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REVIEW

Iron deficiency in pulmonary arterial hypertension: a potential therapeutic target

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ABSTRACT: Iron deficiency is known to be common and detrimental in chronic left heart failure, where parenteral iron treatment has been shown to improve exercise capacity, New York Heart Association functional class and patient wellbeing. There is now increasing interest in the role of iron in the natural history of pulmonary arterial hypertension (PAH). Iron availability influences the pulmonary vasoconstrictor response to hypoxia and accumulating evidence indicates that iron deficiency is prevalent in idiopathic and heritable forms of PAH, iron status being related to exercise capacity, symptoms and poorer survival in patients with idiopathic PAH (IPAH). Potential mechanisms behind iron deficiency in IPAH include inhibition of dietary iron uptake by the master iron regulator hepcidin. High hepcidin levels underlie the anaemia of chronic disease. Possible stimuli of the observed high levels of hepcidin in IPAH include dysfunctional bone morphogenetic protein receptor type II signalling and inflammation. Iron status may influence outcomes through modulation of the pulmonary circulation as well as myocardial and skeletal muscle function. Two parallel studies, from our centre (Hammersmith Hospital, London, UK) and others in the UK and Amsterdam (the Netherlands), investigating the safety and potential benefit of iron supplementation in patients with PAH are currently under way.

KEYWORDS: Heart failure, hypoxia, iron, pulmonary arterial hypertension, pulmonary vascular resistance, pulmonary vasculature

Pulmonary arterial hypertension (PAH) is a heterogeneous condition that is characterised by a sustained increase in pulmonary artery pressure (>25 mmHg) and normal pulmonary capillary wedge pressure (<15 mmHg) with a normal or reduced cardiac output [1]. PAH can be idiopathic (IPAH), inherited or associated with other conditions, such as congenital heart disease (in particular, systemic-to-pulmonary shunts), connective tissue disease and chronic haemolytic anaemias, such as sickle cell disease [2]. It is a progressive vascular disease that leads to increased pulmonary vascular resistance, right ventricular failure and premature death. Recent data suggest that iron deficiency is also prevalent in IPAH [3–5], and may be related to morbidity and mortality [3, 5]. Here, we discuss the potential importance of iron in the regulation of pulmonary vascular tone, heart failure and prognosis in pulmonary hypertension, as well as the potential mechanisms by which it might be dysregulated, and affect symptoms and survival in IPAH.

IRON AND THE PULMONARY VASCULAR RESPONSE TO HYPOXIA

Several human physiology studies indicate that iron availability influences pulmonary vascular homeostasis, in particular the pulmonary vasoconstrictor response to hypoxia. It has been proposed that iron deficiency mimics the pulmonary effects of hypoxia through the stabilisation of hypoxia-inducible factor (HIF), which is primarily regulated by specific prolyl hydroxylase-domain enzymes (PHDs) and degradation *via* the von Hippel–Lindau tumour suppressor protein [6, 7]. Thus, the dependency of PHD activity on iron and oxygen is thought to account for regulation of the HIF pathway by both cellular oxygen and iron statuses. Intravenous infusion of the iron chelator desferrioxamine increased basal pulmonary artery systolic pressure in healthy volunteers, as assessed using Doppler echocardiography to measure the maximal transtricuspid pressure difference [8]. Although the increase was relatively modest (~25%) compared with that caused by hypoxia, the time course was similar and the magnitude of

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individual responses to hypoxia or iron chelation correlated strongly, suggesting that hypoxia might induce pulmonary hypertension, at least in part, *via* an iron-dependent mechanism.

