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Scholarly Review

Iron deficiency anemia in chronic kidney disease: Uncertainties and cautions

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Abstract

Anemia in chronic kidney disease is common and iron deficiency is an important cause. To repair iron-deficiency anemia, replacement of iron is needed. Iron can be replaced either by the oral route or by the intravenous route. In a meta-analysis, 5 of the 6 trials were short-term, 1 to 3 months, and compared to oral iron, the mean increase in hemoglobin with intravenous iron was only 0.31 g/dL. However, one of the studies included in this meta-analysis was 6 months long and had a mean decline in hemoglobin of 0.52 g/dL associated with intravenous iron administration. Given the short duration of most of the clinical trials comparing oral with intravenous administration of iron the long-term safety of these modes of administration of supplemental iron could not be assessed. Replacement of iron by the oral route is associated with mostly minor complications such as black stools, constipation, and abdominal discomfort. In contrast, intravenous administration of iron may lead to severe adverse events such as anaphylaxis and, as a more recent randomized trial has suggested, delayed complications such as infections and cardiovascular disease. Delayed complications of repeated intravenous iron use are difficult to recognize at an individual level therefore inpatients who have had recent cardiovascular events or are infected, intravenous iron should probably be avoided. Balancing safety and efficacy would require clinical judgment because 1 size may not fit all till we have better data to support the liberal use of parenteral iron.

Key words: Chronic kidney disease, iron deficiency anemia, randomized trials, safety issues, efficacy

INTRODUCTION

Anemia in chronic kidney disease (CKD) is common. It occurs when serum creatinine becomes abnormal[1]; this usually occurs when estimated glomerular filtration rate (eGFR) drops to 60 mL/min/1.73 m^2 or less. The prevalence of anemia increases with worsening kidney function. For any given severity of eGFR, anemia is worse in those with diabetes mellitus.[2] Anemia is more prevalent in women than in men.[1] The etiology of anemia in CKD is multifactorial.[3] Relative erythropoietin deficiency is common, but also other factors that make the marrow less responsive to erythropoietin are prevalent. Inflammation and iron deficiency are most common among these factors.[3]

The diagnosis of iron-deficiency anemia in CKD is difficult. The most common biomarkers used to gauge the sufficiency of iron storage are ferritin concentration and transferrin saturation. Both ferritin concentration and transferrin saturation decline in iron-deficiency anemia. The thresholds of ferritin and transferrin at which iron stores are deficient are not known. Although opinions

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exist on what these thresholds should be, the scientific evidence to back these thresholds is soft.[3] Ferritin, for example, is a positive acute-phase reactant. In other words, its concentrations increase in the setting of inflammation. Transferrin, conversely, is a negative acute-phase reactant; its concentrations decrease in patients with inflammation. Accordingly, in an iron-deficient patient, the ferritin concentration may be high and transferrin saturation may be low even in the setting of inflammation.

MANAGEMENT OF IRON-DEFICIENCY ANEMIA IN PATIENTS WITH CKD

To repair iron-deficiency anemia, replacement of iron is needed. Iron can be replaced either by the oral route or by the intravenous route; more recently, replacement through the dialysate has become available, but it will not be the subject of this discussion. Replacement of iron by the oral route is associated with mostly minor complications such as black stools, constipation, and abdominal discomfort. In predisposed populations, even oral iron replacement can be dangerous as discussed later. In contrast, intravenous administration of iron may lead to severe adverse events such as anaphylaxis.[4] Anaphylaxis is rare, but it can occasionally be fatal. Typically seen as a complication of large molecular weight IV dextrans, it has also been reported with small molecular weight iron dextran as well as ferumoxytol.[5] Less recognized are the long-term consequences of intravenous iron replacement in patients with CKD.[6]

EFFICACY OF ORAL VS. INTRAVENOUS IRON IN CKD

A meta-analysis of small randomized trials reported the efficacy of oral compared with intravenous iron on hemoglobin response in CKD patients not on dialysis.[7] Five of the 6 trials reported in this meta-analysis were short-term, 1 to 3 months, and compared to oral iron, the mean increase in hemoglobin with intravenous iron was 0.31 (95% confidence interval (CI) 0.09 to 0.53) g/dL. However, one of the studies included in this meta-analysis was 6 months long and had a mean decline in hemoglobin of 0.52 g/dL associated with intravenous iron administration.[8] Given the short duration of most of the clinical trials comparing oral with intravenous administration of iron the long-term safety of these modes of administration of supplemental iron could not be assessed.

