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Perspective

New Options for Iron Supplementation in Maintenance Hemodialysis Patients

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End-stage renal disease results in anemia caused by shortened erythrocyte survival, erythropoietin deficiency, hepcidin-mediated impairment of intestinal absorption and iron release, recurrent blood loss, and impaired responsiveness to erythropoiesis-stimulating agents (ESAs). Iron malabsorption renders oral iron products generally ineffective, and intravenous (IV) iron supplementation is required in most patients receiving maintenance hemodialysis (HD). IV iron is administered at doses far exceeding normal intestinal iron absorption. Moreover, by bypassing physiologic safeguards, indiscriminate use of IV iron overwhelms transferrin, imposing stress on the reticuloendothelial system that can have long-term adverse consequences. Unlike conventional oral iron preparations, ferric citrate has recently been shown to be effective in increasing serum ferritin, hemoglobin, and transferrin saturation values while significantly reducing IV iron and ESA requirements in patients treated with HD. Ferric pyrophosphate citrate is a novel iron salt delivered by dialysate; by directly reaching transferrin, its obviates the need for storing administered iron and increases transferrin saturation without increasing serum ferritin levels. Ferric pyrophosphate citrate trials have demonstrated effective iron delivery and stable hemoglobin levels with significant reductions in ESA and IV iron requirements. To date, the long-term safety of using these routes of iron administration in patients receiving HD has not been compared to IV iron and therefore awaits future investigations.
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Iron supplementation has become a critical component in the treatment of anemia in patients with end-stage renal disease (ESRD). Nearly all patients with ESRD and ~70% of those with earlier stages of chronic kidney disease (CKD) are anemic.[1] There is increased reliance on iron in the ESRD population, in part from the safety issues related to high doses of erythropoiesis-stimulating agents (ESAs) raised by recent studies (TREAT [Trial to Reduce Cardiovascular Events With Aranesp Therapy][2] and CHOIR [Correction of Anemia With Epoetin Alfa in Chronic Kidney Disease][3]) and changes to Medicare ESRD reimbursement policies.[4,5] Several factors contribute to iron deficiency in patients with ESRD, including recurrent loss of blood in the hemodialysis (HD) circuit, routine blood samples taken for laboratory testing, and mobilization of tissue iron stores occasioned by the erythropoietic response to ESA therapy.[6-8] This is compounded by impairments of intestinal iron absorption and its mobilization from storage sites caused by the prevailing systemic inflammation in the ESRD population.

Iron supplementation can be achieved by oral or intravenous (IV) administration, each with its own set of advantages and disadvantages. Oral iron generally is safe but can cause gastrointestinal side effects that reduce treatment adherence. In addition, due to impaired intestinal absorption, oral iron compounds are usually less effective than IV preparations in maintaining iron stores in patients with ESRD. Although IV iron preparations are effective, their indiscriminate use can have serious adverse consequences that may go undetected in short-term clinical trials. As described in a recent review,[9] use of IV iron preparations can increase the risk for infection,[10,11] cause oxidative stress,[12-19] promote cardiovascular disease,[11,20-24] and lead to iron overload.[25-28] In addition, some IV iron preparations cause life-threatening anaphylactic reactions in susceptible individuals.

Nevertheless, IV iron supplementation is widely used in patients receiving HD. According to the DOPPS (Dialysis Outcomes and Practice Patterns Study) report from December 2014, a total of 81.9% of patients treated with HD in the United States had received iron during the preceding 3 months, most of which was administered intravenously.[29] The balance between the benefits and risks of IV iron is a hotly

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debated topic, further confounded by the uncertainty surrounding the validity of the available blood tests as reliable indicators of body iron status and optimal iron dosing regimens. The authors of the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) anemia guideline recommended that the "long-term safety of oral and intravenous (IV) iron agents…be carefully considered when iron therapy is prescribed, and that the potential for as yet undiscovered toxicities also be taken into account."[30(p293)]

