17–94]	.983

Data are expressed as median and interquartile range. SBP: systolic blood pressure; HR: heart rate; 6MWD: 6 min walking distance; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; RVEDD: right ventricular end-diastolic diameter; RVEDA: RV end-diastolic area; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure; TR: tricuspid regurgitation; LVEI-d: end-diastolic eccentricity index of the left ventricle; RBC: red blood cells; Hb: haemoglobin; HCT: haematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean cellular haemoglobin concentration; TIBC: total iron binding capacity; TS: transferrin saturation; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide.

Anaemic and non-anaemic patients were similar in terms of clinical, functional and echocardiographic characteristics. The clinical, functional, echocardiographic and laboratory characteristics of the entire population and of iron-depleted and not iron-depleted patients at baseline are shown in Table 1. At baseline, iron depleted patients were, albeit in a non-significant manner, slightly more symptomatic according to WHO functional class and had a significantly higher sPAP and worse RV function (significantly lower TAPSE, a greater prevalence of moderate to severe tricuspid regurgitation and a greater end-diastolic compression on the left ventricle).

Effects of oral iron supplementation

Oral liposomal iron supplementation was prescribed in 5 out of 22 patients with iron deficiency. As shown in Table 2, after 16 weeks of oral iron supplementation, there was a slight increase in ferritin and in RBC; importantly, this was associated with a significant improvement in functional capacity and in a decreasing trend, albeit non-significant, in sPAP at echocardiography (Figure 1(A)).

In patients with iron deficiency who did not receive iron supplementation there was not any significant change in the clinical, laboratory and echocardiographic parameters recorded (Table 3). Moreover, in these patients after 16 weeks functional capacity tended to decrease and sPAP remained completely stable (Figure 1(B)).

Discussion

The main results of this study are the confirmation that iron deficiency is extremely common in prevalent patient with PAH and that it is associated with worse clinical and echocardiographic profile. Moreover, our data suggest that this condition may be potentially treated with a new formulation of oral iron.

Iron deficiency is a common finding in chronic heart failure patients and it is associated with reduced exercise performance and poor survival; in such patients intravenous iron supplementation may improve the functional status [7–12]. More recently, it has also been shown that iron deficiency is highly prevalent in patients with different forms of pulmonary hypertension, ranging from as high as 63% to a minimum of 27% [1–5]. Iron deficiency was strikingly

Table 2. Changes in clinical, echocardiographic and laboratory parameters after 16 weeks in patients with iron deficiency who received iron supplementation ($n = 5$).

	Baseline	Follow-up	*p*
SBP (mmHg)	120 [115–120]	120 [115–120]	1
HR (bpm)	65 [62–73]	72 [65–75]	.416
6MWD(m)	500 [390–500]	530 [410–550]	.043
LVEDV (mL)	70 [63–80]	73 [70–73]	1
LVEF (%)	65 [61–66]	62 [60–66]	.465
RVEDD (mm)	30 [28–32]	28 [25–30]	.129
RVEDA (mm^2)	24 [23–25]	22 [20–25]	.194
FAC (%)	27 [25–35]	37 [36–40]	.593
TAPSE (mm)	21 [20–22]	21 [21–22]	1
sPAP (mmHg)	60 [60–90]	60 [55–80]	.066
RBC ($*10^6$/mL)	4.6 [4.5–4.7]	4.8 [4.7–4.8]	.225
Hb (g/dL)	13.7 [12.8–13.7]	13.4 [12.4–13.5]	.686
HCT (%)	41.7 [40.4–40.9]	41.7 [40.2–42.9]	.279
MCV (fl)	86 [85–92]	88 [86–91]	.686
MCH (pg)	27 [27–30]	28 [26–29]	.893
MCHC (%)	32 [31–32]	32 [31–32]	.465
Transferrin (mg/dL)	308 [291–321]	288 [275–308]	.715
TIBC (μg/dL)	437 [413–456]	409 [391–437]	.715
Ferritin (ng/mL)	16 [15–24]	22 [20–24]	.715
TS (%)	12 [10–24]	10 [9–13]	.686
BNP (pg/mL)	6 [4–6]	6 [3–6]	.893

Data are expressed as median and interquartile range. SBP: systolic blood pressure; HR: heart rate; 6MWD: 6 min walking distance; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; RVEDD: right ventricular end-diastolic diameter; RVEDA: RV end-diastolic area; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure; TR: tricuspid regurgitation; LVEI-d: end-diastolic eccentricity index of the left ventricle; RBC: red blood cells; Hb: haemoglobin; HCT: haematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean cellular haemoglobin concentration; TIBC: total iron binding capacity; TS: transferrin saturation; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide.