Although the efficacy of intravenous iron is considered self-evident, it must be recognized that such trials have only lasted about 12 weeks. Steady state levels of hemoglobin with oral iron may not be achieved with such full therapies. In such patients with intravenous iron, it does not prove that there is a better response, just a faster response. Furthermore, the short duration of most of the clinical trials comparing oral with intravenous administration of iron the long-term safety of these modes of administration of supplemental iron could not be assessed. Accordingly, guidelines have no recommendation on the preferred mode of iron administration in such patients.[9]

ASSESSMENT OF THE LONGER TERM TRIALS OF IRON REPLACEMENT IN CKD

Funded by the National Institutes of Health, the randomized trial to evaluate intravenous and oral iron in chronic kidney disease (REVOKE) assigned 69 patients with Stage 3 and 4 CKD and IDA to either open-label oral ferrous sulfate (325 mg 3 times daily for 8 weeks) and 67 patients to intravenous (IV) iron sucrose (200 mg every 2 weeks, total 1 gram). The primary outcome was the between group difference in slope of measured glomerular filtration rate (mGFR) change over 2 years. mGFR was measured using after bolus dose of iothalamate. Clearance of iothalamate was calculated over 5 hours using 13 blood samples on 5 occasions over 2 years. The number of samples provided a high mGFR precision. Despite these arduous measurements in REVOKE, mGFR declined similarly over 2 years in both treatment groups (oral iron −3.6 mL/min/1.73 m^2, IV iron—4.0 mL/min/1.73 m^2, between group difference −0.35 mL/min/1.73 m^2 (95% CI −2.9 to 2.3, $P = 0.79$). However, the trial was terminated early on the recommendation of an independent Data and Safety Monitoring Board based on little chance of finding differences in mGFR slopes, but a higher risk of serious adverse events in the IV iron treatment group. There were 36 serious cardiovascular events among 19 participants assigned to the oral iron treatment group and 55 events among 17 participants of the IV iron group (adjusted incidence rate ratio [IRR] 2.51 (95% CI 1.56–4.04, $P < 0.001$)]. Infections resulting in hospitalizations had an adjusted IRR of 2.12 (95% CI 1.24–3.64, $P = 0.006$). Notably, in REVOKE, the incidences of all-cause hospitalizations, cardiovascular adverse events, as well as infection-related hospitalizations were all increased many fold in those receiving intravenous iron. Furthermore, it was not the number of patients but the number of events per patient that was increased. In other words, intravenous iron can increase the susceptibility of having more frequent

cardiovascular and more frequent infection-related events in those with CKD and iron deficiency anemia.

Funded by the manufacturer, in the Ferinject® assessment in patients with iron deficiency anemia and non-dialysis-dependent chronic kidney disease (FIND-CKD) investigators randomized 626 patients in 193 centers in 1:1:2 ratio to ferric carboxymaltose targeting ferritin to high level (400–600 ng/mL), lower level (100–200 ng/mL) or oral iron with the primary end-point of time to initiation of other anemia management (erythropoetin stimulating agents, other iron therapy or blood transfusion) or hemoglobin trigger of 2 consecutive values <10 g/dL during weeks 8 to 52.[10] The investigators reported the mean change in hemoglobin from baseline to 52 weeks as 1.0 g/dL in oral iron group, 0.9 g/dL when IV ferric carboxymaltose targeted ferritin to 100 to 200 ng/mL and 1.4 g/dL ($P = 0.26$) when IV ferric carboxymaltose targeted ferritin to 400 to 600 ng/mL ($P = 0.014$).[10] Although statistically significant, the difference in hemoglobin of 0.4 g/dL between oral iron and high dose IV iron observed in that study should be interpreted cautiously because the oral ferrous sulfate administration was only 100 mg twice daily which is much below the recommended intake of ferrous sulfate 325 mg 3 times daily. Of note, the REVOKE trial used this regimen and found no between group differences in hemoglobin response over a much longer follow up. Despite using one third of the usual dose, there was no between group differences seen when oral iron was compared to the lower ferritin target with intravenous iron. When iron use was more aggressive in the higher ferritin target, the hemoglobin target was only about 0.4 g/dL higher.

Iron and infections

The association with iron administration and infections is biologically plausible. Iron promotes growth of even common bacteria such as *Staphylococcus epidermidis*.[11] In addition, the inflammatory response to infection is enhanced[12,13] and phagocytic function of neutrophils has been shown to be impaired by iron.[14] In one study, rodents given endotoxin when exposed to intravenous iron were much more likely to die than rodents that did not receive intravenous iron.

Risk of infection with oral iron is evident at least in some studies in humans. In a large randomized year-long trial in Tanzania, Africa, compared to placebo, the incidence of fatal infections was increased when preschool children were supplemented with oral iron and folic acid.[15] With cumulative follow-up of 25524 years, an increased risk of severe illness and death were noted with iron and the differences in event rates did not emerge till after 90 days after being on drug. Thus, the risk was not immediately apparent. Similarly, in the REVOKE trial, the incidence of infections in those receiving intravenous iron was increased.

