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Early View

Research letter

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Karen M Olsson, Jan Fuge, Torben Brod, Jan C Kamp, Jan Schmitto, Tibor Kempf, Johann Bauersachs, Marius M Hoeper

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Oral iron supplementation with ferric maltol in patients with pulmonary hypertension

Karen M Olsson[1,2], Jan Fuge[1,2], Torben Brod[1], Jan C Kamp[1], Jan Schmitto[3], Tibor Kempf[4], Johann Bauersachs[4], Marius M Hoeper[1,2]

[1]Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany, [2]German Centre of Lung Research (DZL), Germany; [3]Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany; [4]Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany.

Author for correspondence: Karen M Olsson, MD, Department of Respiratory Medicine, Hannover Medical School, 30623 Hannover, Germany;

E olsson.karen@mh-hannover.de

P +49 511-532-3530

F +49 511-532-8536

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Take home message: In patients with pulmonary hypertension and iron deficiency anaemia, oral iron supplementation with ferric maltol was well tolerated and restored iron and haemoglobin.

Iron deficiency is common in patients with pulmonary hypertension (PH) [1, 2]. The underlying pathomechanisms are complex and include impaired iron absorption, elevated hepcidin levels, augmented gastro-intestinal loss, and reduced availability from the reticuloendothelial system [1, 3, 4]. In patients with PH, iron deficiency is associated with aggravated symptoms and an increased mortality risk [3, 5].

Currently available oral iron formulations such as ferrous (Fe^{2+}) sulfate, ferrous gluconate and ferrous fumarate are often poorly tolerated. In addition, drug efficacy in terms of iron restoration and haemoglobin regeneration may be impaired in patients with PH [2]. For these reasons, current guidelines, while acknowledging the need for further data, recommend intravenous iron supplementation in patients with PH and iron deficiency [6]. With newer intravenous iron formulations such as ferric carboxymaltose, risk of serious reactions appears to be very low [7], but intravenous iron therapy is nonetheless not entirely free of risk and is more cumbersome than oral therapy.

Ferric maltol is an orally available formulation of ferric (Fe^{3+}) iron and maltol, a naturally occurring sugar derivative [8] that has shown to be safe, effective and well-tolerated in patients with inflammatory bowel disease, including patients who were previously intolerant to other oral iron formulations [9]. Ferric maltol is approved in the US and Europe for treatment of iron deficiency in adults but it is unknown whether this compound is an effective remedy against iron deficiency anaemia in patients with PH.

Here, we present the results of the *ORal IrON Supplementation with Ferric Maltol in Patients with Pulmonary Hypertension* (ORION-PH) study, an explorative, open-label, single-centre study assessing preliminary safety, tolerability and efficacy of ferric maltol in patients with various forms of PH and iron deficiency anaemia (clinical trials.gov, NCT03371173). The study enrolled patients between May 2018 and Nov 2019. Ferric maltol was administered at the approved dose of 30 mg twice daily. The primary study objective was the change in haemoglobin levels from baseline to week 12 of treatment with ferric maltol. Secondary objectives included the effects of oral ferric maltol on iron status, World Health Organization Functional Class (WHO FC), 6 min walking distance (6MWD), serum levels of the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), and echocardiography parameters of right ventricular (RV) function. Per protocol, changes from baseline to week 12 were analysed in patients who completed the 12-week study period. Statistical comparisons of baseline and week 12 data were performed with Chi^2 tests or paired Wilcoxon tests, as appropriate. Safety and tolerability were assessed in all study participants at week 6 and week 12, and 4 weeks after the last intake of study medication. The study was approved by the local ethics committee, and all patients provided written informed consent.

Main inclusion criteria were a diagnosis of any form of PH confirmed by a (historical) right heart catheter showing a mean pulmonary artery pressure ≥25 mmHg at rest and stable PH medication for at least 3 months, the presence of mild-to-moderate iron-deficiency anaemia as defined by a haemoglobin concentration ≥7 g/dl and <12 g/dl in females or ≥8 g/dl and <13 g/dl in males, and serum ferritin <100 µg/l, or 100-300 µg/l and transferrin saturation <20% at screening. Main exclusion criteria were other active haematological disorders, malignancy, active bleeding, ongoing oral or intravenous iron supplementation, concomitant erythropoietin treatment and severe kidney disease with a glomerular filtration rate <30 ml/min.

