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Interpretation of the Kidney Disease: Improving Global Outcomes guidelines for iron therapy: commentary and emerging evidence

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Abstract

The 'Kidney Disease: Improving Global Outcomes' (KDIGO) Clinical Practice Guideline for Anaemia in Chronic Kidney Disease includes detailed recommendations for the use of iron therapy in a variety of clinical circumstances. However, the evidence base regarding the use of iron therapy in patients with chronic kidney disease was relatively incomplete at the time the guideline was developed. As a result, there has been significant debate as to the appropriate use of iron therapy in this population. In this article, the KDIGO guidelines are discussed in the context of recently published commentary pieces and additional research to provide a richer context in which to interpret and understand the guidelines.

Key words: anaemia, CKD, ESA, ESRD, iron

Introduction

Iron therapy, along with the use of erythropoiesis-stimulating agents (ESAs), has served as a cornerstone of anaemia management in patients with chronic kidney disease (CKD) for the past several decades. Oral or intravenous (IV) iron can be used to achieve a variety of therapeutic goals, depending on the individual patient. First and foremost, iron therapy treats the iron deficiency that commonly arises in CKD patients, particularly those treated with hemodialysis (CKD-HD), because of frequent blood sampling, accidental blood loss during dialysis due to blood retention in the dialyzer and tubing, bleeding events, surgery and poor intestinal iron absorption [1]. Iron therapy, with or without the simultaneous use of an ESA, may also be applied in an effort to raise a patient's haemoglobin (Hb) levels, as well as to permit a reduction in ESA dose among patients receiving ESA therapy. Improvements in anaemia resulting from iron therapy can reduce anaemia-related symptoms and the need for transfusions. Thus a trial of iron should be considered in anaemic CKD patients who have diminished or depleted bone marrow iron stores and who are thus likely to have a clinically meaningful erythropoietic response.

The selection of an iron formulation, route of administration (IV versus oral) and dosing regimen (bolus versus maintenance) for each patient must be based on consideration of a variety of factors, including the stage of CKD, dialysis modality and locally available iron formulations. This selection process is covered in detail in the accompanying article by Dr Simon Roger [2]. Recently, several new iron formulations have emerged, including iron-based phosphate binders (ferric citrate, sucroferric oxyhydroxide), long-half-life IV iron products (iron carboxymaltose, iron isomaltoside) and dialysate iron (ferric pyrophosphate citrate). While these new formulations offer potential advantages in terms of reducing pill burden (iron-based phosphate binders), less frequent dosing (long-half-life IV iron products) or passive delivery (dialysate iron), they lack the long safety and efficacy records of older products and

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should be used somewhat cautiously until further evidence is available. There is recent evidence indicating that some newer IV iron preparations may affect various biomarkers of bone metabolism and inflammation differently than older preparations [3].

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anaemia in Chronic Kidney Disease, published in 2012 [4], was developed with the goal of improving the care of patients with CKD by providing evidence-based guidelines and treatment recommendations for all aspects of anaemia management. The guideline, which includes detailed recommendations for the use of iron therapy, is based on a review and appraisal of existing research, including clinical trials, with respect to the treatment of CKD patients. In the case of iron therapy, evidence to guide some of the therapeutic recommendations was sparse. As a result, the quality of evidence supporting the recommendations regarding iron therapy was graded as low or very low. Iron treatment must, therefore, be individualized with clear treatment goals in mind, taking into account the concurrent use of other medications such as ESAs, and with a full understanding of potential risks and benefits of such therapy.

Because the evidence base regarding the use of iron therapy in CKD patients was relatively incomplete at the time the guideline was developed, there was significant room for debate as to the optimal use of iron in this patient population. This debate is reflected in several recently published commentaries on the KDIGO guideline (Table 1). In this article, some of the important but still unresolved issues related to iron therapy, particularly IV iron therapy, are discussed. The full text of the guidelines discussed in this article is presented for the reader's reference in Box 1.

