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Scholarly Review

Ferric pyrophosphate citrate as an iron replacement agent for patients receiving hemodialysis

Steven FISHBANE, Hitesh H. SHAH

Division of Kidney Diseases and Hypertension, Department of Medicine, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra Northwell School of Medicine, Great Neck, New York, USA

Abstract

Treatment of anemia remains an integral component in the care of patients with end stage kidney disease receiving dialysis. Currently, both erythropoiesis stimulating agents and iron replacement agents remain important anemia management strategies for patients undergoing hemodialysis (HD). Ferric pyrophosphate citrate (FPC) was approved by the U.S. Food and Drug Administration in January 2015 as an iron replacement product in adult patients receiving long-term maintenance HD. FPC is administered to patients on HD through the dialysate. Multicenter randomized, placebo-controlled phase three clinical studies (CRUISE 1 and 2) have found dialysate FPC to maintain hemoglobin level and iron balance in patients receiving chronic HD. Adverse events were similar in both the dialysate FPC-treated and placebo groups. Another study showed a significant reduction in the prescribed erythropoietin-stimulating agents dose at the end of treatment in the dialysate FPC-treated group compared with placebo. These studies have shown that dialysate FPC is efficacious and well tolerated. In this article, we review clinical studies evaluating the efficacy and safety of FPC and also propose a protocol for iron replacement in HD units where dialysate FPC is to be used.

Key words: Ferric pyrophosphate citrate, iron therapy, hemodialysis, end stage kidney disease, chronic kidney disease, dialysis, anemia

INTRODUCTION

Iron replacement is an important aspect of hemodialysis treatment. Iron deficiency is common in patients undergoing hemodialysis and is multifactorial in origin. Iron is lost from the body in excess of normal due to retention of blood by the dialysis apparatus, frequent blood testing, surgery, and accidental blood loss.[1] Iron intake is insufficient to replace losses, although iron absorptive capacity may not be different from normal.[2] In addition, the hormone, hepcidin, limits iron availability for erythropoiesis. Hepcidin blocks iron absorption from the intestines and causes iron sequestration in storage tissues. The circulating concentration of hepcidin is often increased among patients undergoing hemodialysis.[3,4]

Options for iron replacement for patients on hemodialysis include oral iron, intravenous iron and ferric pyrophosphate citrate (FPC) delivered via dialysate. Classic forms of oral iron have the advantage of being inexpensive and safe. However, these drugs have a significant burden

Correspondence to: S. Fishbane, MD, Division of Kidney Diseases and Hypertension, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra Northwell School of Medicine, 100 Community Drive, 2nd Floor, Great Neck, NY 11021, USA. E-mail: sfishbane@northwell.edu

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of uncomfortable gastrointestinal side effects that affect many patients. In addition, they are inconvenient. For example, with oral ferrous sulfate, the pill should be ingested between meals thrice daily. Since dialysis patients usually take medications in the morning, at night and with meals, the incremental difficulties with pill burden can be excessive. More importantly, traditional forms of oral iron have no demonstrable efficacy in hemodialysis patients when compared to placebo or no iron treatment.[5–7] Recently, the oral iron-based phosphate binder, ferric citrate, has been found to be efficacious and may be a reasonable treatment option.[8]

Intravenous (IV) iron is usually composed of iron bound to a carbohydrate moiety. Treatment is generally effective for improving hemoglobin (Hb) levels and reducing the required dose of erythropoietin-stimulating agents (ESAs).[9] In fact, these drugs are widely used for iron replacement in hemodialysis patients. Approximately, 70% of patients undergoing hemodialysis in the United States are treated with at least one dose of IV iron per month and the mean serum ferritin in 2015–2016 has been near 750 ng/mL.[10] Whether this represents overtreatment is a subject beyond the scope of this article.

The safety of IV iron injection has not been well studied. There is reason for concern as iron is a highly oxidizing and toxic substance. The human body goes to great lengths to carefully regulate, store, and utilize iron that protects tissues from harmful exposure and overload. This may be more true for iron than any other substance in the human body. Accordingly, treatment with iron should always be thoughtfully considered.

