

Iron therapy in patients with chronic kidney disease: taking the high road?

Walter H. Hörl

Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria.

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■ ABSTRACT

Iron deficiency is common in patients with chronic kidney disease (CKD) as a result of stimulated erythropoiesis, reduced dietary iron intake, inhibition of intestinal iron absorption, inhibition of iron release from macrophages or enterocytes and/or iron losses. Many factors such as iron overload, pro-inflammatory cytokines, haemochromatosis protein, transferrin receptor 2, haemojuvelin, transcription factor Smad 4 and/or bone morphogenetic proteins promote the expression of *Hamp*, the gene encoding hepcidin, while the transmembrane serine protease 6 (TMPRSS6) down-regulates hepcidin mRNA transcription and thus promotes intestinal iron uptake and release of iron from storage cells. Iron can be supplemented orally but intravenous iron therapy is more effective for the correction of iron deficiency in the majority of CKD patients. Iron status should be monitored according to international guidelines. However, while low serum ferritin level is reported to be highly specific in diagnosing iron deficiency, elevated ferritin levels in CKD patients do not exclude iron deficiency, particularly in CKD patients with malnutrition, inflammation, infection, liver disease or malignancy. Serum ferritin does not predict response to intravenous iron therapy in the CKD patient population. Recent data favour more aggressive intravenous iron use, particularly in CKD patients with high erythropoietin stimulating agent (ESA) requirements. Intravenous iron compounds such as low molecular weight iron dextran, ferric gluconate and iron sucrose as well as the newer iron preparations ferumoxytol and ferric carboxymaltose

should allow (in addition to oral iron preparations) optimal iron supply in CKD patients.

Key-Words:

Chronic kidney disease; dialysis patients; ferritin; hepcidin; intravenous iron therapy; oral iron.

■ INTRODUCTION

Anaemia is a common feature of patients with advanced chronic kidney disease (CKD). Multiple factors including impaired renal production of erythropoietin, inflammation as a compound of CKD, decreased red blood cell survival, low vitamin C levels, blood loss and iron deficiency contribute to the anaemia associated with CKD.

The clinical use of erythropoiesis stimulating agents (ESAs) allows correction of renal anaemia in the majority of CKD patients but not in all¹ indicating that anaemia in this patient population is not solely a consequence of ESA deficiency. Inadequate iron availability is the most important of many factors blunting the effectiveness of ESA therapy^{2,3}.

The estimated prevalence of iron deficiency in haemodialysis patients during ESA therapy is around 40-90%⁴⁻⁶. Iron deficiency is also remarkably common in anaemic patients with CKD not on dialysis therapy⁷⁻⁹. Iron can be supplemented orally or intravenously. Intravenous iron therapy is required by

almost all haemodialysis patients to maintain iron stores. Oral iron therapy is usually ineffective in providing sufficient iron in haemodialysis patients but is considered for patients with CKD not on dialysis therapy, for peritoneal dialysis patients and for patients after successful kidney transplantation. Intestinal iron absorption, however, is often impaired in patients treated with oral iron supplementation due to the enhanced hepatic production and/or reduced renal degradation of hepcidin. This liver-derived peptide hormone is produced in response to acute-phase reactions by proinflammatory cytokines (such as interleukin-6 and interleukin-1) but also in response to iron overload. Hepcidin inhibits non-heme intestinal iron absorption via the enterocyte proton driven divalent metal transporter-1. It inhibits also the release of iron from macrophages and other cells by internalisation and degradation of the iron exporter ferroportin. In contrast, anaemia, iron deficiency and ESA stimulated erythropoiesis strongly down-regulate hepatic hepcidin production, allowing intestinal iron absorption and iron release from reticuloendothelial cells under these conditions¹⁰. Storage iron held in intracellular ferritin is released to ferroportin, passes out of the cells and is picked up at the surface of the storage cells by transferrin. Transferrin is usually not saturated. International guidelines recommend that typically 20-50% of its iron binding sites are occupied in CKD patients during iron therapy. Transferrin carries iron from its storage site in the reticuloendothelial system (RES) to the bone marrow. Transferrin saturation (TSAT) decreases when there is limited circulating iron because of iron deficiency. As storage iron increases there is a corresponding increase in a circulating form of ferritin in the plasma.