Subsequently, it has been reported that an infusion of iron prevented the increased acute hypoxic pulmonary vasoconstrictive response normally induced by pre-exposure to hypoxia (~10% oxygen) for 8 h, whereas infusion of desferrioxamine exacerbated hypoxic pulmonary vasoreactivity [9]. Similarly, iron infusion attenuated the pulmonary hypertensive response to hypoxia in healthy volunteers on acute ascent to 4,340 m altitude [10]. In 11 high-altitude residents with chronic mountain sickness, progressive iron deficiency produced by staged venesection of 2 L blood also increased pulmonary artery systolic pressure, although no acute effect of iron replacement was detected. Together, these data indicate that variation in iron availability in the normal physiological range in the absence of overt anaemia can affect pulmonary vascular tone and hypoxic pulmonary hypertension, and clinical iron deficiency could exacerbate pulmonary hypertensive disease [11].

IRON IN CHRONIC HEART FAILURE

Anaemia is a powerful prognostic indicator in patients with chronic heart failure (CHF) [12–14]. A recent prospective study of 546 CHF patients also found that iron deficiency itself, independent of the other prognostic indicators including anaemia, was associated with increased mortality [15]. In fact, several studies (table 1) have now attempted to address the potential value of parenteral iron therapy in CHF [16–20]. The results indicate that iron replacement therapy can improve haemoglobin levels, exercise capacity, functional class, quality of life, and biochemical markers of myocardial stress and inflammation. These investigations culminated in the large multicentre Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency study, which recruited 459 patients with CHF (New York Heart Association (NYHA) class II or III) and iron deficiency, as defined by ferritin <100 $\mu g \cdot L^{-1}$, or 100–299 $\mu g \cdot L^{-1}$ if transferrin saturations were $<20\%$, and haemoglobin between 9.5 and 13.5 $g \cdot dL^{-1}$ [20]. Patients were randomised (iron:placebo 2:1) to receive intravenous ferric carboxymaltose (Ferinject®; Vifor Pharma UK Ltd, Bagshot Park, UK) or placebo and two primary end-points (patient self-reported global assessment and NYHA class) showed significant improvements 24 weeks after infusion. Significant differences were also observed in end-points (including quality-of-life questionnaires and exercise capacity) at other stages of the study. More importantly, improvements were seen irrespective of the presence of anaemia, and no significant difference in haemoglobin levels was observed between the treatment and placebo arms at baseline or 24 weeks later.

The data were consistent with earlier studies in rats, demonstrating the nonanaemic manifestations of iron deficiency [21]. In the presence of normal haemoglobin levels, iron deficiency was shown to impair exercise capacity and induce selective skeletal muscle changes in metabolic enzymes, which were amended by intraperitoneal injections of iron [21]. Parenteral treatment of iron-deficient anaemic subjects with iron–dextran was also reported to increase work capacity independently of

TABLE 1 Intravenous iron replacement therapy studies in left heart failure patients

First author [ref.]	Iron therapy	Patient group	Placebo	Duration	Primary effects	Secondary effects
Bolger [16]	⩽1 g iron–sucrose	Anaemic heart failure (n=16)	No	⩽3 months	Hb improvements	Improved symptoms and 6MWD (average change >40 m), no adverse events
Tobelli [17]	5 weekly 200-mg doses iron–sucrose	Anaemic CHF (n=40)	1:1 randomisation	6 months	Reduced NT-proBNP and CRP	Improved symptoms, LVEF and exercise capacity; all 5 hospitalisations were in placebo group
Okonko [18]	200 $mg \cdot week^{-1}$ until ferritin >500 $\mu g \cdot L^{-1}$, then fortnightly (total mean±SD 1433±365 mg)	CHF (n=35)	2:1 randomisation (iron:placebo)	12 weeks	Peak O_2 consumption only raised in anaemia	Improved NYHA class, adverse events similar
Usmanov [19]	100 mg three times a week for 3 weeks and then once weekly for 26 weeks (total dose 3200 mg)	CHF (NYHA class III/IV) and persistent anaemia (n=32)	No	26 weeks	Significant improvements in LV function and structure	Half of class III patients improved to class II, no improvement from class IV
Anker [20]	Fortnightly 200 mg ferric carboxymaltose until Ganzoni iron deficit replenished	CHF (NYHA class II/III) with iron deficiency and Hb 95–135 $g \cdot L^{-1}$ (n=459)	2:1 randomisation (iron:placebo)	24 weeks	Significant improvements in patient self-reported global assessment and NYHA class	6MWD increased ~40 m *versus* placebo; quality of life improved Improvements irrespective of anaemia; adverse events similar

