Ferric Pyrophosphate Citrate: A Novel Iron Replacement Agent in Patients Undergoing Hemodialysis

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Summary: Management of anemia remains an integral component in the care of patients with chronic kidney disease undergoing hemodialysis. In addition to erythropoiesis-stimulating agents, iron-replacement agents remain a key strategy for anemia treatment in this patient population. Ferric pyrophosphate citrate (FPC), a novel iron-replacement agent, was approved by the US Food and Drug Administration in January 2015 for use in adult patients receiving chronic hemodialysis (HD). This iron product is administered to patients on HD via the dialysate. The recently published, multicenter, randomized, placebo-controlled, phase 3 clinical trials found FPC to maintain hemoglobin level and iron balance in patients undergoing chronic HD. The mean hemoglobin level in these phase 3 clinical studies was maintained from baseline to the end of the treatment in the dialysate iron (FPC-treated) group, however, it decreased by 0.4 g/dL in the control group ($P < 0.001$). Adverse and serious adverse events were similar in both groups. Another recent study showed a significant reduction in the prescribed ESA dose at the end of treatment in the FPC-treated group compared with placebo. These studies have shown that FPC administered via the dialysate is efficacious and apparently well tolerated. In this article, in addition to reviewing the clinical studies evaluating the efficacy and safety of FPC, we propose a protocol for iron management in HD centers where FPC is to be used.

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Anemia remains an important complication of end-stage kidney disease. In addition to erythropoiesis-stimulating agents (ESAs), iron replacement remains a key anemia treatment strategy in patients undergoing hemodialysis (HD). The need for iron arises from blood retention in the dialysis apparatus,[1] frequent blood sampling for testing, and surgical and accidental blood loss.[2] Treatment with ESAs taxes iron stores, resulting in functional iron deficiency.[3]

Oral iron treatment has proved unsatisfactory in hemodialysis,[4-6] probably owing to absorption of insufficient quantities of iron. Since the introduction of ESAs, intravenous (IV) iron has been the major route for iron supplementation. Several of these agents currently are available in the United States.

Although treatment with IV iron appears, by casual inspection, to be well tolerated, there is at least some reason to be concerned by the rapid rate of injection of large quantities of iron. The basis of concern arises from the fact that iron possesses highly oxidizing properties that could be injurious to cells and tissues.[7,8] The human body protects against iron-induced oxidative damage by carefully regulating iron absorption from the intestines[9,10] and by sequestering iron in specialized molecules such as ferritin and hemosiderin.[11] Normally people eat approximately 15 mg of iron per day, of which only 1 to 5 mg is absorbed.[12] This small amount of iron absorption into the body occurs over 24 hours, through the intestines with rigorous regulation.[8] In contrast, IV iron is injected at 50 to 100 mg (or even doses up to 750 mg with ferric carboxymaltose), over minutes or less and directly into the circulation, bypassing intestinal protections. This diversion from biology may not be harmful, but because of iron's potential for causing oxidative tissue injury, and because well-powered safety studies have not been conducted, some concern regarding IV iron's safety remains.[13] Recently, Agarwal et al[14] found an increased rate of cardiovascular and infectious adverse events with IV compared with oral iron in a study of patients with nondialysis chronic kidney disease.

Ferric pyrophosphate citrate (FPC), a novel iron-replacement agent, was approved by the US Food and Drug Administration in January 2015 for use in adult chronic kidney disease patients receiving HD. This

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carbohydrate-free, water-soluble, complex iron salt is administered to HD patients via the dialysate. In addition to providing for iron utilization for erythropoiesis, FPC may avoid potential iron sequestration in reticuloendothelial macrophages in the bone marrow, liver, and spleen.[15] Although it bypasses the intestines like IV iron, it delivers much smaller amounts of iron over hours. This could help to potentially avoid oxidative toxicity and other safety issues related to IV iron. FPC currently is marketed in the United States under the trade name Triferic (Rockwell Medical, Wixom, MI). FPC has not been studied in home HD patients and is not intended for use in patients receiving peritoneal dialysis.

There are currently more options for iron replacement in dialysis patients mainly due to the availability of several IV iron agents in the market. In addition, ferric citrate, an iron-based phosphate binder, is a highly efficacious oral iron supplement. In this article, we review the clinical evidence regarding FPC's safety and efficacy and its potential place as an iron-replacement agent in patients undergoing chronic HD.