Storage iron can be estimated by plasma ferritin, if inflammation, infection, malnutrition, liver disease and/or malignancy do not interfere. Under normal conditions, most cells contain little ferritin, whereas cells in the RES contain larger amounts of ferritin. When iron enters the cell, ferritin mRNA is processed and ferritin H and L subunits are produced. Pro-inflammatory cytokines also increase the synthesis of both H and L subunits of ferritin. During inflammation, higher amounts of ferritin may trap more body iron. In addition, release of storage iron is inhibited during inflammation. Both hepcidin-mediated mechanisms have evolved to protect the individual against microbial infection or against worsening an

already ongoing infection. On the other hand, inflammation induced hyperferritinaemia may result in functional iron deficiency and anaemia of inflammation (anaemia of chronic disease) such as in CKD or other chronic disease states^{11,12}. Mice with constitutively over-expression of hepcidin die from severe iron-deficient anaemia¹³, while mutations in the hepcidin gene result in a severe form of juvenile haemochromatosis¹⁴.

HFE (haemochromatosis protein)¹⁵, transferrin receptor 2¹⁶, haemojuvelin¹⁷, the transcription factor Smad4¹⁸, proinflammatory cytokines^{19,20} and the bone morphogenetic proteins BNP-2, BNP-4, and BNP-9²¹ promote expression of *Hamp*, the gene encoding hepcidin. In contrast, down-regulation of *Hamp* in response to iron deficiency is caused by the transmembrane serine protease 6 (TMPRSS6)²². This recently detected protein provides new insights into the intestinal iron absorption. TMPRSS6 is required to sense iron deficiency and to permit normal uptake of enteric iron in response to iron depletion by prevention of the transcription of *Hamp*²².

■ ORAL VERSUS INTRAVENOUS IRON THERAPY IN CKD PATIENTS

Stoves *et al.*²³ found in predialysis patients with a calculated creatinine clearance between 11 and 21 ml/min that the efficacy of monthly 300 mg iron sucrose given intravenously was not superior with respect to haemoglobin response or ESA dose as compared to a daily oral dose of 600 mg of ferrous sulphate or equivalent. In this study, serum ferritin values ranged from 47 to 155 ng/ml at baseline. Charytan *et al.*²⁴ randomly assigned 96 ESA-treated patients with CKD to intravenous iron sucrose (5 doses of 200 mg every week) or oral iron (three times ferrous sulphate daily) supplementation. There was no significant difference in mean haemoglobin levels between the two groups at the conclusion of the study.

In the study of Mircescu *et al.*²⁵, intravenous administration of 200 mg of iron sucrose per month resulted in an increase of haemoglobin levels from 9.7±1.1 to 11.3±2.5 g/dl after 12 months in non-diabetic CKD patients with a calculated glomerular

filtration rate (Cockcroft-Gault formula) of 36.2 ± 5.2 ml/min. None of these CKD patients received ESA treatment. After one year of iron sucrose therapy, median serum ferritin increased from 98.0 to 442.5 ng/ml. Most importantly, kidney function did not deteriorate over a period of 12 months. After one year of iron sucrose treatment, 80% of the CKD patients of this study had haemoglobin values >10 g/dl (55% had haemoglobin values >11 g/dl), 76% of the patients had a ferritin >100 ng/ml and 97% of the patients had a TSAT >20 %. The authors concluded that intravenous iron sucrose therapy is an effective and safe treatment option to correct anaemia in non-dialysis CKD patients²⁵.

