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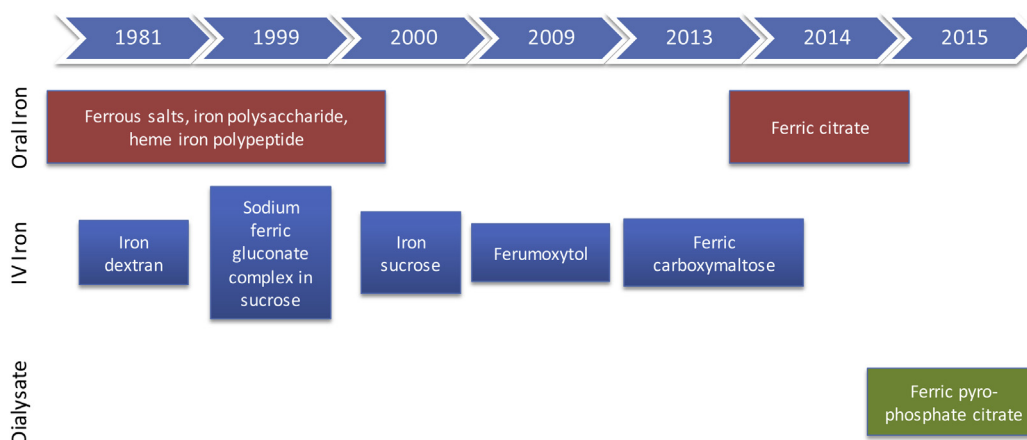
Figure 1. Iron formulations introduced in the United States. Abbreviation: IV, intravenous.

Table 1. Mean Serum Ferritin in US Hemodialysis Patients by Year

Year	Mean Serum Ferritin, ng/mL	Data Source	Target Serum Ferritin per Prevailing Guideline
1993	302	USRDS 1996 Annual Report[32]	None
1994	No data available		
1995	No data available		
1996	377	ESRD Core Indicators Project[a]	
1997	505		100-800 ng/mL, per 1997 DOQI[33]
1998	455	ESRD CPM Project[a]	
1999	489		
2000	529		
2001	600		200-800 ng/mL, per 2001 KDOQI[34]
2002	599		
2003	596		
2004	576		
2005	593		
2006	583		200-500 ng/mL, per 2006 KDOQI[35]
2007	586	Elab Project[b] 4th quarter	
2008	637		
2009	660		
2010	711		
2011	806	DPM[c] December 3-mo average[36]	
2012	808		Administer iron only if ferritin < 500 ng/mL, per 2012 KDIGO[30]
2013	801		
2014	825		

Abbreviations: CPM, Clinical Performance Measures; DOQI, Dialysis Outcomes Quality Initiative; DPM, Dialysis Outcomes and Practice Patterns Study Practice Monitor; ESRD, end-stage renal disease; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; USRDS, US Renal Data System.

[a]A 5% random national sample.
[b]A 97% national sample using electronic upload from laboratories serving dialysis facilities.
[c]A stratified weighted sample of 145 US dialysis facilities.

outcomes between oral and IV iron in patients treated with dialysis found that hemoglobin and ferritin levels were significantly increased in those receiving IV versus oral iron; however, TSAT did not change significantly. Three studies[40-42] showed no difference between oral and IV iron.

A summary of 32 randomized controlled trials[11,38,41,43-70] comparing oral and IV iron, including some published since the Cochrane review, is provided in Table S1 (provided as online supplementary material). One study appearing after the Cochrane review was FIND-CKD (Ferinject Assessment in Patients With Iron Deficiency Anaemia and Non–Dialysis-Dependent Chronic Kidney Disease),[70] a 56-week open-label multicenter study of 626 patients with non–dialysis-dependent CKD and iron deficiency anemia. Patients in the study were randomly assigned

1:1:1 to IV ferric carboxymaltose with a target serum ferritin level of 400 to 600 ng/mL, IV ferric carboxymaltose with a target serum ferritin level of 200 to 400 ng/mL, or oral iron therapy. Patients treated with IV ferric carboxymaltose with the higher serum ferritin target quickly achieved and maintained their hemoglobin levels with no difference in cardiovascular or infectious events compared with the other groups. However, patients in the oral iron arm of the FIND-CKD Study received 100 mg of ferrous sulfate twice daily, which is a total daily oral elemental iron dose of 40 mg. This is considerably less than the 200-mg daily oral elemental iron dose recommended by KDIGO[30] for the treatment of iron deficiency anemia in patients with non–dialysis-dependent CKD.

