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