How to Supplement Iron in Patients with Renal Anemia

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Key Words

Iron · Renal · Anemia · Chronic kidney disease · Dialysis · Hemodialysis · Kidney · Erythropoietin · Cardiovascular risk · Infection

Abstract

Iron deficiency is a major cause of hyporesponsiveness to erythropoiesis-stimulating agents (ESAs) and is often observed in chronic kidney disease (CKD) patients with anemia. With iron supplementation, ESA doses can be decreased, resulting in lower treatment costs and possibly lower cardiovascular risks that are associated with high-dose ESA therapy. The 2012 Kidney Disease: Improving Global Outcomes Guideline specified ferritin ≤ 500 ng/ml and transferrin saturation (TSAT) $\leq 30\%$ as thresholds of iron parameters for CKD patients. However, long-term safety (in terms of mortality, cardiovascular/infection risk and tissue deposition) of high-dose intravenous iron supplementation with such high target levels of ferritin/TSAT has not been confirmed. Recently, there has been increase in the use of intravenous iron and average ferritin levels in dialysis patients in the United States. Clinical trials conducted so far have been underpowered to conclusively establish the long-term safety of intravenous iron supplementation. Results from observational studies are conflicting, and many experimental studies have even shown negative effects of intravenous iron. Clearly, randomized clinical trials are urgently needed, studying various dos-

es of intravenous iron, with sufficient patient numbers and longer observation periods, to investigate mortality, cardiovascular effects and infection risks of this treatment. Until the long-term safety of iron supplementation at high doses is established, a more prudent decision on iron supplementation with lower target levels of ferritin/TSAT seems reasonable, in light of the decades of experience with ESA that has shown that definitive clinical outcomes have been dissociated from surrogate outcomes (especially hemoglobin concentration).

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Introduction

Iron deficiency is often observed in patients with chronic kidney disease (CKD) and is a major cause of hyporesponsiveness to erythropoiesis-stimulating agents (ESAs). Approximately, 50% of patients with CKD (stages 3–5, pre-dialysis) who have anemia and are not receiving ESA or iron supplementation show depleted iron stores in their bone marrow [1]. Although the use of intravenous iron in hemodialysis patients has significantly increased during the last decade [2], the appropriate iron dosing strategy in CKD patients remains debatable. In this review, we summarize and discuss relevant experimental and clinical data that provide conflicting evidence with regard to the iron dosing strategy in the treatment of renal anemia.

Table 1. Comparison of current guidelines and position statements on iron treatment in CKD patients

KDOQI [7]	A trial of iron treatment could be considered when TSAT is $\leq 30\%$, even if ferritin is >500 ng/ml
KDIGO [6]	A trial of iron treatment is suggested in patients with TSAT $\leq 30\%$ and ferritin ≤ 500 ng/ml
KHA-CARI [9]	Target levels: (i) TSAT $>20\%$ (prior to ESA), $20\text{--}30\%$ (during ESA) (ii) Ferritin >100 ng/ml (prior to ESA), $200\text{--}500$ ng/ml (during ESA)
ERBP [12]	Thresholds for iron overload: ferritin >500 ng/ml and TSAT $>30\%$
CSN [11]	Target levels: (i) TSAT $>20\%$ (ii) Ferritin >100 ng/ml (ND and PD), >200 ng/ml (HD)
JSDT [14]	Target levels: (i) TSAT $>20\%$ (ii) Ferritin >100 ng/ml

KDOQI = Kidney Disease Outcomes Quality Initiative; KHA-CARI = Kidney Health Australia Caring for Australasians with Renal Impairment; ERBP = European Renal Best Practice; CSN = Canadian Society of Nephrology; JSDT = Japanese Society for Dialysis Therapy; ND = non-dialysis; PD = peritoneal dialysis; HD = hemodialysis.

* Refer to each guideline or position statement for details.

Diagnosis of Iron Deficiency or Excess

Precise estimation of iron depletion or excess is a challenging task. Liver or bone marrow biopsies are invasive and inappropriate in everyday clinical setting. Instead, serum ferritin and transferrin saturation (TSAT) are often used to assess the iron status in CKD patients. Indeed, most guidelines for renal anemia worldwide have adopted these surrogate parameters. However, these 2 markers are not exempt from limitations. Although a serum ferritin level of <15 ng/ml predicts iron depletion in the healthy population [3], it is influenced by various factors, such as inflammation and infection, that are often seen in CKD patients [4]. TSAT is also influenced by inflammation and nutrition status [5].