CHF: chronic heart failure; NYHA: New York Heart Association; Hb: haemoglobin; NT-proBNP: N-terminal pro-brain natriuretic peptide; CRP: C-reactive protein; LV: left ventricle; 6MWD: 6-min walk distance; LVEF: LV ejection fraction.

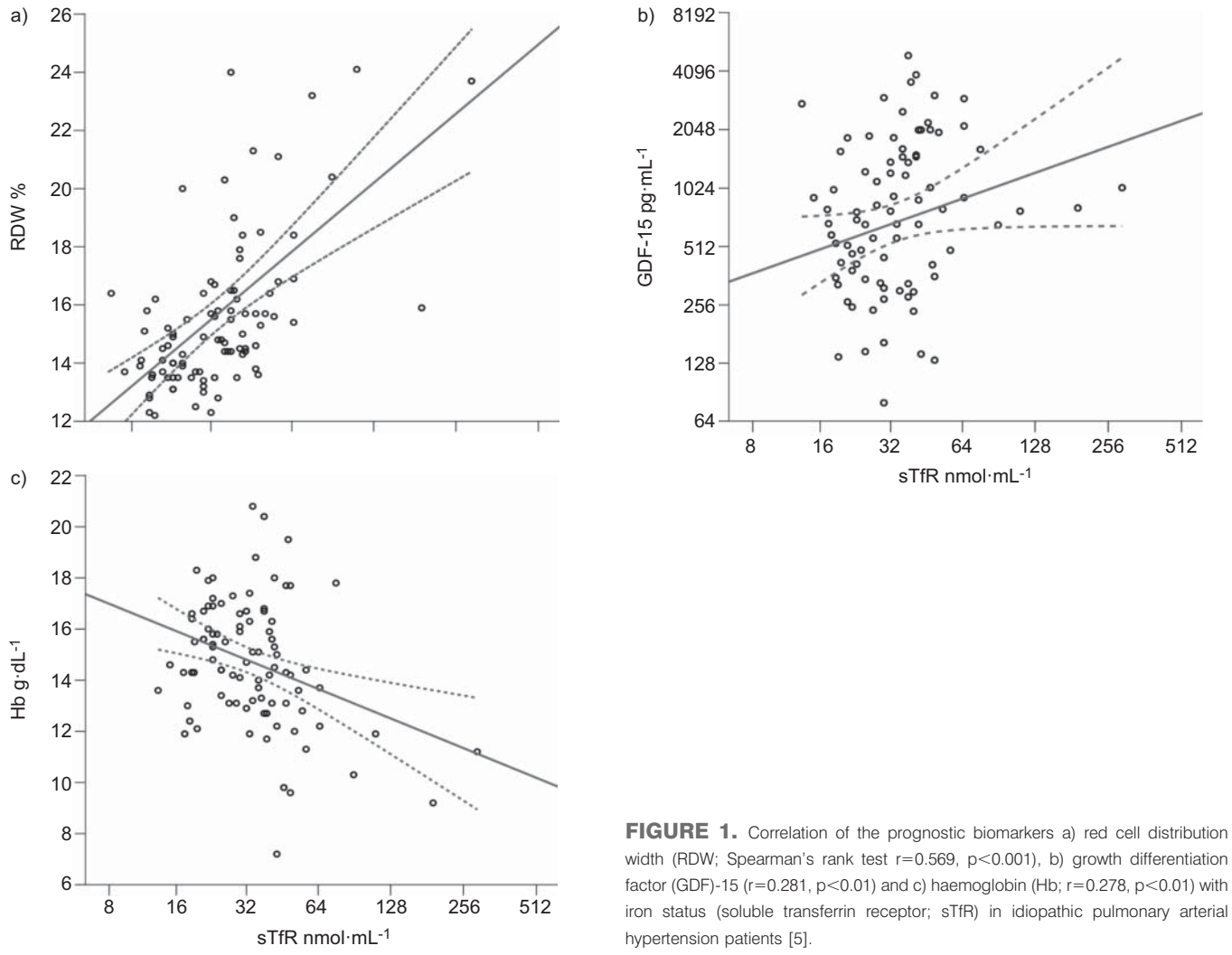

FIGURE 1. Correlation of the prognostic biomarkers a) red cell distribution width (RDW; Spearman's rank test $r=0.569$, $p<0.001$), b) growth differentiation factor (GDF)-15 ($r=0.281$, $p<0.01$) and c) haemoglobin (Hb; $r=0.278$, $p<0.01$) with iron status (soluble transferrin receptor; sTfR) in idiopathic pulmonary arterial hypertension patients [5].

haemoglobin levels [22], but further investigations are required to determine the mechanisms underlying this phenomenon.

IRON STATUS AND PROGNOSTIC BIOMARKERS IN PULMONARY HYPERTENSION

In addition to the effects of iron on pulmonary vascular tone and the symptoms of CHF, iron has been implicated in the pathophysiology of pulmonary hypertension through studies of prognostic biomarkers. Red cell distribution width (RDW) is a measure of the variability of red blood cell size and is used clinically to distinguish iron deficiency anaemias. RDW is predictive of cardiovascular mortality in otherwise healthy older adults [23], and its prognostic power in CHF has been linked to iron deficiency and ineffective erythropoiesis [24]. In patients with pulmonary hypertension, RDW predicted mortality, outperforming more established markers, such as N-terminal pro-brain natriuretic peptide and blood urea nitrogen measurements, in multivariable models [25].