On casual inspection, it appears that patients tolerate iron injection. But this could be misleading and there could potentially be damage occurring that is not immediately discernable. Iron injection differs greatly from normal biology. Normally we eat food that contains approximately 10–15 mg of iron, of which perhaps 1–2 mg is normally absorbed into the body.[11] With a pool of 2000–5000 mg of iron in the body, the daily intake of 1–2 mg is remarkably conservative. The 1–2 mg of ingested iron is consumed over 24 hours, with gradual intestinal absorption that is tightly regulated. In contrast, iron injection is (1) administered not as 1–2 mg, but usually 50–100 mg of iron, (2) not over 24 hours but typically 1–5 min, and (3) not through the intestine's regulatory pathways, but instead directly into the blood stream. Whether these differences from normal biology are clinically important is not known. However, there is evidence that injection of the most popular form of IV iron in the United States, iron sucrose, at a common dose, 100 mg, results in oversaturation of transferrin, oxidative stress with changes in vascular tone and perhaps propensity for bacterial growth.[12–14] While it is unknown if patients undergoing dialysis are actually at any risk as a result, it at least stimulates interest in other ways of administering iron. In this article, we review ferric pyrophosphate citrate, an iron replacement agent that is administered via the dialysate.

FERRIC PYROPHOSPHATE CITRATE BACKGROUND

The FPC complex is a water-soluble iron salt and as opposed to most forms of IV iron it contains no carbohydrate. The citrate and pyrophosphate components are tightly complexed to iron, reducing risk for free iron release into the blood stream.[15] On entering circulation the iron moiety is transferred to transferrin and rapidly cleared.[16] The FDA approved indication for FPC is "for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD)."[17] FPC is currently marketed in the United States under the trade name Triferic (Rockwell Medical). FPC has not been studied in patients on home HD and is not intended for use in patients receiving peritoneal dialysis.

The greatest difference with IV iron is that FPC is administered via the dialysate, not injected. The drug is added to the bicarbonate component, mixes with product water, and the acid component to be delivered via the final dialysate. The dialysate contains 2 μM (110 μg/L) of iron (III).[15] The drug can only be administered if liquid bicarbonate concentrate is used in the dialysis facility.

In clinical studies, the drug was administered to individual patients through their own bicarbonate container. While necessary for clinical studies, this approach may not be as practical in clinical practice as simply adding FPC to centrally delivered bicarbonate concentrate. This, however, requires all patients on circuit to be treated with the drug. Later, we will come back to why this could be a reasonable and practical approach to treatment. First, we will review the clinical trials of FPC.

CLINICAL TRIALS OF FERRIC PYROPHOSPHATE CITRATE

The first published article on dialysate FPC treatment was in 1999. Gupta et al. studied hemodialysis patients with transferrin saturation (TSAT) between 18% and 25% and serum ferritin between 100 and 200 ng/mL.[18] After an initial 4-week pretreatment phase, patients were

randomized to receive FPC by dialysate as their primary iron treatment or iron dextran intravenously. Ten patients received FPC in a dose that was progressively increased from 2 to 12 μg/dL. Eleven control patients were treated with IV iron dextran. Over 6 months of follow-up, dialysate FPC maintained Hb and mean erythropoietin dose to a similar degree as IV iron. Dose requirements for IV iron, however, were reduced by nearly 80% in the dialysate FPC-treated group.[18]