The 2012 Kidney Disease: Improving Global Outcomes Guideline

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anemia in Chronic Kidney Disease states that ‘for adult CKD patients with anemia not on iron or ESA therapy, we suggest a trial of iron therapy if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired and TSAT is $\leq 30\%$ and ferritin is ≤ 500 ng/ml [6]’. The guideline also states that ‘for adult CKD patients on ESA therapy who are not receiving iron supplementation, we

suggest a trial of iron therapy if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is $\leq 30\%$ and ferritin is ≤ 500 ng/ml’. However, methods for supplementing iron in patients with renal anemia vary widely among countries (table 1). In contrast to the Kidney Disease Outcomes Quality Initiative [7] and the Kidney Health Australia Caring for Australasians with Renal Impairment [8, 9], the Canadian Society of Nephrology [10, 11] and the European Renal Best Practice [12] insist on lower TSAT and ferritin thresholds; Japan is even more conservative in its iron prescriptions [13, 14].

The KDIGO Guideline’s high TSAT and ferritin thresholds derive partly from several randomized controlled trials (RCTs) wherein intravenous iron supplementation raised Hb concentrations in CKD patients with high ferritin levels. One multicenter open-label RCT, the Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) trial, demonstrated that, even in hemodialysis patients ($n = 134$) whose ferritin was $500\text{--}1,200$ ng/ml and TSAT was $\leq 25\%$, 1 g of intravenous iron repletion resulted in significantly elevated Hb levels at 6 weeks, accompanied by a greater increase in TSAT [15]. It should be noted that the small number of patients and short observation period of the study limited the significance of these findings.

The Ferinject[®] Assessment in Patients with Iron Deficiency Anaemia and Non-dialysis-dependent Chronic Kidney Disease (FIND-CKD) study, published in 2014, was the first randomized study to compare high and low

ferritin targets for the purpose of adjusting intravenous iron dosing [16]. This 56-week, open-label, multicenter, prospective, randomized study enrolled 626 patients with pre-dialysis CKD, anemia, and iron deficiency who were not receiving ESAs. Patients were assigned to receive either intravenous iron, targeting a higher (400–600 ng/ml) or lower (100–200 ng/ml) ferritin level, or oral iron treatment. The percentage of patients who reached the study's primary end point (time to initiation of other anemia treatment or Hb trigger of 2 consecutive values <10 g/dl during weeks 8–52) was significantly lower and the increase in Hb was significantly greater in the high-ferritin target group than in the oral iron dosing group. Rates of adverse events were similar in all groups. The results of the study favor a high-ferritin target strategy in pre-dialysis CKD patients. However, the way in which this strategy affects clinical outcomes, such as mortality, cardiovascular events, and infections, is yet to be determined because the study was not sufficiently powered to answer this question.

Iron Administration Routes: Intravenous versus Oral

Generally, oral iron is characterized by limited efficacy and frequent gastrointestinal side effects, whereas intravenous iron demonstrates high efficacy but has been associated with acute reactions, including anaphylactoid reactions, hypotension, and abdominal/chest pain. Anaphylactoid reactions may occur because of immunologic interactions with the carbohydrate coating of intravenous iron products, especially dextran; however, it should be noted that all intravenous iron products, including non-dextran irons can cause anaphylactoid reactions [17]. Other acute reactions are likely due to labile plasma iron released from iron products, although this has not been proven yet [18]. Recently developed intravenous iron agents, including ferumoxytol, ferric carboxymaltose and iron isomaltoside 1000 minimize the release of labile iron, permitting high-dose infusions [17, 18].

Routes of iron administration in CKD patients were compared in a recent systematic Cochrane review [19]. The review found significantly higher levels of Hb (mean difference 0.90 g/dl), TSAT, and ferritin in patients who were treated with intravenous iron compared with oral iron. In addition, intravenous iron administration was associated with a significant reduction in ESA dose in dialysis patients. Combined with easy venous access in hemodialysis patients, an intravenous route could be considered a reasonable iron administration route in hemodialysis patients.

By contrast, the advantage of intravenous iron is less clear in patients who are not on dialysis; the differences in Hb levels attained with intravenous versus oral iron have been reported to be smaller in pre-dialysis CKD patients [6]. In addition, the Randomized Trial to Evaluate Intravenous and Oral Iron in Chronic Kidney Disease (REVOKE) trial, published in 2015, raised concern about intravenous iron in pre-dialysis CKD patients [20]. In this trial, 136 anemic patients with stages 3 and 4 CKD and iron deficiency anemia (ferritin <100 ng/ml or TSAT <25%) were randomized to either oral ferrous sulfate (325 mg 3 times daily for 8 weeks) or intravenous iron sucrose (200 mg every 2 weeks, total 1 g). Although Hb, TSAT, ESA dose and blood transfusions did not differ between groups throughout the 2-year observation period, the intravenous iron group was significantly more likely to experience infections and cardiovascular events. The inconsistency of these results with those of FIND-CKD may stem from differences in study design, including oral iron dose (975 mg/day in REVOKE vs. 200 mg/day in FIND-CKD). Therefore, in pre-dialysis CKD patients, the route of iron administration could be either intravenous or oral and should be determined by various factors such as severity of anemia and iron deficiency, patient adherence and future venous access sites.