CLINICAL STUDIES OF FERRIC PYROPHOSPHATE CITRATE

In 1999, Gupta et al[16] published their study evaluating the short-term safety and efficacy of infusing soluble ferric pyrophosphate via hemodialysate solution (Dr. Gupta was the developer of this drug and at the time of this writing remains active in its commercialization). This single-center, open-label study included adult patients on chronic HD who had received erythropoietin (EPO) therapy for anemia management. All study patients had a transferrin saturation (TSAT) between 18% and 25% and a serum ferritin level between 100 and 200 μg/L. All patients also had received IV iron replacement within a 3-month period before the study. The study was conducted in two phases: a 4-week pretreatment phase, followed by a 24-week treatment phase.[16] During the study period, predialysis hemoglobin, hematocrit, serum iron, total iron-binding capacity, and ferritin were measured weekly. EPO was given intravenously during HD up to three times per week and the dose was adjusted every 4 weeks to maintain hemoglobin levels between 10 and 12 g/dL. During the study, patients were not allowed to take any oral iron therapy. However, all patients were eligible to receive varying maintenance doses (0, 25, 50, or 100 mg) of IV iron dextran once a week during HD to maintain a predialysis TSAT of more than 20% and a ferritin level of more than 100 μg/L. In addition, during the study, patients with overt iron deficiency (TSAT $<$ 20%) were treated with 100 to 200 mg of iron dextran with each hemodialysis session, up to a total dose of 400 to 1000 mg.[16] A total of 10 HD patients in the treatment group received escalating doses of soluble ferric pyrophosphate during each HD session for a total of 24 weeks, whereas 11 patients in the control group continued to receive IV iron only. Of note, the patients in the treatment group initially received 2 μg/dL of dialysate iron that subsequently was increased every 4 weeks to 4, 8, and then to 12 μg/dL for the last 12 weeks. Intravenous or dialysate iron-replacement therapy was discontinued if the TSAT increased to more than 50%.[16] During this 28-week study, the hemoglobin level was maintained both within and between the treatment (dialysate iron) and control (IV iron alone) groups. Similarly, during the study, there was no significant difference in EPO requirements within and between the groups. Both serum ferritin levels and TSAT also were maintained in both groups with no significant changes in these iron parameters between the two groups. During the study, the need for IV iron replacement in the dialysate iron treatment group decreased significantly by nearly 80%. The weekly dose of IV iron needed to maintain iron balance during the final month of the study was significantly higher in the control group when compared with the treatment group. All patients in the control group required IV iron therapy as compared with 2 of the 10 patients receiving 12 μg/dL of iron in the hemodialysate.[16] During the study, there were no hypersensitivity reactions seen in either group and there was no clinical or laboratory evidence of iron overload. There was no evidence for bacterial overgrowth in the iron-containing bicarbonate concentrates or any febrile illness related to increased bacterial content in the dialysate in either group. Hypotension was seen with equal frequency in both groups. These investigators concluded that administration of soluble iron pyrophosphate by hemodialysate may be a safe, effective, and alternative iron therapy in chronic HD patients.[16]

Subsequently, in 2002, Rockwell Medical licensed FPC and conducted several pharmacology–toxicology studies and a phase 1 to 3 clinical study program.[17]

More recently, the Physiological Replenishment Iron Maintenance Equivalency study determined if FPC administration via hemodialysate would decrease prescribed ESA use and maintain hemoglobin levels in the target range in patients undergoing chronic HD.[17] This prospective, randomized, placebo-controlled, double-blind, 9-month clinical trial was conducted at 23 sites across the United States.[17] The primary objective of this study was to determine the percentage change in prescribed ESA use from baseline to the end of treatment. This study also examined the safety of FPC administration via hemodialysate and the amount of IV iron use. The study included 103 adult chronic HD patients with stable ESA dose requirements and hemoglobin levels between 9.5 and 12.0 g/dL.[17] Serum