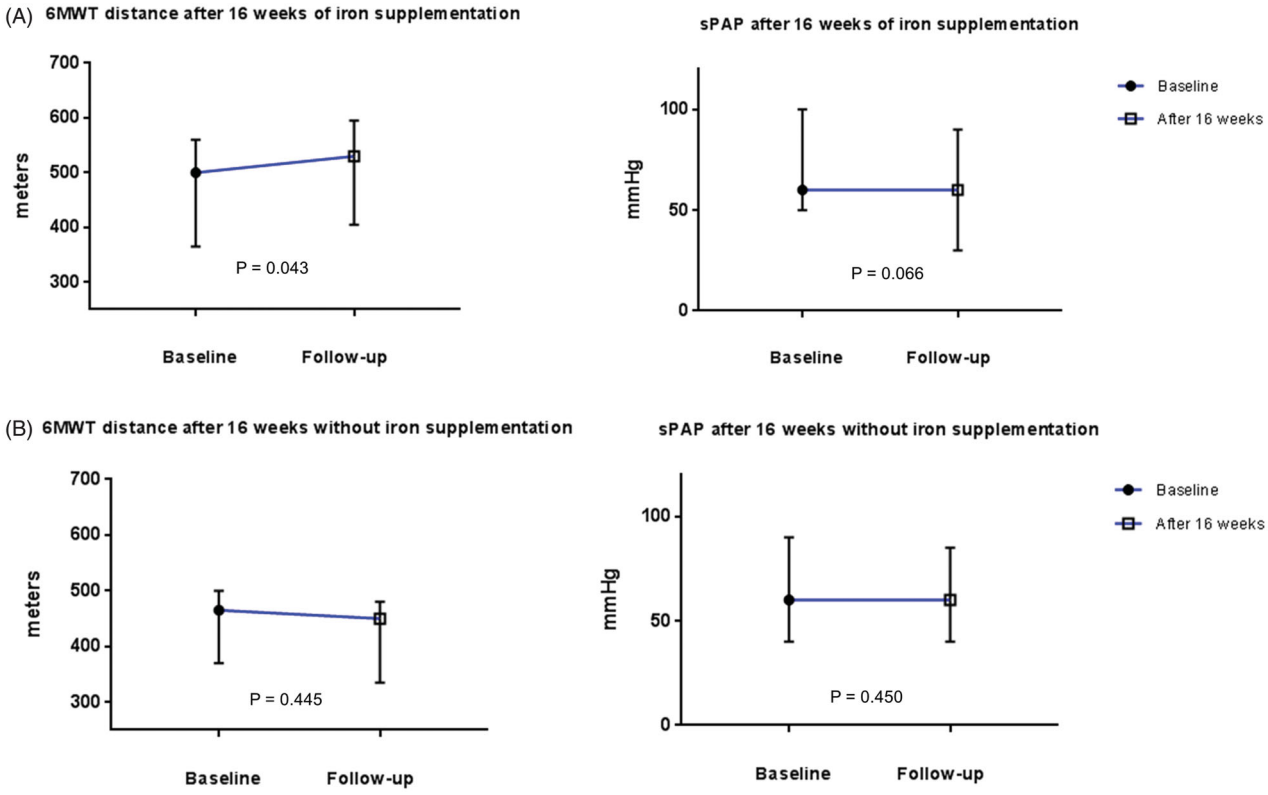

Figure 1. Functional capacity and systolic pulmonary artery pressure after 16 weeks in patients with iron deficiency with oral iron supplementation (A) or without (B). Panel A shows the distance walked at 6 minute walking test and sPAP at echocardiography in patients with pulmonary arterial hypertension and iron deficiency who received 16 weeks of oral iron supplementation, while panel B shows the situation in patients with iron deficiency who did not receive oral iron supplementation. 6MWT: 6-min walking test; sPAP: systolic pulmonary artery pressure.

Table 3. Changes in clinical, echocardiographic and laboratory parameters after 16 weeks in patients with iron deficiency without treatment ($n = 17$).