It was not until 2015 that other clinical trials of dialysate FPC were published. The physiological replenishment iron maintenance equivalency (PRIME) study was designed to test a hypothesis that FPC via dialysate would reduce ESA dose requirements while maintaining Hb in range.[19] The design was a prospective, randomized, placebo-controlled, double-blind trial. Randomization was 1:1 to receive dialysate FPC (2 μmol/L [110 μg/L] iron) or standard dialysate (placebo) at all dialysis treatments. The primary endpoint was the change from baseline in the ESA dose required to maintain Hgb in the target range. One hundred and three chronic hemodialysis patients with Hb levels between 9.5 and 12.0 g/dL were enrolled. Baseline serum ferritin ranged from 200 to 1000 ng/mL, and TSAT 15% and 40%. There was weekly measurement of Hb and biweekly testing for serum iron ferritin and TSAT. To understand iron kinetics with FPC, postdialysis serum iron and TSAT were measured. During study, the patient's ESA dose could be adjusted to maintain Hb between 9.5 and 11.5 g/dL. The primary result was as hypothesized that dialysate FPC maintained Hb with reduced ESA requirements. The reduction in ESA dose compared to controls was 35%. Both groups required IV iron during the study, but less frequently in the FPC group (21.2%) compared to the control group (39.2%). Patients receiving dialysate FPC do still continue to require occasional IV iron; true in this study and we think generally true from compiled knowledge on the drug. Safety appeared to be acceptable for dialysate FPC, particularly in that there were no hypersensitivity events noted and no increase in hypotension. Bradycardia was seen more frequently in the FPC group (13.0% vs. 4.1%); this was a transient finding and was believed to be related to FPC.[19]

The pivotal phase 3 clinical studies were the Continuous Replacement Using Iron Soluble Equivalents 1 and 2 (CRUISE 1-2).[20] These were identical randomized controlled trials. The purpose was to test the hypothesis that dialysate FPC was more effective than placebo in maintaining Hb concentration in patients undergoing hemodialysis. The design was fairly complex, a first stage (1–4 weeks, no study drug treatment); a key second stage, randomized treatment (up to 48 weeks; assessment of primary end point), and Stage 3, open-label treatment. The randomization in stage 2 was dialysate FPC (2 μmoles [110 μg] iron/L) or placebo (standard dialysate), with no oral or IV iron administration allowed in either group. Also, no change in ESA dose was allowed. In the randomized treatment phase, patients were withdrawn and advanced to the third phase if certain anemia specific events occurred prior to completing 48 weeks, (i) Hb <9.0 or >12.0 g/dL, (ii) ferritin <100 ng/mL, or (iii) Hb >11.5 g/dL, with an associated Hb increase of ≥ 1.0 g/dL over 4 weeks. The study was designed during a period of heightened concern over ESA treatment safety, so these criteria were necessary, but they resulted in a large number of patients transitioning out of stage 2 before completing 48 weeks (71.3% of FPC patients and 77.8% of placebo patients). The mean duration of exposure to study drug in stage 2 was 159.4 days in the FPC group and 161.4 days in the placebo group. The study met its primary endpoint by finding a statistically significant improvement in mean Hb in the dialysate FPC group compared to standard dialysate (placebo) group. Since IV iron was prohibited during stage 2, the placebo group results provide an interesting window into how iron stores are depleted during ESA therapy.

Taken, together, the PRIME and CRUISE studies indicate that FPC is an efficacious treatment method for maintaining iron stores in patients on hemodialysis. As for safety, dialysate FPC was generally well tolerated with no important differences between study groups in adverse events. Because of the low quantity of iron delivered and the slow rate of administration, we would anticipate a fairly safe risk profile. However, because of the relatively small size of the phase 3 studies, safety data are somewhat inconclusive. One finding of interest was from the PRIME study, where bradycardia was reported in 13% of FPC treated patients vs. 4.1% of the placebo group.[19] In contrast, no excess of bradycardia was reported in the pivotal CRUISE studies.[20]

A recently published study of FPC pharmacology is instructive.[15] Rather than delivery through dialysate, the drug was instead infused intravenously over 4 hours at doses from 2.5 to 10 mg. The slow infusion mimicked dialysate dosing, but the actual doses of FPC were undoubtedly higher when administered intravenously. Serum iron increased in a dose dependent manner with TSAT rising to just over 100% with the 10-mg dose. Importantly, there was no increase in nontransferrin bound iron (NTBI). There were also no changes in markers of oxidative stress after infusion of FPC.