More recently, anaemia was found to be associated with poor survival in patients with pulmonary hypertension, the prognostic significance of anaemia being independent of known predictors of mortality including age, NYHA functional class, grade of tricuspid regurgitation, pulmonary vascular resistance and the aetiology of pulmonary hypertension [26]. Another potential biomarker in pulmonary hypertension is growth differentiation factor (GDF)-15 [27]. Circulating GDF-15 levels are raised in patients with IPAH [27] and production can be induced in several isolated cell types as well as in healthy volunteers following treatment with desferrioxamine [28]. Data from our own laboratory indicate that RDW, GDF-15 and haemoglobin levels correlate to a varying extent with iron status, as indicated by circulating levels of soluble transferrin receptor (sTfR), in patients with IPAH (fig. 1).

IRON DEFICIENCY IN IPAH

Recently, three research groups have independently examined the prevalence of iron deficiency in IPAH [3–5]. In the first of these studies, RUITER *et al.* [3] found iron deficiency, as defined by reduced serum iron and transferrin saturations, in 30 (43%) out of 70 patients. Iron deficiency, irrespective of the existence of anaemia, was associated with a lower exercise capacity, as assessed by 6-min walk distance (6MWD). Interestingly, oral iron therapy was only effective at increasing ferritin levels in eight (44%) out of 18 patients, suggesting that dietary iron uptake may be dysfunctional in these patients. In a separate

study, SOON *et al.* [4] also described an association between IPAH and iron deficiency, defined primarily on the basis of low ferritin levels (<10 $\mu g \cdot L^{-1}$), with normal transferrin levels. Iron deficiency was most marked in pre-menopausal females, and patients with heritable PAH (HPAH) and mutations in the bone morphogenetic protein receptor type II (BMPR2) [4].