Silverberg *et al.*²⁶ showed that intravenous iron sucrose therapy combined with low-dose ESA treatment is more effective in increasing haemoglobin levels in non-dialysis CKD patients than iron sucrose therapy alone. Agarwal *et al.*²⁷ randomly assigned 40 CKD patients on ESA therapy to either intravenous iron (100 mg of elemental iron two times per month) or oral iron (200 mg ferrous sulphate three times daily). At three months, haemoglobin increased from 5.83 ± 0.60 to 10.05 ± 0.90 g/dl in the intravenous iron group more than in the oral iron group (from 6.26 ± 1.0 to 8.94 ± 1.17 g/dl).

Van Wyck *et al.*²⁸ randomly assigned 161 patients with CKD to treatment with 1g iron sucrose intravenously divided over 14 days, or oral ferrous sulphate (325mg three times daily) for 56 days. An increase in haemoglobin levels of 1.0 g/dl occurred in 44% of patients treated with intravenous iron as compared to 28% of patients treated with oral iron ($P=0.0344$). The increase in mean haemoglobin level as compared to baseline by day 42 was 0.7 g/dl in the iron sucrose group and 0.4 g/dl in the ferrous sulphate group ($P=0.0298$), indicating modestly improved efficacy with intravenous iron over oral iron therapy in CKD patients not on dialysis therapy. It was suggested that intravenous iron therapy is more effective in dialysis patients as compared to non-dialysis CKD patients²⁹. More probably is that oral iron therapy is more effective in non-dialysis CKD patients as compared to dialysis patients, possibly due to lower systemic inflammation associated with lower hepcidin production.

In an open-label, randomised, controlled, multi-centre Phase III trial, 304 patients with non-dial-

ysis CKD were randomly assigned in a 3:1 ratio to two 510-mg doses of intravenous ferumoxytol within 5 ± 3 days or 200 mg of elemental oral iron daily for 21 days. The increase in haemoglobin at day 35 was 0.82 ± 1.24 g/dl with ferumoxytol and 0.16 ± 1.02 g/dl with oral iron ($P=0.0001$). Among CKD patients not treated with ESAs, haemoglobin increased 0.62 ± 1.02 g/dl with ferumoxytol and 0.13 ± 0.93 g/dl with oral iron. Among CKD patients treated with ESAs, haemoglobin increased 1.16 ± 1.49 g/dl with ferumoxytol and 0.19 ± 1.14 g/dl with oral iron. Treatment-related adverse events occurred in 10.6% of the CKD patients treated with ferumoxytol but in 24.0% of the CKD patients on oral iron. None of the adverse events was serious³⁰. A major problem with this study is the fact that non-dialysis CKD patients with a very low TSAT (11.3 ± 6.1 % in the ferumoxytol group and 10.1 ± 5.5 % in the oral group) received only a low-dose and short time oral iron therapy (200mg of ferrous sulphate per day, in other studies 3×200 or 3×325 mg/day). Not surprisingly, TSAT values did not increase in the low-dose oral iron treated CKD patient group³⁰. In a randomised control trial of 250 non-dialysis CKD patients, superior efficacy and lower adverse event incidence of intravenous ferric carboxymaltose as compared to oral iron sulphate was demonstrated³¹.

Taken together, the majority of studies show that intravenous iron therapy is more effective than oral iron in non-dialysis CKD patients with iron deficiency. In the absence of systemic inflammatory disease, oral iron is a therapeutic option for CKD patients, since normal or only mildly elevated hepcidin levels should allow intestinal iron absorption under this condition.