These findings are in distinct contrast to IV iron injection, where abundant NTBI and markers of oxidative stress are found in many patients after typical therapeutic doses.[1]

CLINICAL PERSPECTIVE FOR FPC

In our opinion, the primary potential vulnerability of IV iron treatment relates to the rapid injection of large amounts of iron into the bloodstream. Iron delivery by dialysate FPC is over 3–4 hours and in a much lower dose administered. In the clinical trials, this was reflected in the excellent tolerability of the drug. The treatment does not appear to be as potent as IV iron when comparing the PRIME and CRUISE studies to prior studies of IV iron. The rapid and large magnitude of increase in iron indices seen with IV iron is usually not necessary and might be excessive. In contrast, dialysate FPC iron is

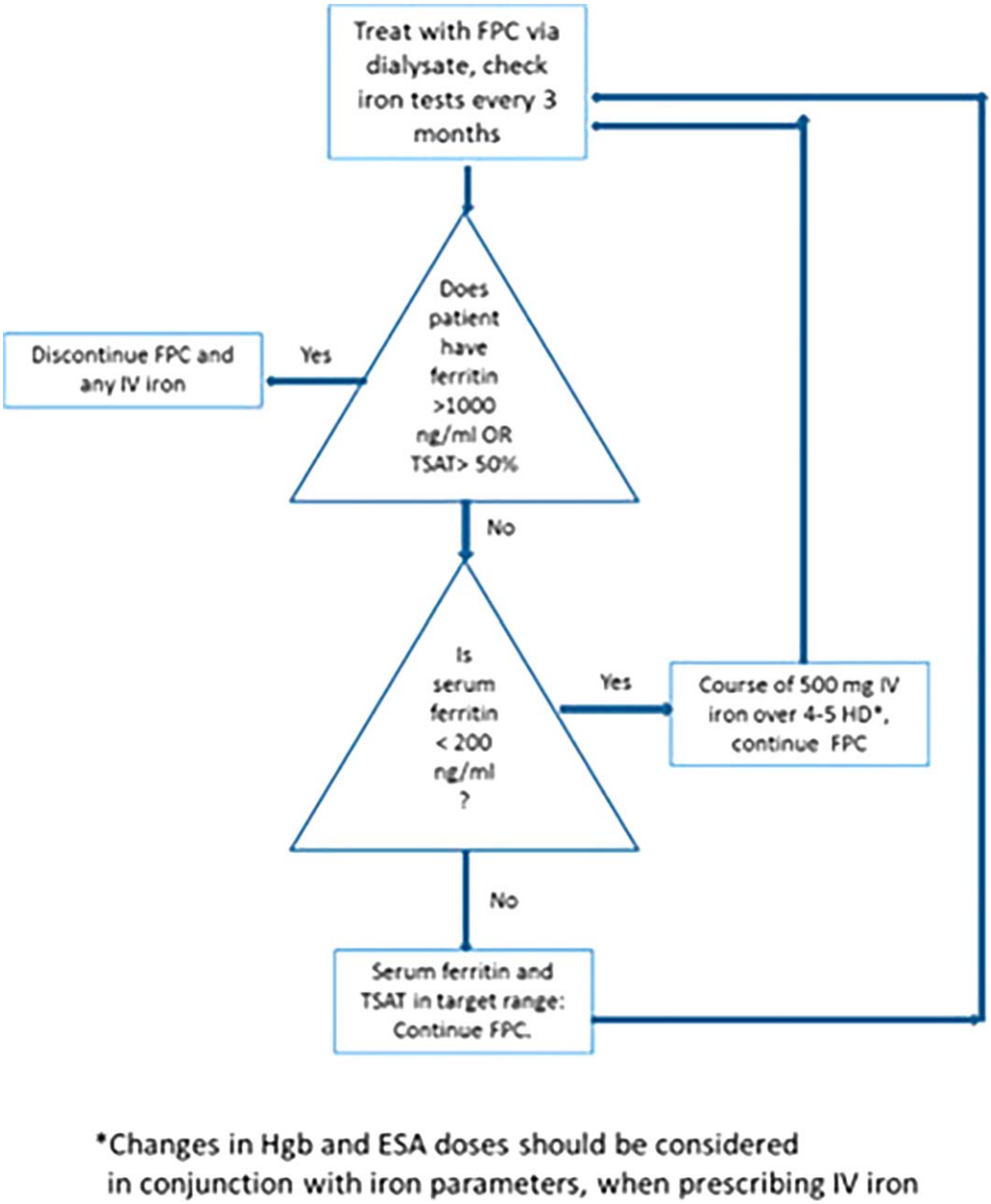

Figure 1 An approach to dialysate IV iron treatment when administered via central bicarbonate delivery system.

administered more gradually and in lower dose. However, given currently published data it is not possible to determine the exact amount of iron delivered with FPC treatment.

While there may be safety advantages to dialysate FPC, until well-studied we choose not to review this further. In contrast, efficacy of dialysate FPC in clinical practice will be different than that found with IV iron. Most patients in the United States are treated with regular, weekly, injections of iron. The vast majority of these patients develop stable and relatively high levels of iron indices. It is possible that the effect on whole body iron storage is excessive as MRI studies have indicated abundant iron present in the livers of dialysis patients.[21] In contrast to IV iron, long term treatment with FPC iron leads to gradual declines in serum ferritin and TSAT. The implications are that, (1) risk for iron overload should be significantly reduced, (2) some patients may obtain sufficient iron to avoid any IV iron exposure, and (3) many patients will probably require occasional IV iron supplementation on top of their basal dialysate FPC. Regarding this later point, it is not clear what percentage of patients would require IV iron. However, in the CRUISE studies discussed above, 7/192 (3.6%) patients randomized to FPC required IV iron supplementation.[20]