One difficulty in assessing the iron status of individuals with chronic diseases such as IPAH is the frequent coincidence of inflammation and the potential effects this may have on iron homeostasis (see later). The presence of inflammation can confound determination of iron status, as ferritin is induced whilst serum iron and transferrin saturations are repressed [29]. sTfR levels offer an alternative means of measuring iron availability that is unaffected by inflammation [30, 31]. Circulating sTfR levels in the normal range reflect erythropoietic activity (*i.e.* the uptake of iron in the bone marrow by transferrin receptors), whereas levels are disproportionately raised in iron deficiency [31] and may be a better marker of iron deficiency in diseases such as IPAH.

RHODES *et al.* [5] determined circulating sTfR levels in 98 patients with IPAH and found a high prevalence (63%) of iron deficiency (as defined by sTfR levels raised above the upper end of the normal range, 28.1 $nmol \cdot L^{-1}$) without overt anaemia. Furthermore, raised sTfR levels were associated with lower exercise capacity, higher World Health Organization (WHO) functional class and mortality, predicting survival independently of WHO class, 6MWD and age [5]. These data highlight the prevalence of iron deficiency in IPAH and suggest that it is clinically important, although the underlying cause is not clear. Possible reasons include reduced iron intake, chronic blood loss and impaired iron absorption. There is no reason to indicate that patients with IPAH have a diet that is deficient in iron and, although these patients are predominantly female, the differences could not be attributed to the potentially confounding effects of warfarin or targeted therapies for PAH [3–5].

Patients with IPAH exhibit significant changes in skeletal muscle [32]. One hypothesis is that the reduced exercise capacity observed in iron-deficient IPAH patients [3, 5] reflects iron-dependent alterations in myoglobin and muscle oxygen homeostasis. Aside from haemoglobin, myoglobin is the most abundant haem-containing, and therefore iron-dependent, protein in humans [33]. This extensively studied protein has a number of key functions, acting to maintain tissue oxygen concentrations, facilitate oxygen diffusion from capillaries to mitochondria and regulate nitric oxide levels. Myoglobin scavenges nitric oxide and reactive oxygen species under oxygenated conditions and produces nitric oxide from nitrite under deoxygenated conditions [34, 35]. Studies in human volunteers indicate that in some situations where erythropoiesis is strongly stimulated, for example at high altitude (4,500 m), myoglobin may represent a source of iron for haemoglobin production [36]. This effect contrasts with previously noted adaptations to chronic hypoxia; increased skeletal muscle myoglobin has been demonstrated in humans and animals living at high altitude and deep-sea diving animals [37–39]. However, myoglobin expression is not directly induced by hypoxia alone but by hypoxia in combination with exercise or other stimuli of calcium signalling in muscle [40].

Muscle myoglobin levels may also be low in patients with IPAH (A. Vonk-Noordegraaf, unpublished observations). Since myoglobin acts as an ''intracellular haemoglobin'', reducing oxygen tension in the cytoplasm and, therefore, facilitating further oxygen diffusion into the cell, low myoglobin levels could directly affect oxygen extraction and so exercise capacity. A similar hypothesis has been raised in CHF, though recent data suggested exercise intolerance in these patients was not due to myoglobin deficiency [41]. At present, it is unknown whether skeletal muscle myoglobin levels are substantially affected in iron-deficient IPAH patients.