The study was originally designed to enrol 25 patients but was closed after inclusion of 22 patients due to slow recruitment. The median age of the enrolled patients was 57 (range, 49-71) years; 82% were female. Underlying conditions were pulmonary arterial hypertension (n=14; 64%), PH due to left heart disease (n=1; 5%), and inoperable chronic thromboembolic PH (n=7; 32%). Haemodynamics at the time of diagnosis showed severe pre-capillary PH with mean pulmonary artery pressure of (mean ± SD) 50 ± 11 mmHg, pulmonary artery wedge pressure of 10 ± 4 mmHg and pulmonary vascular resistance of 875 ± 385 dyn·s·cm^{-5}. The median time from diagnosis to study inclusion was 4.5 (range, 2.5-7.3) years. All patients received medical therapy for PH, the majority (64%) combination therapy with endothelin receptor antagonists and phosphodiesterase-5 inhibitors. These treatments were not changed during the course of the study.

Treatment with ferric maltol was well tolerated by the vast majority of patients. All but two patients completed the 12-week study period; the reasons for premature discontinuations were gastrointestinal side effects (n=1, related to study medication) and pneumonia (n=1, unrelated to study medication). The only treatment-emergent adverse events occurring in ≥2 patients were diarrhoea (n=3; 14%, including the abovementioned patient who discontinued study medication because of diarrhoea) and common cold (n=2; 9%). No deaths occurred during the main study period, but one patient died from right-sided heart failure during the 4-week safety follow-up. This death was considered unrelated to study medication.

The main results are shown in the Table: In the 20 patients who completed the 12-week study period, haemoglobin (median, +2.9 g/dl; interquartile range, 2.6-3.7 g/dl) and iron status significantly improved. In addition, we observed improvements in 6MWD and NT-proBNP. Echocardiography showed decreased RV dimensions and increased RV fractional area change while tricuspid annular plane systolic excursion remained unchanged. Functional class improved in 5 patients, deteriorated in none and remained unchanged in the remaining patients. These changes were comparable to those observed previously with intravenous iron supplementation in patients with PH and iron deficiency [10, 11].

By design, our study had several limitations, including small sample size, open-label design, heterogeneous patient population and lack of a control group. The objective of the study was to generate preliminary data on the safety, tolerability and efficacy of ferric maltol in patients with PH to set the stage for larger trials comparing this approach with intravenous iron supplementation. Despite the outlined limitations, we believe that the results of the study are encouraging and provide a clear signal to move forward.

In conclusion, in this exploratory open-label study in patients with PH and iron deficiency anaemia, ferric maltol was well tolerated by the vast majority of patients and resulted in significant improvements in iron status and haemoglobin levels. These changes were accompanied by signs of improved right ventricular function and improved exercise capacity, supporting the notion that iron deficiency has detrimental effects in patients with PH and that treating iron deficiency anaemia in these patients is important. Despite the limitations of a small, uncontrolled and unblinded study, our results suggest that oral iron supplementation with ferric maltol might become a safe, effective and convenient treatment option for patients with PH and iron deficiency. Further studies are needed to compare oral and intravenous iron supplementation in this cohort of patients.

Table Per protocol analysis of patients (n=20) who completed the 12-week study

	Baseline	Week 12	p value
Haemoglobin (g/dl)	10.7 ±0.9	13.6 ±1.3	< 0.001*
Iron (µmol/l)	5.4 ±2.0	19.7 ±11.7	< 0.001*
Transferrin saturation (%)	7.5 ±3.1	31.7 ±19.6	< 0.001*
Ferritin (µg/l)	13.1 ±6.7	36.6 ±19.8	< 0.001*
FC I, n (%)	0 (0%)	0 (0%)	0.091#
FC II, n (%)	4 (17%)	9 (45%)	
FC III, n (%)	16 (83%)	11 (55%)	
FC IV, n (%)	0 (0%)	0 (0%)	
6 min walking distance (m), mean ± SD	331 ±147	381 ±131	0.004*
NT-proBNP (ng/l), median (Q1;Q3)	496 (254-902)	298 (160-484)	0.003*
Right atrial area (cm^2), mean ± SD	23.7 ± 8.4	23.3 ± 8.3	0.070*
Right ventricular diastolic diameter (mm) (4 chamber view), mean ± SD	45.4 ± 8.9	42.3 ± 8.4	0.050*
Right ventricular diastolic diameter (mm) (parasternal long axis), mean ± SD	38.7 ± 7.3	35.0 ± 6.3	0.002*
Right ventricular fractional area change (%), mean ± SD	30.5 ± 12.8	37.0 ± 11.3	0.005*
TAPSE (mm), mean ± SD	21.6 ± 5.6	21.3 ± 5.6	1.000*

