



Global Action. Local Change.

KDIGO Controversies Conference on Iron Management in Chronic Kidney Disease

**March 27-30, 2014
San Francisco, USA**

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask conference participants to determine what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline efforts and other times they highlight areas for which additional research is needed to produce evidence that might lead to guidelines in the future.

Background

Anemia is a common complication in patients with chronic kidney disease (CKD). Although this condition most often occurs in those with glomerular filtration rate (GFR) below 30 ml/min, mild degrees of anemia are observed in early stages of CKD with a reported prevalence rate of 12% (1). As CKD progresses, the prevalence of anemia dramatically increases to over 90% by the time maintenance dialysis is required (2). Though the causes of anemia associated with CKD are multifactorial, some of the primary causal factors include: erythropoietin deficiency, iron deficiency, presence of uremic



inhibitors and inflammatory factors, and overproduction of hepcidin (2). In the recent KDIGO Anemia Guideline (3), a stepwise approach to the effective management of anemia in CKD involves: 1) excluding other causes of anemia; 2) addressing iron deficiency; 3) utilizing erythropoiesis –stimulating agent (ESA); and 4) employing blood transfusions as the means of last resort. Both absolute and functional iron deficiency are often observed in patients with advanced CKD and treatment with iron therapy has clearly shown to be effective in increasing hemoglobin (Hgb) levels and improving ESA dose response. Although iron can be administered orally or intravenously, the effectiveness of the enteral route is limited by poor patient adherence due to gastrointestinal side effects and absorption interference by medications such as phosphate binders, proton pump inhibitors and certain antibiotics (2). In particular, iron requirements in dialysis patients are far too great to be met by oral supplementation to effectively increase Hgb or iron indices (4). Despite the known benefits of iron therapy, there are still major uncertainties among various intravenous (IV) preparations concerning their long-term safety and efficacy, given the paucity of hard patient outcomes in large prospective randomized controlled trials.

Relevance of the topic and the conference

A recent survey has revealed a substantial increase in IV iron use among dialysis patients (50 to 71%) in 12 countries from 1999 to 2011 (5). Furthermore, the mean monthly doses received by patients increased from 232 to 282 mg and likewise the proportion of patients with serum ferritin values rose during this period. Much of this increase in iron utilization may be attributed to the minimization of ESA use as recent clinical trials suggested safety concerns with full normalization of Hgb with ESAs. In this



vein, the US DOPPS Practice Monitor has observed that “the ferritin threshold at which IV iron administration is discontinued exceeds 800 ng/mL in over 80% of facilities” and that “25% of surveyed facilities have serum ferritin levels exceeding 800 ng/mL in at least two-thirds of their patients.” (6) However, patient safety and outcomes associated with such aggressive use of iron agents remain unknown given the uncertainty surrounding the quantity of iron considered safe for patients and the level of ferritin at which iron administration should be discontinued.

Despite the essential roles that iron plays in basic biological processes, potential toxicities associated with IV iron include: A) Iron overload; B) Inflammation and oxidative stress; C) Iron and infections; D) Hypersensitivity reactions. Multiple studies have documented the presence of iron overload in dialysis patients treated with ESAs and IV iron. Canavese et al. (7) reported iron overload in 70% of their patients and Ferrari et al. (8) found 13% of their patients had liver iron concentrations $>130 \mu\text{mol/g}$, levels above which are comparable to those found in hemochromatosis. One recent study (9) further corroborated these findings and observed that 84% of patients exhibited mild to severe hepatic iron overload, noting a strong correlation between IV iron dosing and hepatic iron storage. Introduction of IV iron can also result in oxidative stress by generating hydroxyl radicals and other reactive oxygen species (ROS) that could cause endothelial injury and promote atherosclerosis. Both *in vitro* and *in vivo* data provide evidentiary support that IV iron can induce cytotoxicity in tissue cultures and cause elevated lipid peroxidation, protein oxidation, ROS generation in dialysis patients following iron infusion (10). At least two studies (11,12) have also shown that carotid artery intima media thickness is correlated with the annual dose of IV iron given. Along this line, IV iron also promotes inflammation by increasing pro-inflammatory



mediators and hepcidin, a known key regulator of systemic iron balance (13). One study (14) recently found hepcidin to be significantly associated with fatal and nonfatal cardiovascular events with a hazard ratio of 1.24 per 10 nmol/L increment of hepcidin.