REGULATION OF IRON HOMEOSTASIS IN IPAH

The control of circulating and intracellular iron concentrations is important to enable both effective erythropoiesis and the activity of iron-dependent biochemical reactions, iron being essential for normal cellular metabolism and respiration. Iron overload is also detrimental, leading to toxicity and cell death, primarily due to formation of free radicals *via* the Fenton or Haber–Weiss reactions [42, 43]. Thus, iron homeostasis is tightly controlled. Around two-thirds of the body's iron is found in haemoglobin in erythrocytes, and ~10% in muscle myoglobin or enzymes and cytochromes in other tissues. Under normal iron-replete conditions, the majority of the remaining iron is stored intracellularly, bound to ferritin or haemosiderin molecules, in the reticuloendothelial system and bone marrow [33]. Erythrocyte iron is effectively recycled by macrophages of the reticuloendothelial system, with cell-free haemoglobin and haem being scavenged by haptoglobin and haemopexin molecules, respectively. There is no mechanism for iron excretion and the small daily loss of iron (1–3 mg), due to sloughing of intestinal mucous cells, menstruation and other blood loss, is balanced by dietary iron absorption.

The master regulator of iron homeostasis is hepcidin, which acts to inhibit the efflux of iron into the blood from enterocytes and iron storing cells by binding to ferroportin and inducing its degradation in lysosomes [44]. Hepcidin is thought to be expressed mainly in the liver and its production is inhibited by iron deficiency and increased erythropoiesis, and induced by iron overload and inflammation (fig. 2). Chronically raised hepcidin levels cause systemic iron deficiency and underlie the anaemia of chronic disease [29]. Some patients with IPAH exhibit raised circulating hepcidin levels in the face of iron deficiency, suggesting that inhibition of dietary iron uptake by hepcidin might contribute to iron deficiency [5]. This is also consistent with the lack of an effect of oral iron therapy in a majority of IPAH patients [3].

The mechanisms of iron sensing are not well understood, but it has become apparent that bone morphogenetic protein (BMP) signalling has a critical role in controlling hepcidin expression. The BMPs are a multifunctional family of proteins that act through binding to heteromeric combinations of type 1 and 2 receptors, leading to the activation (phosphorylation) and nuclear translocation of receptor-activated SMADs (SMAD1, 5 and 8) and the common SMAD4 [45]. BMP-6 has emerged as the principal BMP regulating hepatic hepcidin expression *in vivo*. Iron stimulates BMP-6 expression, leading to increased hepcidin expression, whereas BMP-6 knockout mice display severe iron overload and reduced hepcidin expression [46–49]. This pathway is of particular interest in PAH as BMPR2

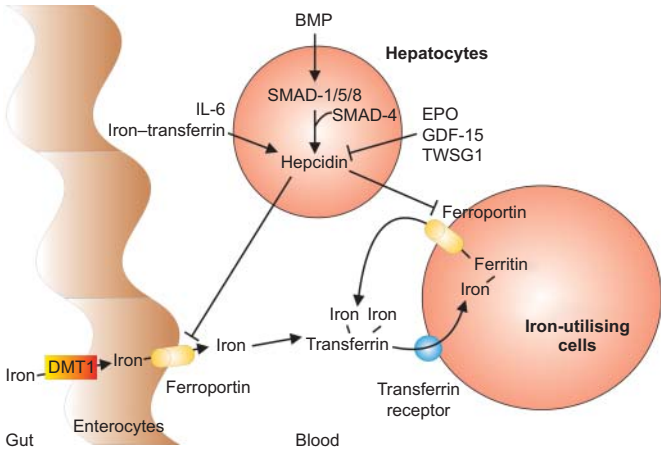

FIGURE 2. Regulation of dietary iron uptake and release from iron-utilising cells by hepcidin. Hepcidin acts to internalise ferroportin, leading to its degradation and inhibition of dietary iron uptake and release of iron from iron-utilising or -storing cells. Hepcidin is regulated by several factors, though bone morphogenetic protein (BMP) signalling through the SMAD transcription factors, which can be modulated by haemojuvelin, appears to be of particular importance. Hepcidin expression can be stimulated by inflammation (through interleukin (IL)-6) and circulating iron (iron–transferrin). Erythropoiesis (and erythropoietin (EPO)) indirectly inhibits hepcidin, and circulating erythroid factors, such as growth differentiation factor (GDF)-15 and twisted gastrulation (TWSG)1, have been proposed to directly inhibit hepcidin. Divalent metal transporter (DMT)1 is responsible for uptake of dietary iron into enterocytes.