■ INTRAVENOUS IRON THERAPY IN HAEMODIALYSIS PATIENTS

Intravenous iron therapy reduces ESA dose and/or increase haemoglobin levels in haemodialysis patients. For example, in haemodialysis patients with severe iron deficiency (pre-treatment TSAT values of 11%) an ESA dosage reduction of 70% was achievable when patients were supplemented adequately with parenteral iron³². Iron dextran-treated haemodialysis patients were targeted to serum ferritin

levels of 200 or 400 ng/ml. In this study, mean serum ferritin levels of 299 ng/ml and 469 ng/ml were achieved. The higher ferritin group had 28% lower ESA dosage requirements³³. An aggressive iron dextran protocol (501 mg iron/month over a period of 6 months) resulted in an increase of TSAT >30% and dropped ESA dosage requirements by 40% as compared to a more moderate iron dextran protocol (176 mg iron/month with a TSAT between 20% and 30%). The patients in the high TSAT group, however, achieved mean serum ferritin levels of 730 ng/ml (which is above the recommendations made by international guidelines), whereas those patients in the low TSAT group had a mean serum ferritin of 297 ng/ml³⁴.

The DRIVE (Dialysis Patients' Response to IV Iron with Elevated Ferritin) study evaluated the efficacy of intravenous ferric gluconate (125 mg after eight consecutive haemodialysis sessions) in haemodialysis patients with haemoglobin ≤ 11 g/dl, ferritin between 500 and 1200 ng/ml, TSAT ≤ 25 % and ESA dosage ≥ 225 IU/kg per week or $\geq 22,500$ IU/week. At six weeks, haemoglobin increased significantly more ($P=0.028$) in the intravenous iron group (from 10.4 ± 0.8 to 11.9 ± 1.3 g/dl) as compared to the control group (from 10.2 ± 0.7 to 11.3 ± 1.4 g/dl). Serum ferritin increased in the intravenous iron group from 759 ± 190 to 929 ± 297 ng/ml, and decreased from 765 ± 193 to 591 ± 274 ng/ml in the control group³⁵. The data indicate that intravenous iron therapy is superior to no iron therapy in anaemic ESA treated haemodialysis patients even if serum ferritin levels are in a range between 500 and 1200 ng/ml. A six week observational extension of the DRIVE study (DRIVE-II) was designed to investigate how ferric gluconate impacted ESA dosage after DRIVE. During DRIVE-II dose of ESA and intravenous iron were adjusted as clinically indicated. By the end of observation, patients in the ferric gluconate group required significantly less ESA than their DRIVE dose (mean change of $-7527 \pm 10,021$ IU/week, $P=0.003$), whereas the ESA dose essentially did not change for patients in the control group. Mean haemoglobin, TSAT and serum ferritin levels remained significantly higher in the ferric gluconate group as compared to the control group. It was concluded that ferric gluconate maintains haemoglobin and allows lower ESA doses in anaemic haemodialysis patients with low TSAT and serum ferritin levels up to 1200 ng/ml³⁶.

■ ORAL VERSUS INTRAVENOUS IRON THERAPY IN PERITONEAL DIALYSIS PATIENTS

The route of iron administration can be either intravenous or oral in peritoneal dialysis (PD) patients. PD patients with minimal iron deficiency may respond to oral iron. A recent study by Li and Wang³⁷ suggest that intravenous iron should be favoured over oral iron in PD patients with haemoglobin <9 g/dl, serum ferritin <500 ng/ml and TSAT <30%. This study confirmed earlier work of Ashan³⁸ who already demonstrated that intravenous iron administration is more efficacious than oral iron therapy also in PD patients. Extrapolation of studies from the haemodialysis patient population may favour even more aggressive intravenous iron use in PD patients with high ESA requirements³⁹.

Ferric carboxymaltose⁴⁰ and iron dextran can be given in a single dose up to 1000 mg, while two visits and vein punctures are required to administer 1000 mg ferumoxytol, and 4-8 visits and vein punctures are usually required to administer 1000 mg iron sucrose or ferric gluconate.

■ IS THERE EVIDENCE FOR A FERRITIN LIMIT IN IRON ADMINISTRATION?