The issue of whether iron use could increase the risk of infection has been reviewed as far back as 1999 and data have suggested that excess iron can lead to impaired neutrophil and T-cell function, and serve as a growth factor for bacteria and other pathogens. As summarized by Ishida & Johansen (15), 13 studies have investigated the link between serum ferritin and infection in dialysis patients with 9 studies reporting a positive association. Concerning iron usage and risk of infection, there are 24 such studies (mostly observational) which yielded conflicting results. Despite these mixed findings, the current KDIGO guideline (3) has taken a cautious approach in advising avoidance of IV iron during active systemic infections. However, it has been argued that the act of withholding iron may result in iron deficiency which in turn leads to an increased risk for infection (15).

Currently there is a multitude of IV iron preparations available globally all of which carry a potential for causing hypersensitivity-type anaphylactoid reactions. Older agents such as iron dextran formulations- particularly high molecular weight dextrans- have been known to cause anaphylactic reactions. Since 2009, there are newer IV iron preparations which bind iron more avidly, thereby minimizing the release of free iron into circulation and enabling larger dose infusions (16). Although there are preliminary data comparing adverse events, serious allergic reactions, short-term safety and efficacy for several formulations (17-22), clearly larger and longer-term direct head-to-head trials are needed for more definitive conclusions.



CONFERENCE OVERVIEW

The scope of this KDIGO conference is to gather a global panel of multi-disciplinary clinical and scientific expertise that will identify key issues relevant to the optimal iron management in CKD. The objective of this conference is to assess our current state of knowledge related to iron metabolism and the mechanisms underlying its pathophysiology in CKD; address key controversial issues concerning the use of iron therapeutic agents in the treatment of anemia in CKD; summarize the outstanding knowledge gaps; and to propose a research agenda to resolve standing controversial issues. It is hoped that this conference will inform clinicians of the evidence base for present treatment options and help pave the way for future studies in this area.

Drs. Glenn M Chertow (Stanford University School of Medicine, USA) and Iain C Macdougall (King's College Hospital, UK) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus-building. Invited participants and speakers will include worldwide leading experts who will address key clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a position statement that will help guide KDIGO and others on therapeutic management and future research.



References

- (1) Inker LA, Coresh J, Levey AS, et al. Estimated GFR, albuminuria, and complications of chronic kidney disease. *J Am Soc Nephrol*. 2011; 22(12): 2322-2331.
- (2) Macdougall IC. Pocket reference to renal anemia, 2nd Edition, Springer. 2013
- (3) Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl*. 2012; 2: 279–335.
- (4) Hodson EM, Craig JC. Oral Iron for patients receiving dialysis: What is the evidence? *Semin Dial*. 2014; 27(1): 8-10.
- (5) Bailie GR, Larkina M, Goodkin DA, et al. Variation in intravenous iron use internationally and over time: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2013; 28 (10): 2570-2579.
- (6) Weiner DE, Winkelmayer WC. Commentary on 'The DOPPS practice monitor for U.S. dialysis care: update on trends in anemia management 2 years into the bundle': iron(y) abounds 2 years later. *Am J Kidney Dis*. 2013; 62(6):1217-1220.
- (7) Canavese C, Bergamo D, Ciccione G, et al. Validation of serum ferritin values by magnetic susceptometry in predicting iron overload in dialysis patients. *Kidney Int*. 2004; 65(3): 1091-1098.
- (8) Ferrari P, Kulkarni H, Dheda S, et al. Serum iron markers are inadequate for guiding iron repletion in chronic kidney disease. *Clin J Am Soc Nephrol*. 2011; 6: 77-83.
- (9) Rostoker G, Griuncelli M, Loridon C, et al. Hemodialysis associated hemosiderosis in the era of erythropoiesis-stimulating agents. *Am J Med*. 2012; 125:991-999.
- (10) Fishbane S, Mathew A, Vaziri ND. Iron toxicity: relevance for dialysis patients. *Nephrol Dial Transplant*. 2014; 29(2):255-259.
- (11) Drueke T, Witko-Sarsat V, Massy Z, et al. Iron therapy, advanced oxidation protein products, and carotid artery intima media thickness in end-stage renal disease. *Circulation*. 2002; 106: 2212-2217.