Guideline 2.1.2: Iron therapy in anaemic CKD patients not currently on iron or ESA

In routine clinical practice, the diagnosis of iron deficiency is commonly based on measurement of the serum ferritin level and the percent transferrin saturation (TSAT). Absolute iron deficiency is widely defined as TSAT <20% accompanied by ferritin <100 ng/mL in patients with CKD who are not receiving dialysis (CKD-ND) or those treated with peritoneal dialysis (CKD-PD) [4], or ferritin <200 ng/mL in CKD-HD patients [9]. However, the ability of these iron tests to accurately reflect bone marrow iron stores in CKD patients and to predict the erythropoietic response to IV iron therapy is imperfect [10]. Thus there continues to be active discussion with respect to appropriate cut-off values of these tests for initiation and cessation of IV iron therapy. While other tests, such as percent hypochromic red blood cells and reticulocyte haemoglobin content, have been proposed, they have not found their way into routine clinical practice. Hence the best test of iron adequacy is often a hematological response to IV iron.

The KDIGO guideline recommends a trial of IV iron in CKD-HD patients if TSAT is <30% and ferritin is ≤500 ng/mL [4]. In CKD-ND patients, a 1- to 3-month trial of oral iron may be attempted instead, although the side effects of oral iron may limit patient adherence. Although the guideline does provide separate recommendations for routes of iron administration in CKD-HD and CKD-ND patients, it does not distinguish between functional and absolute iron deficiency, nor does it provide separate recommendations for CKD-ND and CKD-HD patients in terms of TSAT and/or ferritin thresholds that provide an upper bound for the administration of iron therapy [5, 7]. One critique of the guideline pointed out that the distinction between absolute (ferritin <200 ng/mL in CKD-HD or <100 ng/mL in CKD-ND) and functional iron deficiency is important, in that indications for IV iron may be stronger and more evidence-based in patients with absolute iron deficiency, since the chance of obtaining an increase in Hb level in response to iron therapy is greater [10]. Benefits of IV iron may still be seen in patients with functional iron deficiency in spite of adequate bone marrow iron stores, although the magnitude of the effect may be smaller [10,11]. For example, the European Renal Best Practice (ERBP) commentary suggests that it may be prudent to initiate ESA and IV iron together in patients with ferritin >300 ng/mL (unless ESA is contraindicated), because iron alone may not have a significant impact on anaemia [5] .

The use of ferritin ≤500 ng/mL as an upper limit for the initiation of iron therapy remains controversial due to the paucity of hard evidence from randomized controlled trials (RCT), and some nephrologists have raised questions as to the long-term safety of administering IV iron to patients with high serum ferritin levels [5]. The recommendation in the guideline was based in large part on the likelihood of response to additional IV iron alone in patients with higher ferritin levels; at higher serum ferritin levels a clinically meaningful response is less likely.

Given the lack of concrete, RCT-derived evidence of risk associated with ferritin levels >500 ng/mL, clinicians may evaluate the risks and benefits of IV iron treatment in individual anaemic patients with higher serum ferritin. In particular, the health risks that may be imposed by withholding iron therapy (sustained anaemia, higher ESA dose requirements and greater need for blood transfusions) should also be considered [6].

A major reason for caution when prescribing IV iron is the risk of iron overload, particularly hepatic iron deposition. Although reliable biomarkers of iron overload in CKD patients do not exist, a combination of high TSAT and high serum ferritin, rather than either individually, may be most indicative of the condition; hyperferritinemia alone is not synonymous with iron overload since ferritin is also an acute phase reactant [12–14]. From a treatment perspective, IV iron doses in excess of 2–3 g/year in CKD-HD patients and 1–2 g/year in CKD-PD patients are likely to exceed iron loss and therefore result in positive iron balance [15]. Patients with CKD-ND will have even lower iron needs. Positive iron balance can be associated with a risk of iron-related organ dysfunction [8]. Consequences of excess body iron vary among patients, with target organs including the liver, myocardium, endocrine glands and joints [16]. Furthermore, iron overload that occurs as a result of genetic disease (i.e. hemochromatosis) or frequent blood transfusions (e.g. in thalassemia) may be very different than that observed in patients receiving supplemental IV iron and thus conclusions drawn from patients with iron overload arising from other causes cannot necessarily be extended to patients with CKD [8]. Parenchymal iron may be more harmful than iron stored in the reticuloendothelial system (RES) [17, 18]. Oxidative damage resulting from IV iron administration [19–21] may pose a particular problem, given higher baseline levels of oxidative stress already present in CKD patients [22, 23].