As shown in Fig 1, there has been an evolution in iron delivery options in recent years. Iron delivery by phosphate binders or dialysate, which has been shown to be effective in patients treated with HD, has provided the opportunity to contrast the effects of intermittent IV administration of large loads of iron versus oral and dialysate iron on the well-being of this vulnerable population. Administration of a new iron-containing phosphate binder, ferric citrate, has been shown to effectively increase iron parameters, increase hemoglobin levels, and lower requirements for ESAs and IV iron in patients with ESRD.[31] The observed reduction in ESA resistance tends to exclude the exacerbation of oxidative stress and inflammation as a cause of the increase in ferritin levels in patients treated with ferric citrate. Ferric pyrophosphate citrate delivered by dialysate has been shown to replace the small amounts of iron lost with each HD treatment and to maintain hemoglobin levels. Unlike large boluses of IV iron, this delivery route does not overwhelm the transferrin pool and does not require significant storage of iron in the reticuloendothelial system. IV iron can lead to transient oxidative stress by increasing the level of non–transferrin-bound iron in the circulation and the catalytically active labile iron pool. In US patients treated with HD, the use of IV iron as the primary route of iron supplementation following the introduction of ESAs in 1989 has led to a progressive increase in mean serum ferritin levels in this population (Table 1[30,32-36]). This has raised concerns regarding the safety of IV iron for HD patients and was a key factor in a 2014 report by the Dialysis Advisory Group of the American Society of Nephrology stressing an "urgent obligation to initiate well designed investigations of intravenous iron in order to ensure the safety of the dialysis population."[37(p1238)] By describing the available data for the use of IV, oral, and dialysate iron products in the HD population, this Perspective provides an overview of the potential impact of administration route in iron supplementation strategies.

Oral Versus IV Iron Use in ESRD and Earlier Stages of CKD

A comprehensive Cochrane review conducted in 2012 comparing oral versus IV iron therapy in patients with CKD concluded that hemoglobin, ferritin, and transferrin saturation (TSAT) values were increased significantly more with IV iron therapy than with oral iron therapy.[38] In the IV iron groups, the final or change in hemoglobin level was 0.9 (95% confidence interval [CI], 0.44-1.37) g/dL higher in 22 studies, ferritin level was 243 (95% CI, 189-298) μg/L higher in 24 studies, and TSAT was 10.2% (95% CI, 5.6%-14.8%) higher in 18 studies. In the 9 included studies reporting change in ESA dose, the standardized mean difference favored IV iron (−0.76, 95% CI, −1.22 to −0.30; $P < 0.002$) compared to oral iron. No significant difference was noted between oral and IV iron for all-cause and cardiovascular mortality, but a few studies (5 and 2, respectively) reported these outcomes and most were 6 months or longer in duration. The authors cautioned that there was a high level of heterogeneity in the analyses and called for studies focusing on patient-reported outcomes, mortality, and cardiovascular morbidity. A 2008 systematic review[39] of 7 studies comparing

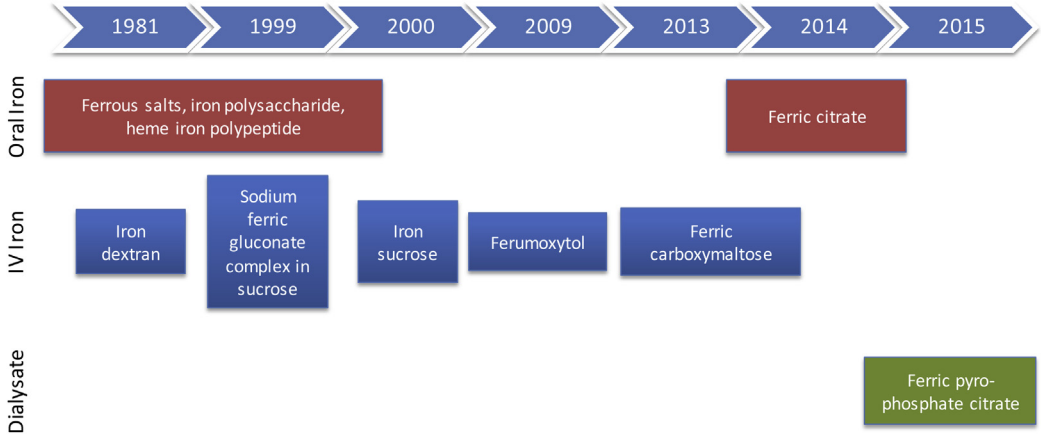

Figure 1. Iron formulations introduced in the United States. Abbreviation: IV, intravenous.