Iron and cardiovascular events

The association between adverse cardiovascular events and the administration of intravenous iron is poorly recognized but is biologically plausible.[16–20] Compared with oral iron, a greater iron saturation and a higher serum ferritin concentration was seen in the IV iron group which may increase the likelihood for the generation of free iron. Free iron induces the generation of the hydroxyl ion via the Haber-Weiss Fenton reaction, quenching of nitric oxide, endothelial dysfunction and may accelerate atherosclerosis.[21] In the iron deficient state, the endothelium expresses the transferrin receptor, which can internalize diferric transferrin within the endothelial cell. This can lead to endothelial dysfunction and down-stream events. Repeated administration of iron sucrose results in post infusion proteinuria[22]; if this results in impaired sodium handling by the kidney it may explain excess heart failure hospitalizations. As an example, in the REVOKE trial, the incidence of cardiovascular events and especially hospitalization for heart failure was elevated several fold.

UNCERTAINTIES AND CAUTIONS

Despite about year long duration of FIND-CKD and 2 years for REVOKE, the safety data are disparate and difficult to compare for several reasons.[10] First, FIND-CKD excluded patients whose CKD was progressing rapidly and they could reach ESRD within 12 months. Second, adverse events and serious adverse events are reported up to the point at which another anemia therapy was initiated and/or the randomized study medication was discontinued. In other words, if ESA was initiated or patient transfused, the study stopped reporting serious adverse events. The latter is a violation of the intention-to-treat analysis. Third, serious adverse events were reported if they occurred in at least 1% of the patients. Even so, the investigators reported serious adverse events in 25.3%, 24.0%, and 18.9% of patients in the high-ferritin IV iron, low-ferritin IV iron, and oral iron groups, respectively. Thus, compared to oral iron group, IV iron SAE was between 27% and 34% higher. Fourth, multiple events within patients were not reported. In other words, multiple CHF events in 1 patient would only be reported once. REVOKE counted each event as a separate SAE. In fact, the number of patients who had SAEs in REVOKE

were similar between oral and IV iron groups. Indeed REVOKE found that exposure to IV iron increased the frequency—not the number of participants—with serious adverse events.

Following the publication of REVOKE, the authors of FIND-CKD reported a post hoc analysis of adverse event rates per 100 patient-years to assess the safety of FCM over oral iron.[23] They criticize the REVOKE study for using a nonstandard way of reporting adverse events where repeated events per patient are reported instead of just the first event. In their post hoc analyses the FIND-CKD investigators did not find an elevated risk for infections or cardiovascular events. But they note: "Additionally, it should be borne in mind that safety reporting was censored at the point at which another anemia therapy (e.g., ESA or blood transfusion was initiated and/or the patient discontinued the study drug). This approach was taken in an attempt to obtain 'clean' data sets, but this advantage is counterbalanced by the risk that adverse events which first manifested after drug discontinuation would not be captured, and is thus a potential source of underreporting." Besides, this is analysis is violation of intention to treat—a standard of reporting in clinical trials—and their report is what would be considered a per protocol analysis which is subject to bias. Therefore, despite these post hoc reports the data gathered during the conduct of FIND-CKD is inadequate to prove safety.

In dialysis patients, intravenous iron is being used liberally but there is no randomized trial to show safety of this approach. Compared with patients studied in REVOKE or FIND-CKD, dialysis patients are even at high risk for cardiovascular events and infections. Cardiovascular complications and infection complications are difficult to recognize outside a randomized trial setting. Oral iron is apparently considered ineffective in this population, but high quality trials are missing. Intravenous iron, although considered standard of care, probably needs to be compared with oral iron in such populations over a longer duration to provide greater confidence that oral iron truly is not effective. A new development has been the use of dialysate iron. Whether such a strategy, which exposes to less iron load, will result in fewer infections and cardiovascular events remains to be seen.

For approval of drugs used to treat a high risk populations, the FDA requires establishing cardiovascular safety of such drugs.[15] For example, the FDA guidance states, "if the premarketing application contains clinical data that show that the upper bound of the 2-sided 95% CI for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the 2-sided 95% CI for the estimated risk ratio is less than 1.3."[15] IV iron is liberally used in patients with CKD, a population that has a cardiovascular risk that is even higher than diabetes. Given that serious adverse events seen with IV iron was between 27% and 34% higher even in the FIND-CKD trial (and much higher in REVOKE), a trial to demonstrate long-term safety is now needed.[9]

KDIGO guidelines on anemia management (2012) state that "for CKD not-on-dialysis patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost."[9] This statement is not graded. Since these guidelines, several new trials suggest that a more cautious approach would be to replete iron using the oral route as first line therapy. Using elemental iron in a dose of at least 200 mg/day (equivalent to ferrous sulfate 325 mg orally 3 times daily) is recommended by the guidelines[9] and would be my first choice. If oral iron is not effective after a rigorous attempt for 1 to 3 months, then compliance with therapy should be evaluated and changes in frequency of the agent may have to be addressed. If oral iron is deemed ineffective, then intravenous iron in the lowest dose possible to replete iron may be administered. Delayed complications of repeated intravenous iron use are difficult to recognize at an individual level therefore inpatients who have had recent cardiovascular events or are infected, intravenous iron should probably be avoided since it can aggravate inflammation and promote adverse cardiovascular events. Balancing safety and efficacy would require clinical judgement because 1 size may not fit all till we have better data to support the liberal use of parenteral iron.

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