	Baseline	Follow-up	*p*
SBP (mmHg)	120 [110–120]	120 [115–120]	.725
HR (bpm)	72 [63–76]	68 [63–71]	.286
6MWD(m)	470 [370–500]	415 [335–480]	.445
LVEDV (mL)	68 [57–85]	76 [60–94]	.083
LVEF (%)	60 [60–64]	61 [60–65]	.722
RVEDD (mm)	33 [28–39]	32 [25–35]	.759
RVEDA (mm^2)	25 [21–31]	25 [19–26]	.471
FAC (%)	30 [28–40]	36 [31–43]	.446
TAPSE (mm)	19 [18–20]	20 [19–23]	.211
sPAP (mmHg)	58 [45–90]	58 [40–85]	.450
RBC ($*10^6$/mL)	4.9 [4.3–5.2]	4.7 [4.4–4.8]	.594
Hb (g/dL)	13.7 [11.9–14.5]	13.0 [12.8–13.4]	.137
HCT (%)	43.0 [38.3–44.6]	39.9 [38.9–41.7]	.138
MCV (fl)	92 [79–96]	88 [85–94]	.594
MCH (pg)	30 [25–31]	29 [27–30]	.476
MCHC (%)	32 [32–33]	32 [31–32]	.310
Transferrin (mg/dL)	275 [241–308]	288 [275–342]	.249
TIBC (μg/dL)	391 [342–437]	409 [391–486]	.249
Ferritin (ng/mL)	18 [8–59]	13 [4–22]	.612
TS (%)	13 [8–18]	14 [10–20]	.114
BNP (pg/mL)	43 [22–159]	36 [21–82]	.176

Data are expressed as median and interquartile range. SBP: systolic blood pressure; HR: heart rate; 6MWD: 6 min walking distance; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; RVEDD: right ventricular end-diastolic diameter; RVEDA: RV end-diastolic area; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure; TR: tricuspid regurgitation; LVEI-d: end-diastolic eccentricity index of the left ventricle; RBC: red blood cells; Hb: haemoglobin; HCT: haematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean cellular haemoglobin concentration; TIBC: total iron binding capacity; TS: transferrin saturation; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide.

prevalent in the present population (71%) and it was also significantly more frequent than anaemia, which could possibly reflect the fact that they were all prevalent patients, and that iron deficiency was never specifically looked for. Interestingly, iron deficiency was associated with a worse clinical and echocardiographic status and these data are in line with what has been shown in experimental animal models where iron deficiency was related to profound pulmonary vascular remodelling along with a rise in pulmonary arterial pressure and right ventricular dysfunction which were reversible with treatment [13].

It has to be acknowledged that true iron status can be difficult to ascertain in chronic diseases such as PAH using standard laboratory techniques, due to the presence of inflammation, which induces ferritin while repressing serum iron and transferrin saturations. Therefore, iron deficiency should be best defined on the basis of circulating soluble transferrin receptor levels, which are largely unaffected by inflammation [11,12]. However, this measurement is not routinely available. In addition, it could be argued that the present simple definition of iron deficiency according to serum iron levels and transferrin saturation was still effective in identifying patients with a more advanced clinical and echocardiographic profile, who did benefit from treatment.

Previous observations in chronic heart failure patients have led to hypothesise that iron supplementation could have a favourable effect in patients with PAH as well [14]. As a matter of fact, the optimum route of administration of iron in heart failure as well as in patients with PAH is still controversial. Oral iron replacement may be hampered by poor gastrointestinal absorption and high rate of adverse events [2,15]. On the contrary, there are concerns that intravenous iron may accelerate kidney damage, promote infections by supplying iron to pathogenic bacteria, enhance atherosclerosis by generating oxidative stress and cause endothelial damage and anaphylaxis [16,17]. A promising new strategy of iron replacement is represented by liposomal iron, which is a preparation of ferric pyrophosphate conveyed within a phospholipid membrane associated with ascorbic acid, which shows high gastrointestinal absorption and high bioavailability with a low incidence of side effects, due to lack of direct contact with intestinal mucosa. The liposome is in fact directly absorbed by the M cells in the intestinal lumen of the small intestine; subsequently, it is incorporated by endocytosis by macrophages and through the lymphatic system it reaches the hepatocytes, where the liposome makes the iron available.

The trend in haemoglobin levels in patients with PAH in this study was comparable to that observed after 4 months of treatment with the same drug in patients with chronic kidney disease [18]. In addition, in this study the replenishment of iron stores was

associated with a significant improvement in the distance walked in a 6 min walking test and an improvement, albeit non-significant, in systolic pulmonary artery pressure at echocardiography. These preliminary data would suggest that testing the efficacy of oral liposomal iron in iron deficient patients with PAH is worthwhile of future focused investigations. There is an important need for further therapy in patients with PAH and iron supplementation has the desirable requirement of being cost effective and convenient.

Conclusions

Iron deficiency is highly prevalent in patients with PAH, and it is associated with more advanced clinical conditions. This study suggests that treatment of iron deficiency should be considered in patients with PAH and oral liposomal iron is a therapeutic option which should be tested in future focused trials.

Disclosure statement

No potential conflict of interest was reported by the authors.

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