As mentioned, many of the analyses summarized in Table S1 were limited by high heterogeneity across the various studies. In studies involving patients who were not prescribed ESAs,[43,67] there was no significant difference in ferritin or hemoglobin levels between those treated with oral or IV iron. This finding suggests that the increased iron demand from ESAs may overwhelm the iron absorption process in the gastrointestinal tract. Because chronic iron toxicity takes years to manifest, it is unlikely that demonstrable differences in adverse outcomes could be detected in these studies with less than 26 weeks' follow-up. The mentioned Cochrane review[38] confirmed previously observed differences in side effects between IV and oral iron therapy. Allergic reactions and hypotension were significantly more common with IV iron therapy (risk difference, 0.02; 95% CI, 0.00-0.04; 8 studies; 1,199 patients). Gastrointestinal side effects were significantly more common with oral iron therapy (risk difference, −0.17; 95% CI, −0.27 to −0.06; 8 studies, 925 patients).[38]

Fatal adverse event rates have been reported at 1.4, 0.6, and 0 per million 100-mg dosage equivalents for the IV preparations of iron dextran, ferric gluconate, and iron sucrose, respectively.[71] Tabulations of all adverse events associated with these IV iron compounds give 29.2, 10.5, and 4.2 reports per million 100-mg dosage equivalents, respectively. Differences in all-cause and cardiovascular mortality have not been detected in the individual studies or combined analyses that reported those outcomes.[46,52,56,66,67] This may be due to the short duration of these trials because results of a recently published long-term randomized trial of oral versus IV iron therapy in patients with CKD revealed a significantly greater incidence of cardiovascular (2.15-fold) and infectious (2.12-fold) complications in patients receiving IV iron therapy.[11] Moreover, information for inflammatory markers has not been reported in comparisons of oral and IV iron therapy. Long-term trials are needed to provide meaningful

comparison of the safety of oral versus IV iron therapy in patients with ESRD and earlier stages of CKD.

There is a trend among dialysis providers to drive TSAT to 50% in the quest for lowering ESA doses. Because TSAT in healthy individuals is ~33%, this trend may promote excessive dosing of IV iron. To avoid potential adverse effects of large bolus doses of IV iron, investigators of a 2002 study[72] explored the possibility that smaller IV iron doses administered more frequently might be more effective than larger less frequently administered doses. To this end, they compared 6.25 to 21.3 mg of IV sodium ferric gluconate administered during each HD session against 62.5 mg given every 1 to 4 weeks. At 16 weeks, patients receiving IV iron every HD session showed a greater increase in hemoglobin levels than the group that received intermittent doses.[73] In an observational study looking at conversion of a baseline variable intermittent dosage regimen to a thrice-weekly fixed 10-mg dose of iron sucrose, the total monthly dose of iron sucrose declined from a mean of 230 to 130 mg, mean monthly darbepoetin dose decreased from 90 to 70 μg, and mean TSAT increased from 23.8% to 29.4%, whereas mean serum ferritin and hemoglobin levels were unchanged.[73] Unfortunately, in the United States, administration of small frequent doses of IV iron products is not economically feasible because the most commonly used products are supplied in nonreusable fixed-dose vials. The understanding that small frequent doses is more physiologic than large intermittent iron doses and the economic and logistical barriers to administering IV iron with every dialysis treatment has led to the exploration of alternate routes of administration that allow for small frequent dosing of bioavailable forms of iron.

