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The ferric conundrum: which intravenous iron preparations are preferred for chronic kidney disease patients?

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Implication for health policy/practice/research/medical education:
It has been demonstrated that iron deposition in the kidney is a harbinger of poor prognosis, but it is not clear whether kidney failure/damage predisposes iron deposition, or iron deposition activates an oxidative cascade and causes kidney damage. Until this issue is clarified, it will be difficult to predict the risks or benefits of any iron infusion for chronic kidney disease.

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Editorial

Introduction

Prevalence of iron deficiency anemia in the general population is around 12.2% (1). Iron deficiency anemia is a very common finding in patients with chronic kidney disease (CKD). Low-appetite, dietary restrictions, inflammation, and occult intestinal bleeding are common causes of iron deficiency. This problem is more prominent in patients with end stage renal disease on chronic hemodialysis (2). Using erythropoiesis-stimulating agents (ESAs) is a common cause of iron deficiency in patients on hemodialysis as ESA increases iron demand for erythropoiesis (3).

Iron supplementation is associated with low mortality in the pre-dialysis stage 5 of CKD. The kidney disease: Improving Global Outcomes (KDIGO) Guideline 2012 recommends a trial of oral or intravenous (IV) infusion in patients with CKD to treat anemia without using ESA. Subsequently, a couple of clinical trials demonstrated higher effectiveness of IV iron infusions compared to oral iron agents to increase hemoglobin. The Proactive Iron Therapy in Dialysis Patients (PIVOTAL) trial demonstrated that high dose IV iron therapy was superior to a low dose IV iron regimen in terms of maintaining hemoglobin levels, lower doses of ESA agents and lower risk of death or major cardiovascular events. Infection was a concern, but both high dose and low-dose iron groups exhibited the same infection rates. Other study showed mixed results between the relationship of IV iron and infection rates (4).

The choice of IV iron preparation in treating anemia may be dictated not only by its safety profile but also by cost and availability. There are many IV iron formulations available (Table 1).

Although, there is a trend of using IV iron infusion in treating iron deficiency anemia in patients with CKD, there are two trials that have different conclusions in terms of safety and long-term efficacy. In the Ferinject assessment in patients with Iron deficiency anemia and non-dialysis-dependent chronic kidney disease (FIND-CKD), 626 patients were followed for 56 weeks after randomization to the low-dose and high-dose IV ferric carboxymaltose, or oral iron. The hematological response was significantly greater in high dose IV iron infusion arm compared to oral iron with similar adverse events. In the Randomized

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Table 1. Common IV iron formulations profile

Iron formulation	Molecular weight	Price ($)/dose	Half-life
Iron sucrose	34-60 kDa	583.70/1 g	6 h
LMW iron dextran	165 kDa	329.73/1 g	5-20 h
Sodium ferric gluconate	289-440 kDa	546.40/1 g	1 h
Ferumoxytol	750 kDa	2511.28/1 g	15 h
Ferric derisomaltose	1000 kDa	2659.38/1 g	20 h
Ferric carboxymaltose	788 kDa	1695.70/1 g	7.5-12 h

Trial to Evaluate IV and Oral Iron in Chronic Kidney Disease (REVOKE) trial 136 subjects were randomized to oral ferrous sulfate or IV iron sucrose and were followed for 2 years. There was no difference in the decline of measured glomerular filtration rate (mGFR) in both groups, however, higher risk of adverse events, including cardiovascular and infection leading to hospitalization, in the IV iron infusion arm were observed. There are many potential explanations for the differences in findings in those studies. One of the most important and significant differences was the different iron formulations used.

Iron isomaltose and iron sucrose have comparative efficacy in maintaining Hb concentration in HD patients. Both were well tolerated and had similar short-term safety profiles (5). Short-term safety of IV sodium ferric gluconate vs. iron sucrose revealed a slightly lower risk of infection-related outcomes in the ferric gluconate arm. On the contrary, long-term outcomes in another similar study demonstrated that there was a small decrease in hospitalizations and deaths in the group that received iron sucrose (6). It has been also advocated to use sodium ferric gluconate rather than iron dextran, due to lower case-fatality rate (15.8% versus 0%) and achieving optimal response in anemia level (7).