- (12) Reis K, Guz G, Ozdemir H, et al. Intravenous iron therapy as a possible risk factor for atherosclerosis in end stage renal disease. *Int Heart J.* 2005; 46: 255-264.
- (13) Zumbrennen-Bullough K, Babitt JL. The iron cycle in CKD: from genetics and experimental models to CKD patients. *Nephrol Dial Transplant.* 2014; 29(2):263-273.
- (14) van der Weerd NC, Grooteman MP, CONTRAST Investigators. Heparin-25 is related to cardiovascular events in chronic haemodialysis patients. *Nephrol Dial Transplant.* 2013; 28(12): 3062-3071.
- (15) Ishida JH, Johansen KL. Iron and infection in hemodialysis patients. *Semin Dial.* 2014; 27(1): 26-36.
- (16) Larson DS, Coyne DW. Update on intravenous iron choices. *Curr Opin Nephrol Hypertens.* 2014; 23(2):186-191.
- (17) Bailie GR, Verhoef JJ. Differences in the reporting rates of serious allergic adverse events from intravenous iron by country and population. *Clin Adv Hematol Oncol.* 2012; 10(2):101-108.
- (18) Bailie GR. Comparison of rates of reported adverse events associated with i.v. iron products in the United States. *Am J Health Syst Pharm.* 2012; 69(4):310-320.
- (19) Charytan C, Bernardo MV, Koch TA, et al. Intravenous ferric carboxymaltose versus standard medical care in the treatment of iron deficiency anemia in patients with chronic kidney disease: a randomized, active-controlled, multi-center study. *Nephrol Dial Transplant.* 2013; 28(4):953-964.
- (20) Onken JE, Bregman DB, Harrington RA. et al. Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. *Nephrol Dial Transplant.* 2013 Aug 20. [Epub ahead of print]
- (21) Onken JE, Bregman DB, Harrington RA, et al. A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia. *Transfusion.* 2014; 54(2):306-315.
- (22) Macdougall IC, Strauss WE, McLaughlin J, et al. A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. *Clin J Am Soc Nephrol.* 2014 Jan 23. [Epub ahead of print]

APPENDIX: SCOPE OF COVERAGE

A. Iron overload

- What is the cause of iron deficiency in CKD patients?
- What is the usual iron loss in non-dialysis, hemodialysis and peritoneal dialysis patients?
- What doses of iron are required to compensate for the patients' iron losses?
- What is the definition of iron overload in a CKD setting?
 - Is there a threshold? (upper limit on serum ferritin/TSAT?)
- How best to diagnose iron overload in a CKD setting?
 - What laboratory tests*? MRI scanning?
- How best to guide decisions on initiation, maintenance and discontinuation of iron supplementation?
 - What laboratory tests*? MRI scanning?
- What are the effects of iron accumulation in various tissues (e.g., hemochromatosis)
- How does iron accumulation affect organs on a functional level? (e.g., liver, heart, pancreas, kidney, etc.)
- What is the optimal administration of iron?
 - In terms of dosing, frequency, ESA-to-iron balance in CKD patients – dialysis vs. non-dialysis

B. Inflammation and oxidative stress

- Mechanisms of IV iron-induced oxidative stress
- Endogenous protective mechanisms against oxidative stress (triggered by iron)
- Critical review of methods to measure oxidative stress
- Relationship between inflammation and oxidative stress
- Relationship between oxidative stress and atherogenesis
- Evidence for IV iron exacerbating oxidative stress – laboratory data
- Evidence for IV iron exacerbating oxidative stress – animal data

*Lab tests:

Iron parameters (1): serum ferritin, TSAT;

Iron parameters (2): serum transferrin receptor (sTfR), erythrocyte zinc protoporphyrin (ZnPP)

Red cell indices (MCH, MCV, hypochromic cells); reticulocyte parameters (CHr, RetHe),

Novel lab tests (e.g. hepcidin)

- Evidence for IV iron exacerbating oxidative stress – observational data
- Evidence for IV iron exacerbating oxidative stress – randomised controlled trials
- IV iron and risk of CVD or malignancy
- Role of antioxidants in blunting oxidative stress from IV iron therapy
- Are there differences between different IV iron products with respect to induction of inflammation and oxidative stress?
- Are there differences between IV iron originators vs IV iron similars with respect to induction of inflammation and oxidative stress?

C. Iron and infections

- Impact of iron supplementation on host immune function
- How could IV iron exacerbate the risk of infections? (e.g., neutrophil killing potential; bacterial proliferation)
- What type of infections should we be concerned about? (e.g., bacterial, fungal, viral, or parasitic)
- Real or just a theoretical risk? – laboratory data; animal data; observational data; RCT data
- Dosing strategy (bolus vs maintenance) and infection risk

D. Hypersensitivity reactions

- What are the characteristics of a drug hypersensitivity reaction? What are the risk factors for these reactions and how should these reactions be classified?
- What is the pathogenesis of immediate reactions to IV iron? Are they immune mediated?
- Are some of the reactions to IV iron caused by ‘free’ iron in the circulation?
- What is the difference between ‘free’ iron, ‘labile’ iron, and ‘non-transferrin-bound’ iron?
- How commonly do reactions to IV iron occur?
- How often are these reactions serious or life-threatening?
- Are there differences in the risk of reactions to IV iron between the various iron preparations?
- How should reactions to IV iron be treated?
- How should patients with previous reactions to IV iron be managed in the future? Can another formulation be used and if so, what additional testing might be required?