Newer Oral Iron Agents

As noted, conventional oral ferrous salt preparations in patients treated with HD have been ineffective in providing adequate iron for erythropoiesis. Accordingly, the 2012 KDIGO guideline for anemia in CKD[30] does not recommend considering a 1- to 3-month trial of oral iron therapy for iron-deficient dialysis patients as it does for patients with non–dialysis-dependent CKD. Heme iron polypeptide, which is absorbed through a different intestinal pathway than ferrous salts,[74] showed initial promise as an effective oral iron supplement in patients treated with HD.[75] However, a randomized clinical trial in patients receiving peritoneal dialysis demonstrated no clear efficacy or safety benefit of this polypeptide compared with conventional oral iron supplements.[76]

A recent clinical trial of a novel phosphate binder, ferric citrate, showed it is effective in increasing iron stores in the dialysis population.[77] In this clinical trial, 441 patients receiving dialysis were randomly

assigned to ferric citrate or active control phosphate binder (calcium acetate or sevelamer) for a 52-week period. This period was followed by 4 weeks of placebo control, during which patients taking ferric citrate were re–randomly assigned to ferric citrate or placebo. In addition to proving effective in controlling hyperphosphatemia, ferric citrate significantly increased serum ferritin, TSAT, and hemoglobin values and significantly reduced the need for IV iron preparations and ESAs. Serum ferritin levels increased by a mean of 114.1 ng/mL in the ferric citrate group, with the greatest increase occurring in the first 24 weeks, after which levels remained relatively stable. In participants taking ferric citrate, mean serum ferritin level at 52 weeks was 895 ng/mL, which is modestly higher than the national mean in 2014 (Table 1). The mean TSAT value increased by 8.62% in the ferric citrate group by week 12 and then was stable, ranging from 39% to 40%. During the 52-week period, patients receiving ferric citrate required less IV iron than those in the active control group (median dose, 12.9 vs 26.8 mg/wk; $P < 0.001$); further, the percentage of participants not requiring IV iron was higher with ferric citrate ($P < 0.001$). The cumulative ESA dose over 52 weeks was lower with ferric citrate than active control (median weekly epoetin dose, 5,303 vs 6,954 U; $P = 0.04$).[78]

An editorial[79] accompanying the report raised the concern of whether long-term ferric citrate use has the potential to result in iron overload. Of note, for adequate control of serum phosphorus levels, the daily dose of ferric citrate contains 2,000 mg of elemental iron, though it is not clear how much of this iron is absorbed. Although a plateau was observed in TSAT at 12 weeks and in serum ferritin levels at 24 weeks, almost 20% of patients treated with ferric citrate had at least 1 serum ferritin measurement > 1,500 ng/mL (compared to 10% in the control group). This observation indicates that iron overload can also occur with ferric citrate and as such, it is necessary to regularly monitor iron parameters in patients receiving this agent and discontinue or reduce the dose when TSAT and/or serum ferritin values increase above the target range. The most common treatment-emergent side effect of ferric citrate use was diarrhea, which occurred in 25.6% of patients in the ferric citrate group. However, the sum of all adverse events (serious and nonserious) was similar between ferric citrate and active control groups (90.3% and 89.3%, respectively).[77,78]

The reason for the greater bioavailability of iron in ferric citrate than in conventional oral iron preparations is unclear and requires further investigation. Possible mechanisms include but are not limited to differences in the nature of the accompanying anion (citrate vs others), possible vesicular or paracellular

transport of ferric citrate as opposed to the tightly regulated DMT-1 (divalent metal transporter 1) pathway, extended sites of absorption beyond the duodenum/proximal jejunum, and uremia-induced changes in the structure and function of the gut epithelial barrier. Another likely mechanism for bioavailability of iron in ferric citrate is the high iron content (1,200-2,400 mg of elemental iron per day) of the prescribed dose, which far exceeds the iron content prescribed in the standard oral iron compounds (200 mg/d). The resulting high iron concentration gradient may allow increased iron absorption by overcoming the regulatory barriers. It has been suggested that citrate chelates calcium in the tight junctions between intestinal epithelial cells, thereby allowing paracellular absorption of metals such as ferric iron and aluminum.[80] However, in the 52-week study comparing ferric citrate with active control, there was no difference in serum aluminum levels between the 2 groups.[81] Nonetheless, the impact of coadministration of aluminum-containing products with ferric citrate is unknown and requires further investigation.