Guideline 2.1.3: Iron therapy in anaemic CKD patients currently on ESA but not iron

The increased erythropoiesis resulting from ESA administration places great demands on bone marrow iron stores. Even among patients who are iron replete there may be insufficient available

Table 1. Summary of commentary pieces and key recommendations

Group	Title	Key recommendations	Citation
National Institute for Health and Care Excellence	Anaemia Management in Chronic Kidney Disease: Partial Update 2015	Initiation of IV iron therapy: • Serum ferritin should not exceed 800 ng/mL. Review dose of iron when ferritin reaches 500 ng/mL Evaluation of iron status: • Do not use TSAT or serum ferritin measurement alone to assess iron deficiency status in people with anaemia of CKD	https://www.nice.org.uk/guidance/ng8/evidence/full-guideline-70545133
European Renal Best Practices (ERBP)	Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement	Initiation of IV iron therapy in patients not on ESA: • Initiate a trial of IV iron if there is absolute iron deficiency (TSAT <20%, ferritin <100 ng/mL) or if TSAT <25%, ferritin <200 ng/mL in CKD-ND patients, or TSAT<25%, ferritin <300 ng/mL in patients on dialysis • TSAT 30% ferritin 500 ng/mL should not be intentionally exceeded • Initiate ESA and IV iron together in patients with ferritin >300 ng/mL Initiation of IV iron therapy in patients on ESA: • Use oral iron as a first step if tolerated • Initiate IV iron if TSAT <30%, ferritin <300 ng/mL • Do not exceed ferritin 500 ng/mL, especially if TSAT >30%	Locatelli *et al.* [5]
Kidney Disease Outcomes Quality Initiative (KDOQI)	KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anaemia in CKD	Initiation of IV iron therapy in patients on ESA: • Initiate a trial of IV iron if TSAT <30%, even if ferritin is > 500 ng/mL Cautions regarding iron therapy: • High molecular weight iron dextran should be avoided • Have resuscitative facilities and personnel available when administering IV iron IV iron and systemic infections: • No evidence that IV iron exacerbates infection; iron deficiency may worsen ability to respond to infection	Kliger *et al.* [6]
Canadian Society of Nephrology	Canadian Society of Nephrology Commentary on the 2012 KDIGO Clinical Practice Guideline for Anaemia in CKD	Initiation of IV iron therapy: • Increase in Hb is less likely when TSAT >30% and ferritin >500 ng/mL Iron status evaluation: • Be mindful of the half-life of iron products administered; time testing of iron status accordingly Cautions regarding iron therapy: • 30 min of monitoring postadministration is probably sufficient • Important to distinguish between allergic reactions and reactions to high amounts of free iron	Moist *et al.* [7]
KDIGO Controversies Conference	Iron management in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference	Initiation of IV iron therapy: • Doses >3 g/year are more likely to cause positive iron balance; if high doses seem necessary, look for causes of increased iron loss Iron status evaluation: • Current methods to assess iron status are insufficient • Elevated ferritin does not always correlate with high liver iron Cautions regarding iron therapy: • Important to distinguish between allergic reactions and reactions to large amounts of free iron • High molecular weight iron dextran should be avoided, lower molecular weight formulations should be used IV iron and systemic infections: • RCT evidence is lacking • Observational studies may be confounded	Macdougall *et al.* [8]

iron to support ESA-stimulated erythropoiesis, resulting in ESA hyporesponsiveness [24, 25]. The addition of iron therapy may therefore boost ESA responsiveness and reduce ESA dose requirements. IV iron may produce superior results to oral iron in this respect, particularly in CKD-HD patients [26]. The ability of iron therapy to minimize ESA requirements is of particular importance given the recent safety concerns with regard to the use of high ESA doses.