Iron Deposition in the Tissues

High ferritin levels and high doses of iron supplementation have been associated with hepatic iron overload, which was measured by a superconducting quantum interference device [21] or MRI [22–24]. Rostoker et al. [24] prospectively examined iron concentrations in the liver of patients undergoing hemodialysis using MRI. They found that >80% of patients exhibited hepatic iron overload. Importantly, iron withdrawal or a major reduction in the iron dose resulted in decreased iron concentrations in the liver. The long-term effects of iron deposition in these tissues are still unclear.

Iron and Cardiovascular Risk

In vitro experiments have demonstrated that iron treatment results in a dose-dependent increase in the expression of adhesion molecules in human aortic endothelial cells, accompanied by enhanced mononuclear cell adhesion to the endothelial cells [25]. In 5/6 nephrectomized rats, intravenous iron induced oxidative stress in cardio-

vascular tissues [26]. A recent experimental study has furthered our understanding of how iron is involved in atherogenesis in CKD [27]. By conducting both in vitro and in vivo experiments, Kuo et al. [27] demonstrated that iron treatment increased mononuclear-endothelial cell adhesion through NADPH oxidase/NF- κ B/cell-adhesion molecule signaling, thus exacerbating atherosclerosis. These results are in line with previous observations that cumulative iron doses are positively related to carotid intima media thickness in hemodialysis patients [28, 29]. Recent observational studies have also demonstrated that intravenous iron administration of ≥ 50 mg per week [30] or > 800 mg within 6 months [25] is associated with a significantly increased risk of cardiovascular events. However, it should be noted that, as these studies were observational, causality could not be shown because of the remaining confounding factors. In contrast, another observational study of hemodialysis patients in the United States found an association between intravenous iron treatment (≤ 400 mg/month) and significantly better survival [31].

Iron supplementation was recently shown to benefit patients with heart failure, one of the main comorbidities in CKD. The Ferinject[®] Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF), an RCT that enrolled 459 patients with heart failure and iron deficiency (defined as ferritin < 100 or 100 – 299 ng/ml if TSAT $< 20\%$), with or without anemia, investigated whether intravenous iron would improve symptoms associated with heart failure [32]. Twenty-four weeks from commencing treatment with iron or placebo, the symptoms, functional capacity and quality of life were significantly better among patients receiving iron repletion than in the placebo-treated patients; rates of adverse events did not differ between the groups. The effects of iron supplementation were observed regardless of the presence of anemia, and iron treatment was associated with a modest but significant improvement in renal function (difference in estimated glomerular filtration rate 2.98 ml/min/ 1.73 m² at week 24) [33].

The Ferric Carboxymaltose Evaluation on Performance in Patients with Iron Deficiency in Combination with Chronic Heart Failure (CONFIRM-HF) trial is another recently published RCT that examined the effects of iron treatment for approximately 1 year in 304 ambulatory symptomatic heart failure patients who had nearly identical iron profiles as those of the subjects in the FAIR-HF trial [34]. This trial demonstrated that intravenous iron treatment was associated with a significant reduction in the risk of hospitalizations for worsening heart failure (hazards ratio 0.39 , $p = 0.009$) without increasing

the number of deaths or the incidence of adverse events. Although these studies did not target CKD patients or an improvement in anemia, they do suggest that iron supplementation could benefit iron-depleted CKD patients with heart failure, with or without anemia.

Iron and Infection Risk

Most pathogens require iron for their growth and proliferation [35]. In addition, in many in vitro studies, iron has been shown to impair the immune response against pathogens. For example, incubation with iron-induced apoptosis, reduced phagocytic function and impaired transendothelial migration of polymorphonuclear leukocytes [36, 37]. In keeping with these in vitro observations, iron overload resulted in the worsening of infections in various animal models in vivo [38–40].

Brookhart et al. [41] investigated patterns of iron dosing in a cohort of more than 100,000 hemodialysis patients. They demonstrated that administration of large boluses of intravenous iron was associated with significant increases in infection-related hospitalizations. Another recent observational study including more than 14,000 hemodialysis patients also found a non-significant increase in infection-related mortality with high-dose intravenous iron administration ($> 1,050$ mg in 3 months and $> 2,100$ mg in 6 months) [42]. Moreover, in a recent systematic review in which the study population was not limited to CKD patients, intravenous iron supplementation was associated with a significant increase in the risk of infection [43]. In contrast, other observational studies have not found an association between iron administration and infection risk in hemodialysis patients [44, 45]. One multicenter, prospective, cross-sectional study from France demonstrated that iron supplementation within the previous 6 months and serum ferritin levels were not associated with bacteremia [45]. These discrepant results possibly stem from the remaining confounding factors, which are inevitable in observational studies.