expression is reportedly reduced in IPAH patients and loss-of-function BMPR2 mutations have been linked to >70% of familial and ~20% of idiopathic cases of PAH [50, 51]. Interestingly, the stimulation of hepcidin expression and protein production by BMP-6 in human hepatoma HepG2 cells is increased following the knockdown of BMPR2 by small interfering RNA transfection, raising the possibility that dysfunctional BMPR2 signalling may contribute to raised hepcidin levels and, therefore, iron deficiency in PAH [5].

Hepcidin is an acute-phase reactant protein [52] that is induced by interleukin (IL)-6 during inflammation [53]. IL-6 levels are known to be increased in IPAH but, as discussed previously, attempts to establish a relationship with iron status may be confounded by the effect of inflammation on indices such as serum iron, ferritin and transferrin saturations. Nonetheless, RHODES *et al.* [5] found no correlation between hepcidin levels and IL-6 or C-reactive protein in IPAH patients, whether or not iron status was taken into account by considering sTfR or ferritin levels. SOON *et al.* [4] also found that higher IL-6 levels were not accompanied by increased hepcidin in IPAH, suggesting that inflammation and IL-6 are not the principal cause of raised hepcidin and iron deficiency in these patients. Nonetheless, BMP signalling and IL-6 may act together to regulate iron homeostasis and the inhibition of BMP signalling has been put forward as a means of targeting hepcidin production and anaemia associated with inflammation [54].

Erythropoietin is another potential regulator of hepcidin that is increased in IPAH. However, as in healthy controls, there is a negative correlation between the two that is consistent with a reduction in hepcidin production as erythropoietic demand for iron increases [5, 55]. Iron deficiency or anaemia may also drive increases in other HIF-inducible factors, including the myeloid-activating factors stromal-derived factor-1α, stem cell factor and hepatocyte growth factor [55]. This might contribute to myeloproliferative processes and recruitment of pro-angiogenic progenitor (CD34+ CD133+) cells to the pulmonary vasculature in PAH patients [55]. Interestingly, myeloid abnormalities were also demonstrated in unaffected relations of HPAH patients, suggesting that HIF-inducible factors and myeloid abnormalities may have a role in the pathology of PAH prior to the clinical manifestation of the disease. It remains to be determined whether these processes are exacerbated by iron deficiency or anaemia in PAH. Nevertheless, iron chelation with desferrioxamine has recently been shown to increase the pro-angiogenic activity of vascular endothelial cells [56].

GENETIC DETERMINANTS OF IRON STATUS

Genetic factors are thought to make a substantial contribution to variation in iron status [57–59]. Indeed, genome-wide association studies have identified common gene variants connected with haemoglobin levels and blood cell traits indicative of altered erythropoiesis and iron regulation. These include single-nucleotide polymorphisms in the *TMPRSS6* and *TRF2* genes, encoding the serine protease matriptase-2 and transferrin receptor type-2, which associate with variation in iron and haemoglobin levels and RDW [60–63]. In addition, a recent study has linked the *TMPRSS6* genotype with hepcidin production and suggested that some variants may be more susceptible to an imbalance in iron homeostasis [64]. Further studies are required to investigate whether such genetic differences contribute to the dysregulation of iron homeostasis in pulmonary hypertension.