Low serum ferritin level is reported to be highly specific in diagnosing iron deficiency but moderately high serum ferritin concentration is not necessarily a sign of iron overload in dialysis patients⁴¹. The level of serum ferritin at which CKD patients are considered to be in an iron overload state has not been determined. It is probable that haemodialysis patients will have little to no risk of iron-related tissue damage at ferritin levels approaching 1000 ng/ml⁴². Patients with haemochromatosis and serum ferritin <1000 ng/ml do not have evidence of liver pathology⁴³. Almost half of all maintenance haemodialysis patients in the United States already have a serum ferritin above the international recommended upper limit of 500 ng/ml. Serum ferritin levels up to 1200 ng/ml do not increase all-cause mortality in haemodialysis patients⁴⁴. ESA-treated dialysis patients benefit from intravenous iron administration by an increase of their haemoglobin

level even in the presence of serum ferritin levels between 500 and 1200 ng/ml^{35,36}, but serum ferritin does not predict response to intravenous iron therapy in this patient population⁴⁵. Ali *et al.*⁴⁶ investigated the relation between serum ferritin levels and stainable-iron deposits in the liver, spleen, and bone marrow in 36 CKD patients who died after being on haemodialysis for 1-103 months. These patients were treated with iron dextran before. Serum ferritin levels correlated with the degree of hepatosplenic siderosis. The authors identified 10 marrow-iron-depleted subjects with a mean serum ferritin of 1336 ng/ml. These data demonstrate that in a single haemodialysis patient even a serum ferritin of 1336 ng/ml does not exclude bone marrow iron depletion⁴⁶.

Patients with end-stage renal disease have elevated markers of oxidative stress caused by uraemic toxins, haemodialysis therapy, smoking and/or systemic inflammatory disease. Aggravation of oxidative stress occurs by the generation of bioactive iron (nontransferrin binding iron) during intravenous iron therapy. Oxidative stress is evaluated by measurement of oxidative by products generated by oxidative damage to cellular constituents, such as membrane lipids (e.g. malondialdehyde), proteins (advanced oxidation protein products, carbonylated fibrinogen) and/or DNA (8-hydroxy 2'-deoxyguanosine (8-OHdG)). Oxidative stress is also evaluated by the assessment of reactive oxygen species and the antioxidant levels. The use of 8-OHdG was recommended as a dosimeter of oxidative stress induced by iron therapy⁴⁷.

Kuo *et al.*⁴⁷ found a time- and dose-dependent rise in lymphocyte 8-OHdG levels in lymphocyte DNA. Mean lymphocyte 8-OHdG content was significantly higher in haemodialysis patients receiving 100 mg iron sucrose every week for 12 weeks as compared to control patients, especially if plasma ferritin levels were between 500 and 800 ng/ml. It was concluded that intravenous iron sucrose provokes oxidative damage to peripheral blood lymphocyte DNA in haemodialysis patients, especially among those patients with high levels of plasma ferritin⁴⁷. These data argue for an upper ferritin limit of 500 ng/ml in end-stage renal disease patients without malnutrition, inflammation, infection, liver disease or malignancy.

CONCLUSIONS

Inadequate iron availability is the most important factor blunting the effectiveness of ESA therapy. Iron can be supplemented orally or intravenously. Intestinal iron absorption is often impaired in CKD patients treated with oral iron supplementation due to the enhanced hepatic production and/or reduced renal degradation of hepcidin. Thus, intravenous iron therapy reduces ESA dose and/or increase haemoglobin levels in non-dialysis CKD patients and in dialysis patients more than oral iron therapy. Iron status of these patients should be monitored according to international recommendations (guidelines). The upper limit of serum (plasma) ferritin, however, is currently opinion based, and higher levels should be considered for CKD patients with malnutrition, inflammation, infection, liver disease and/or malignancy.

Conflict of interest statement. None declared.

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Correspondence to:

Walter H. Hörl MD, PhD, FRCP

Professor of Medicine

Chief, Division of Nephrology and Dialysis

Department of Medicine III

Währinger Gürtel 18-20

A-1090 Vienna, Austria

E-mail: Walter.hoerl@meduniwien.ac.at