Renal Toxicity of Iron

Zager et al. [46] showed that tubular cells are damaged on in vitro incubation with iron; moreover, they demonstrated the deleterious effects of iron on mouse kidneys. Similarly, reports indicate that human kidneys are also damaged by intravenous iron administration. Agarwal et al. [47] observed that after administration of parenteral

Table 2. Risks and benefits of high-dose iron in CKD patients*Risks*

Unknown long-term effects: mortality, cardiovascular events, infection and tissue deposition
Acute reactions (intravenous): anaphylactoid reactions, abdominal/chest pain, shortness of breath, nausea, hypotension, pruritus and rash

Benefits

Lower ESA dose and treatment costs
Possible prevention of cardiovascular events associated with high-dose ESA
Improvement of heart failure

iron, CKD patients had increased urinary protein excretion as well as higher oxidative stress, which were transient and resolved within 24 h. Limited data suggest that various iron preparations have different degrees of renal toxicity [48]. However, the majority of large clinical trials have not demonstrated renal toxicity associated with iron treatment (e.g., the FIND-CKD study [16]). Instead, iron supplementation has been associated with better renal function in patients with heart failure and iron deficiency (FAIR-HF) [33], as discussed earlier. Another RCT enrolling 40 patients with anemia, iron deficiency (defined as ferritin <100 ng/ml and TSAT <20%), heart failure and impaired renal function (mean creatinine clearance ~40 ml/min) found that iron supplementation (200 mg/week for 5 weeks) significantly improved renal function, raised Hb levels and increased the left ventricular ejection fraction [49].

Recent Advances in the Mechanisms of Iron Regulation: Hepcidin and Ferroportin

There have been recent advances in our understanding of iron homeostasis within the human body [50]. Ferroportin – a membrane transporter – stimulates iron uptake by intestinal epithelial cells and iron excretion by macrophages. Hepcidin, a short peptide produced by the liver, binds and degrades ferroportin, resulting in reduced iron absorption by the intestine and iron accumulation within the reticuloendothelial system. In anemia of chronic disease, inflammatory cytokines such as interleukin-6 are elevated and promote hepcidin production in the liver, thereby decreasing the amount of iron that is available for erythropoiesis through the degradation of ferroportin. Although it remains an open question whether modulation (reduction) of hepcidin levels contributes to the correction of anemia in the CKD subpopulation, new drugs are under development on the basis of the premise that modulating hepcidin and ferroportin

can be a novel therapeutic target and yield significant benefits in CKD patients who generally have high hepcidin levels [51].

Summary and Second Opinion

The potential risks and benefits of high-dose iron supplementation with high ferritin and TSAT target levels are summarized in table 2. As discussed earlier, the results of clinical trials are inconclusive with regard to the long-term safety of this therapeutic strategy; epidemiological data have raised questions about its effects on cardiovascular outcomes, infections, deposition in tissues and mortality; and many experimental studies have provided supporting evidence of the negative effects of intravenous iron. Very recently, the Dialysis Outcomes and Practice Patterns Study reviewed data of more than 30,000 hemodialysis patients and reported that mortality was elevated among patients with high-dose intravenous iron supplementation (≥ 300 mg/month over 4 months), with no differences in cause-specific mortality [52]. It is now obvious that RCTs studying various doses of intravenous iron with sufficient numbers of patients and longer observation periods are urgently needed to study end points of survival, cardiovascular effects and infection [53]. The Proactive IV Iron Therapy for Haemodialysis Patients (PIVOTAL) trial in the United Kingdom began in 2013 and was ongoing at the time of writing and is expected to determine optimal iron dosing for definitive outcomes [54]. The study is recruiting ESA-treated hemodialysis patients with ferritin <400 ng/ml and TSAT <30% and will compare the effects of proactive high-dose iron supplementation with reactive low-dose iron supplementation.

The 2012 KDIGO Guideline, if followed, could increase the proportion of CKD patients with iron overload. Indeed, the mean serum ferritin level exceeded 800 ng/ml in dialysis patients in the United States from January 2012 through December 2013 (although the increase seems to

be mainly the result of changes in the payment system for ESA and revision of the ESA label by the US FDA) [55]. However, in consideration of the last 2 decades of experience with ESA indicating that important outcomes can be dissociated from surrogate outcomes (especially Hb concentration) in the normal hematocrit trial [56], CHOIR [57] and TREAT [58], a more prudent attitude targeting lower levels of ferritin and TSAT in iron supplementation may be warranted until the long-term safety of high-dose iron supplementation is established.

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