ferritin levels ranged from 200 to 1000 μg/L, and TSATs were between 15% and 40%. Patients were randomized to receive either dialysate containing FPC (2 μmoles [110 μg] iron/L) or standard dialysate (control group) at every HD session. The predialysis hemoglobin level was measured on a weekly basis and predialysis serum iron, serum ferritin, and TSAT were measured every 2 weeks. Postdialysis serum iron and TSAT also were measured. Of note, for the first 4 weeks of the study, use of IV iron was not allowed, neither were any changes in ESA dose, type, and administration route except when ESA dose reductions were needed to manage high hemoglobin levels. Subsequently, IV iron use was allowed beginning week 5 and the ESA dose also could be administered or adjusted to maintain hemoglobin level between 9.5 and 11.5 g/dL. Intravenous iron was given when serum ferritin levels decreased to less than 200 μg/L. During this 9-month study, the hemoglobin level was maintained at baseline in both the dialysate iron (FPC-treated) and the standard dialysate groups.[17] However, at the end of treatment, the ESA dose requirement was not changed significantly from baseline in the FPC-treated group, but had increased by nearly 40% from baseline in the control group (Fig. 1). There were more patients in the placebo group (20 of 51; 39.2%) who required IV iron replacement than patients in the FPC-treated group (11 of 52; 21.2%). Although the mean increase in serum iron level during the HD session in the FPC-treated group was 102.3 μg/dL compared with 2.9 μg/dL in the standard dialysate (placebo) group, predialysis serum iron levels were not significantly different in both groups, suggesting the iron was cleared rapidly in the FPC-treated patients. As compared with baseline, the mean predialysis serum ferritin level was not significantly different in the FPC-treated group at the end of treatment, but had decreased in the placebo group. There were, however, no statistically significant differences in the serum ferritin level between the groups at the end of treatment. There were no hypersensitivity reactions seen in the FPC-treated group. Bradycardia was seen more frequently in the FPC group (13.0% versus 4.1%), however, it was transient and was not believed to be related to FPC. Similarly, there was an increase in cough in the FPC-treated patients (22.2% versus 6.1%), but it was not attributed to FPC. Intradialytic hypotension occurred similarly in both groups. There was no increased frequency or severity of infections or cardiac events in the FPC-treated group. As compared with the standard dialysate group, there was also no increase in markers of inflammation or oxidative stress seen in the FPC group.[17]

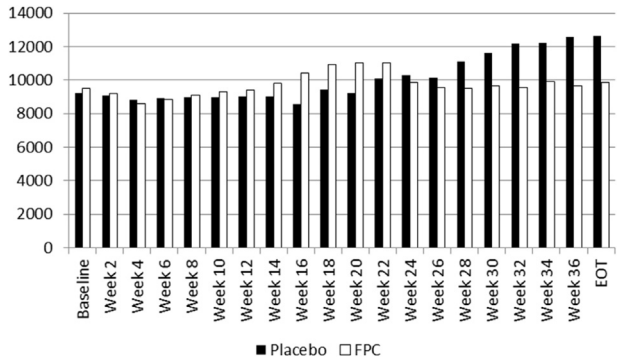

Figure 1. Prescribed dose of ESA increased in both groups from baseline to the end of treatment, but there was a significant reduction with FPC compared with placebo. EOT, end of treatment. Adapted from Gupta et al.[17]

The results of the two identical phase 3 clinical studies, Continuous Replacement Using Iron Soluble Equivalents 1 and 2, also recently were published.[18] These 2 prospective, randomized, placebo-controlled, clinical trials were conducted at 88 sites across the United States and Canada.[18] The primary outcome was the mean change in hemoglobin level from baseline to the last one-sixth of time in the randomized stage of the study. A total of 599 adult patients undergoing chronic HD were randomized to either HD with dialysate containing FPC (2 μmoles [110 μg] iron/L) or HD with standard dialysate (control group) for a period of up to 48 weeks.[18] The study included patients with stable mean hemoglobin levels between 9.5 and 11.5 g/dL. Serum ferritin levels ranged from 200 to 800 μg/L, and TSAT ranged between 15% and 40%. The use of either oral or IV iron therapy during the randomized treatment phase was not allowed, and neither were changes in the ESA dose. The predialysis hemoglobin level was measured on a weekly basis whereas predialysis serum ferritin, reticulocyte hemoglobin content, C-reactive protein, and serum iron panel were measured every 2 weeks. A posthemodialysis serum iron panel also was measured monthly.