Controversy exists as to whether a trial of IV iron should be initiated in patients receiving an ESA with a serum ferritin level ≥500 ng/mL. The Dialysis Patients Response to Intravenous Iron with Elevated Ferritin (DRIVE) [27] and follow-up DRIVE II [28] studies provide some evidence to guide decision making in this respect. The DRIVE study sought to determine the response rate to IV iron (1 g ferric gluconate administered as 8 × 125 mg doses administered over 6 weeks) in CKD-HD patients who were anaemic with serum ferritin 500–1200 ng/mL and TSAT ≤25%. A total of 134 patients were randomized to treatment and control groups. Importantly, the ESA dose was increased by 25% upon randomization in both groups, so these studies do not directly assess the more common clinical practice of providing IV iron alone without a simultaneous increase in ESA dose. At the conclusion of the trial, Hb had increased more in the IV iron group than in the control group (by 1.6 ± 1.3 versus 1.1 ± 1.4 g/dL, respectively; $P = 0.028$). Responsiveness to iron was similar in patients with serum ferritin >800 and <800 ng/mL and with TSAT >19% and <19% [27]. During the 6-week DRIVE II observational extension of the DRIVE study, mean Hb, TSAT and ferritin levels remained higher in the patients who had received IV iron compared with the controls, while mean ESA dose significantly decreased [28]. While there were no significant safety concerns in this small study of short duration, the long-term benefit of this approach beyond the relatively small difference in achieved Hb and short-term reduction in ESA dose is unclear.

In the absence of data indicating that long-term IV iron is associated with worse outcomes, it may be reasonable to initiate a trial of IV iron in anaemic patients on ESA even when ferritin is >500 ng/mL, provided that TSAT is <30% [6, 29]. It would be essential to monitor the individual patient's response to IV iron and titrate therapy appropriately, stopping IV iron therapy if the ferritin level and/or TSAT are increasing without a significant increase in Hb and/or a reduction in ESA dose.

Guideline 2.2.2: Frequency of testing for iron status

Assessment of iron status in CKD patients remains challenging, with ferritin and TSAT representing imperfect biomarkers of iron status. Interpretation may be further clouded by measurements taken too soon after IV iron administration [7]. It is therefore important to be mindful of the half-life of iron products being administered [30–33] and to time testing such that iron status has restabilized in order to avoid misleading measurements.

Even when the timing of iron status evaluation is appropriate, interpretation of ferritin values is complex. While a higher serum ferritin value may be indicative of an iron-replete state, ferritin is also up-regulated in response to inflammation [34]. Because inflammation is often elevated in CKD patients, high ferritin values may be indicative of increased inflammation, not iron status. Indeed, elevated ferritin does not always correlate well with liver iron stores. The implications of high ferritin for adverse patient outcomes are likewise unclear. It has not yet been resolved whether ferritin is a marker for increased risk of cardiovascular disease or whether high ferritin is itself a risk factor [8]. Given the lack of clarity around the meaning of a high ferritin level, assessment of iron overload with this marker is not possible. Although detection of excess liver iron with magnetic resonance imaging (MRI) has been reported [35, 36], this approach has not been validated in CKD-HD patients and is not likely to be used in routine clinical practice .