Sucroferric oxyhydroxide is another iron-based phosphate binder that is currently available. Unlike ferric citrate, the iron in sucroferric oxyhydroxide is poorly absorbed; therefore, it is not considered as an oral iron supplement and is not discussed further in this article.

Iron Delivery by Dialysate

Use of dialysate as a delivery vehicle for iron supplementation was first reported by Gupta et al[82] in 1999. In that study, patients treated with ferric pyrophosphate citrate by dialysate for 6 months were noted to have a decrease in IV iron requirements to maintain iron balance compared to the control group (6 vs 10 mg/wk, respectively; $P = 0.001$). Since that time, 2 large randomized controlled trials comparing this iron salt to placebo have been conducted,[83,84] and the product was approved by the US Food and Drug Administration (FDA) in 2015. At a dialysate iron concentration of 2 μmol/L (110 μg/L), ferric pyrophosphate citrate provides 5 to 7 mg of iron to the patient during each dialysis session, equivalent to the estimated amount of iron lost during a dialysis treatment. Thus, the goal of therapy is to maintain iron balance, not to replace accumulated iron deficits or extraordinary iron losses. Ferric pyrophosphate citrate crosses the dialyzer membrane during HD treatment and the iron binds to apotransferrin, which has a higher affinity for the iron than does pyrophosphate. There is little if any free iron in plasma and no iron load to exceed transferrin-binding capacity.

The first of the randomized trials mentioned in the preceding paragraph examining the safety and efficacy of ferric pyrophosphate citrate was the PRIME (Physiological Replenishment Iron Maintenance Equivalency) Study, in which HD patients with stable hemoglobin levels during treatment with consistent ESA doses were randomly assigned to the iron salt (n = 54) or placebo (n = 54) for 36 weeks.[83] IV iron administration during the randomization period was based on TSAT and serum ferritin values, and prescribed ESA dose was based on hemoglobin levels and the rate of change. At the conclusion of the study, mean hemoglobin levels were not statistically different between the 2 groups, but there was a 48% lower IV requirement ($P = 0.044$) and 35% lower ESA requirement ($P = 0.045$) among patients treated with the iron salt–containing dialysate. In addition, there were no intergroup differences in treatment-emergent, serious, or severe treatment-emergent adverse events. Markers of inflammation and oxidative stress also were not significantly different between the 2 groups.

The second study examining the safety and efficacy of ferric pyrophosphate citrate was Continuous Replacement Using Iron Soluble Equivalents (CRUISE), which comprised 2 identical phase 3, multicenter, single-blind, placebo-controlled trials of 599 patients.[84] After a 4-week run-in period during which hemoglobin level and ESA dose were stable (IV iron was prohibited), eligible patients were randomly assigned 1:1 to the iron salt or placebo, and no ESA dose changes were allowed. Patients completed randomization when they met 1 of 3 criteria: hemoglobin level < 9 or >12 g/dL, serum ferritin level <100 ng/dL, or hemoglobin level > 11.5 g/dL and 1 g/dL increase over 4 weeks. If patients did not meet any of these criteria, their participation in the study was stopped at 48 weeks. A total of 413 patients completed the study. The primary end point was mean change in hemoglobin levels from baseline to end of treatment. Patients treated with the investigational compound maintained stable hemoglobin levels, whereas those receiving placebo sustained a 0.3- to 0.4-g/dL decrease in hemoglobin levels, for an intergroup difference of 0.36 g/dL ($P = 0.011$). There was a significantly greater decrease in reticulocyte hemoglobin content ($P < 0.001$) and serum ferritin levels ($P < 0.001$) in patients receiving placebo versus treatment. An increase in serum iron levels pre- to posttreatment was demonstrated without an increase in serum ferritin levels. Only 10 patients in the study developed treatment-emergent adverse events requiring discontinuation of treatment.