Dialysate FPC is delivered to the patient in the bicarbonate component. This can be achieved in one of two ways. In the published studies, the drug was administered to individual patients; with a 5-mL ampule of FPC added to each 2.5 gallons of bicarbonate concentrate. In contrast, FPC may also be delivered by central bicarbonate delivery. This requires adding 50 mL of FPC to each 25 gallons of master bicarbonate mix. The resulting concentration of FPC would be 110 μg/L (2 μmoles/L). All patients in the dialysis facility that are on circuit would receive dialysate FPC iron treatment. This is sensible in that all patients receiving hemodialysis lose iron progressively through dialysis apparatus blood retention, frequent blood testing, surgery, and accidental blood loss. The total average iron loss is often estimated to be 1000–2000 mg per year. While it is unclear what the exact absorbed dose of FPC from the dialysate is, a good amount of iron absorption does takes place given the consistent study data on robust increases in serum iron levels from predialysis to postdialysis and the consistent demonstrated efficacy of dialysate FPC. Because of this, we believe that most patients in a hemodialysis unit will achieve adequate replacement of lost iron with dialysate FPC, with some patients requiring additional IV iron supplementation. In contrast to IV iron, iron overload with dialysate FPC should be quite rare. However, patients who do develop positive iron balance with increasing serum ferritin levels should be treated off the central dialysate FPC delivery system. These patients will require treatment with an individual bicarbonate concentrate container.

We propose a protocol for dialysate FPC treatment.[22] When patients are treated individually, the drug should be administered with every dialysis treatment and serum ferritin and TSAT monitored every 3 months. If serum ferritin increases to over 1000 ng/mL or TSAT $>$ 50% then FPC iron should be placed on hold. If serum ferritin should at any time fall to below 200 ng/mL then a course of IV iron should be administered (Figure 1).

CONCLUSION

Dialysate FPC iron is a novel option for iron replacement in patients receiving hemodialysis. There are potential advantages compared to IV iron injection. In particular, the quantitative matching of iron losses and replacement are more physiologic with dialysate FPC. The slower delivery rates may help to avoid oxidative stress and other potential safety issues with IV iron treatment. Ideally, studies will need to be performed to help better understand the utility of dialysate FPC administered by central delivery system.

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