It has been observed that iron deposition in renal biopsy was significantly higher in patients with higher serum creatinine, proteinuria, hematuria and urinary N-acetyl-beta-D-Glucosaminidase [u-NGAL] levels. The renal iron deposition may harbor the progression of CKD and may be an early indicator of renal damage (8). It also has been shown that different types of iron infusion cause different degrees of proteinuria and nephrotoxicity. Meanwhile, it has been demonstrated that infusion of ferumoxytol caused scattered interstitial intracytoplasmic granules within histocytes, but after a dextran infusion, there was no iron deposition in the interstitial of the kidneys noted (9). Although, another observation showed iron dextran deposition in a patient with hematuria (Figure 1).

In a retrospective review of two other cases that had renal biopsies after receiving iron infusions (One iron sucrose 100 mg for 5 days prior the biopsy and ferric gluconate 150 mg/daily for three days prior to the biopsy), iron deposition was identified with iron sucrose but not with iron gluconate (Figure 2).

Mitochondrial dysfunction has been demonstrated in kidneys of uremic animals by proton/electron leak and it has been postulated that improving mitochondrial function, can restore renal function (10). It has been assumed that using IV iron may improve mitochondrial function and mitigate renal damage.

In rat models with CKD, a single dose of Iron dextran infusion induced oxidative stress and reduced antioxidant enzymes (11). Meanwhile, a bolus of ferumoxytol in uremic animals alleviated oxidative stress without increasing proteinuria or worsening of renal function (12). A single dose of third generation of iron infusion like ferric derisomaltose in patients with CKD does not induce oxidative stress (13).

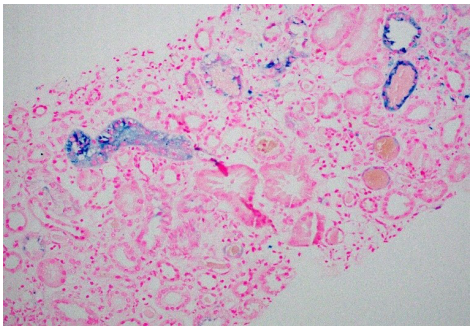

Figure 1. Iron staining in a patient with hematuria after iron dextran.

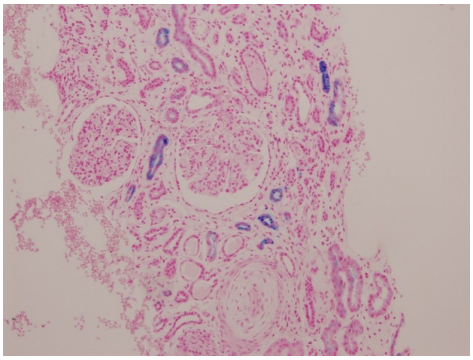

Figure 2. Iron deposition in renal tubular cells after infusion of iron sucrose.

Conclusion

There is a tremendous amount of unknown when trying to answer which iron product is superior to treat anemia in CKD. The results of many available studies were not validated by the others, as we discussed above. Nephrologists have many therapeutic iron infusion options to treat iron deficiency anemia in CKD and patients with ESRD on dialysis modalities. Currently, there is no available recommendation to guide choosing a specific iron product.

It has been demonstrated that iron deposition in the kidney is a harbinger of poor prognosis, but it is not clear if different types of iron infusion cause iron deposition in the kidney. It is hard to distinguish, whether kidney failure/damage predisposes iron deposition, or iron deposition activates an oxidative cascade and causes kidney damage. Until clarification of this issue, physicians continue order iron products based on cost, safety profile and availability of those in the hospital or dialysis units. Further studies will pave the way to choose different iron products wisely.

Authors' contribution

AH and RT contributed to study conceptualization, original draft, writing and editing. PM and KR contributed to literature review, preparation of figures, table, and final editing. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

Nothing to report except Ramin Tolouian received speaker honorarium from Sanofi and consulting fee from Travere therapeutics.

Ethical issues

This editorial article was conducted in accord with the World Medical Association Declaration of Helsinki. Ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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