During the randomized evaluation phase of the study (stage 2), there were few patients who completed the full 48 weeks of evaluation (55 of 192 in the FPC group and 49 of 221 in the placebo group). Because this stage of the study was the best opportunity to understand the efficacy and safety of the drug, the loss of patients during this stage was potentially a weakness. The major reason that patients transitioned out of stage 2 was not drop-out or loss to follow-up evaluation, but rather because of protocol-mandated transition for changes in anemia management. For example, if patients' hemoglobin levels increased or decreased beyond certain thresholds, they were transitioned to stage 3.

During the randomized treatment phase of these studies, the mean hemoglobin level was maintained from baseline to the end of treatment in the dialysate iron (FPC-treated) group, however, it decreased by

0.4 g/dL in the control group ($P < 0.001$, combined results; 95% confidence interval, 0.2–0.6).[18] Compared with the dialysate iron (FPC-treated) group, there were significant decreases in both serum ferritin and reticulocyte hemoglobin levels ($P < 0.001$) in the standard dialysate (control) group. As expected, both serum iron and TSAT levels increased markedly during HD in the FPC-treated group.

The percentages of patients with adverse and serious adverse events were similar in both treatment groups. Drug-related events occurred in 7.5% and 4.1% of the combined FPC and placebo groups, respectively. The most commonly reported adverse event in both groups was hypotension, which occurred in 21.6% of FPC-treated patients and in 19.3% of placebo-treated patients. A case of suspected hypersensitivity was reported (as hypotension) in one FPC-treated patient, however, it was thought to be secondary to hypovolemia.[18]

Taken together, these studies indicated that FPC delivered via the dialysate is generally efficacious and well tolerated. The amount of iron delivered appears to be insufficient to completely replace ongoing iron losses, as indicated by trends toward decreasing serum ferritin concentrations in the FPC treatment arms. Therefore, some continued treatment with IV iron, although at a reduced level, will be required for many patients.

PRACTICAL CONSIDERATIONS IN TREATMENT WITH FERRIC PYROPHOSPHATE CITRATE

FPC is delivered via the bicarbonate component of the dialysate.[15] There are two ways in which the treatment may be accomplished. One is the treatment of individual dialysis patients. To do this, one 5-mL ampule of FPC may be added to each 2.5 gallons of bicarbonate concentrate. The patient of course must be removed from any central bicarbonate delivery. Treatment of individual patients with FPC was the manner of treatment in the phase 3 studies. Alternatively, with a central delivery system, all (or most) patients in the dialysis facility (on the circuit) could be treated with the drug. A 50-mL ampule would be added to each 25 gallons of master bicarbonate mix; the final FPC–iron concentration in the hemodialysate is 110 μg/L (2 μmoles/L). The FPC containing dialysate would become part of the dialysate for all patients in the HD facility who are connected to the circuit. The idea of treating all or most patients in the dialysis facility with routine iron supplementation with each treatment is a new concept that would require substantial education. Whether treatment with FPC is for an individual patient or for all patients in a facility, an important difference from IV iron dosing is that FPC should be administered with every HD session.

Because patients undergoing HD lose iron with every treatment, iron replacement is needed on a regular basis in most patients. The dose of iron delivered by FPC is quite low compared with IV iron, but it is believed to be nearly the same amount of iron lost by HD patients, thus approximately maintaining iron balance. As a result, iron overload should be exceedingly rare with FPC. This is supported by the results from pivotal phase 3 trials in which the mean serum ferritin concentration was stable over time.[17] In fact, the serum ferritin concentration decreased slightly over time in the FPC group in the trials (-69.7 μg/L; 95% confidence interval, -87.2 to -52.2).[18] This is a positive characteristic for iron supplementation in hemodialysis patients. For most patients it will result in stable to slightly decreasing iron stores, with an occasional need for a short course of IV iron. The benefit to this group of patients would be a reduction in IV iron exposure and protection from the potential attendant risks with these drugs,[7] while receiving a more balanced form of iron repletion. For a small number of HD patients who have greater iron needs (occult blood loss, and so forth), there will be a more frequent need for IV iron treatment. A few patients predisposed to iron overload[19] will need to be taken off FPC owing to high serum ferritin concentrations. However, for most patients receiving FPC with every HD treatment, replacing the obligate dialysis iron losses potentially will avoid the occasional very high ferritin values that are observed with IV iron.