* NPAR (Wilcoxon-Test [paired])

Chi^2-Test

Abbreviations: FC, functional class; NT-proBNP, N-terminal fragment of pro-brain BNP; TAPSE, tricuspid annular plane systolic excursion

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Conflicts of interest:

Karen M Olsson has received renumerations for lectures and/or consultations from Acceleron, Actelion, MSD and United Therapeutics, all outside the present study.

Jan Fuge has nothing to declare.

Torben Brod has nothing to declare.

Jan Kamp has nothing to declare.

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References

1. Rhodes CJ, Howard LS, Busbridge M, Ashby D, Kondili E, Gibbs JS, Wharton J, Wilkins MR. Iron deficiency and raised hepcidin in idiopathic pulmonary arterial hypertension clinical prevalence, outcomes, and mechanistic insights. *J Am Coll Cardiol* 2011: 58(3): 300-309.10.1016/j.jacc.2011.02.057.
2. Rhodes CJ, Wharton J, Howard L, Gibbs JS, Vonk-Noordegraaf A, Wilkins MR. Iron deficiency in pulmonary arterial hypertension: a potential therapeutic target. *Eur Respir J* 2011: 38(6): 1453-1460.10.1183/09031936.00037711.
3. Ruiter G, Lankhorst S, Boonstra A, Postmus PE, Zweegman S, Westerhof N, van der Laarse WJ, Vonk-Noordegraaf A. Iron deficiency is common in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2011: 37(6): 1386-1391.10.1183/09031936.00100510.
4. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron Deficiency in Heart Failure: An Overview. *JACC Heart failure* 2019: 7(1): 36-46.10.1016/j.jchf.2018.07.015.
5. Ruiter G, Lanser IJ, de Man FS, van der Laarse WJ, Wharton J, Wilkins MR, Howard LS, Vonk-Noordegraaf A, Voskuyl AE. Iron deficiency in systemic sclerosis patients with and without pulmonary hypertension. *Rheumatology (Oxford)* 2013.10.1093/rheumatology/ket331.
6. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016: 37(1): 67-119.10.1093/eurheartj/ehv317.
7. Mulder MB, van den Hoek HL, Birnie E, van Tilburg AJP, Westerman EM. Comparison of hypersensitivity reactions of intravenous iron: iron isomaltoside-1000 (Monofer((R))) versus ferric carboxy-maltose (Ferinject((R))). A single center, cohort study. *Br J Clin Pharmacol* 2019: 85(2): 385-392.10.1111/bcp.13805.
8. Kelsey SM, Blake DR, Hider RC, Gutteridge CN, Newland AC. Absorption of ferric maltol, a novel ferric iron compound, in iron-deficient subjects. *Clinical and laboratory haematology* 1989: 11(3): 287-288
9. Gasche C, Ahmad T, Tulassay Z, Baumgart DC, Bokemeyer B, Buning C, Howaldt S, Stallmach A. Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease: results from a phase-3 clinical trial program. *Inflammatory bowel diseases* 2015: 21(3): 579-588.10.1097/mib.0000000000000314.
10. Viethen T, Gerhardt F, Dumitrescu D, Knoop-Busch S, ten Freyhaus H, Rudolph TK, Baldus S, Rosenkranz S. Ferric carboxymaltose improves exercise capacity and quality of life in patients with pulmonary arterial hypertension and iron deficiency: a pilot study. *Int J Cardiol* 2014: 175(2): 233-239.10.1016/j.ijcard.2014.04.233.
11. Ruiter G, Manders E, Happe CM, Schalij I, Groepenhoff H, Howard LS, Wilkins MR, Bogaard HJ, Westerhof N, van der Laarse WJ, de Man FS, Vonk-Noordegraaf A. Intravenous iron therapy in patients with idiopathic pulmonary arterial hypertension and iron deficiency. *Pulmonary circulation* 2015: 5(3): 466-472