Guideline 2.3: Monitor for 60 min after administration of IV iron dextran

Early IV iron formulations, such as high molecular weight iron dextran products, were known to occasionally provoke allergic reactions that were sometimes life threatening. In the modern context, with the availability of IV iron formulations that are better tolerated, high molecular weight iron dextran is no longer used. Even when using these newer iron preparations, it is advisable to have resuscitative facilities and personnel available [6]. The importance of postadministration monitoring is still debated, with some recommending 30 min of monitoring after administration [8] and others of the opinion that there is no physiological basis to recommend even this shorter period of postadministration monitoring [8]. Some patients may have minor infusion reactions that can be managed by slowing the rate of infusion or switching to an alternate formulation [8].

When analyzing adverse reactions to iron administration, it is important to be cognizant of the fact that both allergic reactions and reactions to high amounts of free iron may occur [7, 8]. In practice, it may be difficult to distinguish between these two causes of adverse reactions following large doses or rapid administration of IV iron [37–39]. In some patients, there are identifiable risk factors for severe reactions, including asthma, mastocytosis, prior drug allergies and atopic status [8].

Guideline 2.4: Avoid IV iron in patients with systemic infections

Many pathogens rely on iron as a key metabolite [40, 41], and iron overload may stimulate bacterial growth [42]. Because of this, it is often recommended to avoid administration of iron in patients with systemic infections. However, clinical evidence to support a link between iron use and infection is inconclusive [6, 7]. In 24 studies that evaluated IV iron use and infection risk in CKD-HD patients, only 12 found an association [43]. Generally speaking, RCTs that have examined this question have been small, had short follow-up and were not specifically designed to address infection risk. Recently, two studies have provided conflicting information in this regard. The FIND-CKD study was a 56-week open-label, multicenter RCT comparing IV ferric carboxymaltose to oral iron in >600 patients with CKD not on dialysis [44]. There was no difference in infection-related events in the IV versus oral iron groups. In contrast, another recent study compared oral iron and IV iron sucrose in a single-center RCT of 136 CKD patients [45]. The study was terminated early by its data safety monitoring board due to an increase in the number of adverse events in the IV iron group, including infections requiring hospitalization. This study has generated significant controversy that is discussed in detail in the accompanying article authored by Dr Macdougall [46].

Future research directions

Much additional research is required to further inform the use of IV iron in patients with CKD. Additional information with regard to the safety of IV iron is required in several contexts. First, a more robust understanding of the safety of long-term IV iron therapy, especially in patients with high serum ferritin, is needed. These safety analyses should include an intercomparison of various iron preparations. Relatedly, longer-term safety data on the newer iron preparations is required. A better understanding of the relative costs of IV iron in patients with different characteristics could also inform prescribing practices. Finally, the development of improved biomarkers of iron deficiency would provide additional guidance for clinicians with respect to the decision to prescribe IV iron treatment. The execution of studies to address these points will continue to refine the use of IV iron, ensuring that this essential therapy is applied in the safest and most effective manner possible.

Box 1. Guidelines discussed in this article

2.1.2. For adult CKD patients with anaemia not on iron or ESA therapy we suggest a trial of IV iron (or alternatively in CKD-ND patients, a 1- to 3-month trial of oral iron therapy) if (2C):

- an increase in Hb concentration without starting ESA treatment is desired and
- TSAT is $< 30\%$ and ferritin is ≤ 500 ng/mL (≤ 500 mg/L).

2.1.3. For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or alternatively in CKD-ND patients, a 1- to 3-month trial of oral iron therapy) if (2C):

- an increase in Hb concentration or a decrease in ESA dose is desired and
- TSAT is $< 30\%$ and ferritin is ≤ 500 ng/mL (≤ 500 mg/L)

2.2.2. Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron and in other circumstances where iron stores may become depleted (not graded).

2.3. When the initial dose of IV iron dextran is administered, we recommend (1B) that patients be monitored for 60 min after the infusion and when the initial dose of IV nondextran iron is administered, we suggest (2C) that patients be monitored for 60 min after the infusion, and that resuscitative facilities (including medications) and personnel trained to evaluate and treat serious adverse reactions be available.

2.4. Avoid administering IV iron to patients with active systemic infections (not graded).

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