We propose a protocol for iron management with FPC (Fig. 2). FPC iron should be administered with every dialysis treatment. Serum ferritin and TSAT should be measured every 3 months. For patients with serum ferritin values between 200 and 1,000 ng/mL, we recommend IV iron be discontinued (all iron replacement is provided by dialysate FPC). For patients with serum ferritin values less than 200 ng /mL, we recommend a 500-mg course of IV iron over 4 to 5 dialysis treatments and to continue dialysate FPC both during and after the IV iron course. If the serum ferritin concentration is greater than 1,000 ng/mL or the TSAT is greater than 50% then FPC–iron replacement should be stopped and the patient should be treated with standard dialysate bicarbonate. Note that these suggested upper limits for serum ferritin concentration and TSAT are intended to apply to FPC-based iron treatment. These upper limits are higher than we would suggest for IV iron-based treatment because IV iron causes an acute surge in circulatory iron values and risk for iron overload.

A more difficult decision is how to treat patients with a history of allergy to IV iron. The risk of hypersensitivity reactions to FPC is probably lower

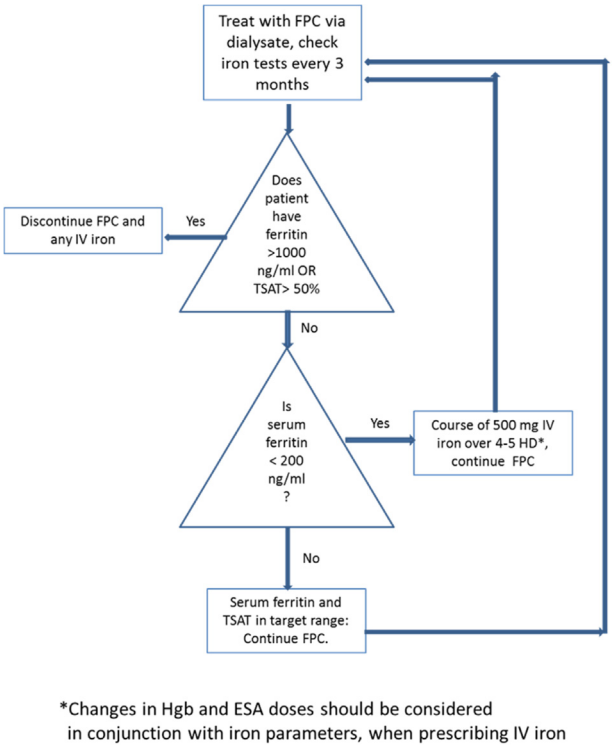

Figure 2. Approach to treatment with ferric pyrophosphate citrate via dialysate. Note that the suggested upper limits for serum ferritin and TSAT in the figure are intended to apply to FPC-based iron treatment. These upper limits are higher than we would suggest for IV iron-based treatment because IV iron causes an acute surge in circulatory iron and a risk for iron overload.

than that for IV iron formulations because FPC is carbohydrate-free and delivers iron into the circulation very slowly at a rate of only approximately 1 to 2 mg/h.[18] In the pivotal phase 3 controlled studies there was one event reported as a suspected hypersensitivity reaction that was considered related to FPC among 292 patients treated.[18] In the entire development program there were no serious hypersensitivity reactions requiring steroids, resuscitation, or hospitalization. Furthermore, the FPC clinical trials did not exclude patients with a prior history of hypersensitivity to IV iron. Two patients with a prior history of hypersensitivity to IV iron were treated with FPC uneventfully 3 times a week for more than 10 months. Although the risk of allergy with FPC is probably quite low, we would recommend that patients with a history of IV iron allergy be treated conservatively: either without FPC or treated with FPC, but cautiously with observation.

CONCLUSIONS

Treatment of anemia with iron-replacement agents remains an important component in the care of patients on chronic HD. The novel drug FPC is a useful iron-replacement agent available for use in chronic HD patients. It offers an approach to maintaining iron balance that is somewhat more physiologic than IV iron, with much slower delivery rates, bringing iron replacement into closer proximate balance to HD iron losses. Although FPC has potentially favorable properties and showed good efficacy and safety in phase 3 studies, longer-term studies would be helpful to characterize the drug's utility more fully.

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