IRON DEFICIENCY AS A POTENTIAL THERAPEUTIC TARGET IN IPAH

Although iron deficiency is prevalent in IPAH and may impact on the exercise capacity, disease severity and survival of these patients, it is unclear whether this involves effects on pulmonary haemodynamics, cardiac function and/or skeletal muscle function. It will also be important to explore the safety and efficacy of therapeutic strategies designed to improve iron homeostasis in IPAH. Thus, in contrast to the negative pulmonary effects of iron deficiency, increasing pulmonary vascular tone and exacerbating hypoxia-induced pulmonary hypertension [8–10], it has recently been proposed that iron depletion may inhibit the development of right ventricular hypertrophy in pulmonary hypertension [65]. This suggestion arose from the finding that expression of the transcription factor GATA4, a major regulator of cardiac hypertrophy, was enhanced in the right ventricle of rats following pulmonary artery banding or exposure to chronic hypoxia, and was dependent on iron-catalysed protein oxidation and degradation. The expression of GATA4 has also been implicated in regulating transcription of the S100 calcium-binding protein S100A4/Mts1 [66], which is overexpressed in pulmonary vascular lesions [67], and in mediating the growth effects of serotonin and endothelin-1, which are known to be related to pulmonary vascular remodelling in PAH [68, 69], in pulmonary artery smooth muscle cells [70].

Studies on iron in rat models of systemic cardiovascular disease have provided inconsistent results, with protective [71] as well as detrimental effects being attributed to iron deficiency [72, 73]. Such differences may reflect variations in iron handling between

rat strains [71, 74]. Iron loading has also been proposed as a risk factor for atherosclerosis [75]; accumulation of iron in atherosclerotic plaque macrophages being linked with oxidative stress, the release of pro-inflammatory cytokines and raised hepcidin levels, whereas low levels of hepcidin may be associated with reduced macrophage iron stores [76]. The normal pulmonary vascular bed is protected from atherosclerosis and it is unclear if inappropriately raised hepcidin levels in IPAH are associated with pulmonary vascular lesions.

There are a number of challenges to the design of therapeutic strategies for iron supplementation in IPAH. Dosing is a complex issue, as the use of the Ganzoni formula to calculate iron deficiency [77] is not applicable in a patient population such as those with IPAH, where haemoglobin levels are within the normal range. Nevertheless, the use of ferric carboxymaltose (Ferinject®) could potentially enable a single dose of $\leqslant$1 g to be administered by infusion to individuals with a body weight of >35 kg. Half of this amount would be expected to replenish the iron stores of an individual with a body weight of >35 kg, the remainder being sufficient to increase haemoglobin levels by up to ~3 $g \cdot dL^{-1}$ [77].

Another important issue is the selection of appropriate end-points to evaluate the effects of intravenous iron supplementation, in particular, novel end-points that require relatively few patients [78]. Trials of new therapies in PAH have traditionally assessed effects on exercise capacity by measuring 6MWD, but in the case of iron supplementation, direct measurements of skeletal muscle strength and endurance, muscle histochemistry and oxygen utilisation are also warranted. The apparent impact of iron status on the regulation of pulmonary vascular tone [8–10] and relatively low variability in measurements of pulmonary vascular resistance, as determined by cardiac catheterisation, make this an attractive end-point for investigating the possible pulmonary haemodynamic benefits of iron therapy. Other potentially useful end-points include cardiopulmonary exercise testing and exercise endurance, which may provide further insight into how iron availability affects functional capacity [79], and cardiac magnetic resonance imaging, which, like pulmonary vascular resistance, exhibits relatively little variation and, hence, higher power to detect structural and functional differences of the ventricles in small patient populations [80, 81]. Two parallel studies from our centre (Hammersmith Hospital, London, UK) and others in the UK and Amsterdam (the Netherlands) have been established to examine the multifaceted aspects of the response to intravenous iron replacement in PAH, incorporating these end-points in addition to safety measures.

SUMMARY AND CONCLUSIONS

Iron status influences several important aspects of physiology that are relevant to pulmonary hypertension. The prevalence and prognostic power of iron deficiency in IPAH patients indicates that it is a potential therapeutic target. Dietary iron absorption may be repressed in these patients, and clinical studies are underway to explore the safety and possible benefit of parenteral iron treatment in IPAH.

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STATEMENT OF INTEREST

None declared.

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