Ferric pyrophosphate citrate is added to the bicarbonate concentrate of the dialysate mix. For dialysis machines not using liquid bicarbonate concentrate, an IV form of the iron salt has been developed and is undergoing evaluation. Until the IV form of the compound is approved by the FDA, patients undergoing dialysis treatment with machines that use solid

Table 2. Advantages and Disadvantages of Routes of Iron Administration

Route of Administration	Advantages	Disadvantages
IV	Significant experience regarding safety and efficacy; does not depend on patient adherence between dialysis treatments	Immediate reactions (nausea, hypotension, anaphylactoid); oxidative stress to cells; may promote growth of certain pathogens; may decrease leukocyte function; high potential for excessive iron in stores due to large doses given infrequently; inside bundled payment for US dialysis facilities
Oral (ferric citrate)	Functions as phosphate binder; decreases IV iron and ESA requirements; outside bundled payment for US dialysis facilities (advantage to provider)	May lead to high levels of storage iron if iron parameters not followed closely; dependent upon patient adherence between dialysis treatments; outside bundled payment for US dialysis facilities (may be disadvantage to patient due to copays); may require prior authorization or additional paperwork vs other phosphate binders; no long-term studies regarding safety
Dialysate (ferric pyrophosphate citrate)	Can be administered simultaneously to many patients by central dialysate delivery system; nursing time significantly decreased compared to IV iron administration; decreases IV iron and ESA requirements; all administered iron is bound to transferrin with very little if any going to stores; does not depend on patient adherence between dialysis treatments	May require individual iron-free dialysate for patients not requiring iron; no long term studies regarding safety

Abbreviations: ESA, erythropoiesis-stimulating agent; IV, intravenous.

bicarbonate concentrate will not have access to ferric pyrophosphate citrate. In a dialysis facility using a bicarbonate central delivery system with ferric pyrophosphate citrate added, patients for whom this iron salt is not indicated will require individual standard liquid bicarbonate concentrate.

Summary and Conclusions

Although traditional oral iron products are generally ineffective in restoring body iron stores, indiscriminate use of IV iron may overwhelm the plasma free transferrin pool and impose extensive stress on the reticuloendothelial system, events that can lead to adverse long-term consequences. To date, if adjusted for case-mix, observational studies have not demonstrated any adverse effects on mortality with average monthly IV iron doses < 400 mg,[85,86] which is far in excess of the mean monthly IV iron dose of 200 mg in US HD patients as of 2014.[87] However, a recent long-term randomized clinical trial comparing oral with IV iron supplementation in patients with CKD revealed a significant increase in cardiovascular and infectious complications in the IV iron–treated group.[11] In contrast to conventional oral iron preparations, the iron-based phosphate binder ferric citrate has been shown to be highly effective in increasing serum ferritin, TSAT, and hemoglobin values and significantly reduced IV iron and ESA requirements.[77,78] Ferric pyrophosphate citrate, iron that is delivered by dialysate, has been shown to be highly effective in maintaining TSAT and reducing IV iron and ESA requirements without increasing serum ferritin levels. Given the immediate side effects and potential long-term adverse effects of IV iron products and adverse cardiovascular effects of high ESA doses, alternate routes for iron administration that decrease IV iron and ESA requirements seem worthy of consideration. Ferric citrate and ferric pyrophosphate citrate are new agents, and although they have demonstrated safety in clinical trials, long-term safety data have not been reported. Some of the advantages and disadvantages of the routes of iron administration are summarized in Table 2. No single route of iron administration is best for all patients. It must be recognized that different patients have different needs (related to finances, physiology, and quality of life) that may be met with different agents or even a combination of agents.

SUPPLEMENTARY MATERIAL

Table S1: Randomized controlled trials comparing oral and IV iron.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.09.031) is available at www.ajkd.org

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