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See related article, “Anti-Phospholipase A<sub>2</sub> Receptor Antibody Titer Predicts Post-Rituximab Outcome of Membranous Nephropathy,” on pages 2545–2558.

## Is It Too Much of a Good Thing? A New Era in Phosphate Binder Therapy in ESRD

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Hyperphosphatemia and anemia are common complications in patients with advanced CKD, and both contribute to their increased morbidity and mortality from cardiovascular disease. Fortunately, both conditions can be effectively treated with currently available therapeutic agents: phosphate binders, erythropoiesis-stimulating agents (ESAs), and iron supplementation. Regrettably, we now recognize that use of these agents, while indispensable, may also be associated with harm.

The optimal control of serum phosphate with phosphate-binding agents has evolved over the last five decades. Aluminum hydroxide was essentially abandoned, because aluminum accumulates in the brain, bone, and bone marrow, causing serious harm. Calcium-based phosphate binder use was restricted because of concerns about the potential of calcium load for enhancing progression of vascular calcification. The above concerns led to the development of a new class of binders, such as sevelamer and lanthanum carbonate, that do not contain aluminum or calcium. However, sevelamer usually requires large numbers of pills and may be associated with significant gastrointestinal adverse effects, whereas a small amount of lanthanum is absorbed from lanthanum carbonate and deposited in various organs.<sup>1</sup> Thus, the availability of the newer iron-based phosphate binders is bound to be welcome.

Treatment of anemia in patients on dialysis and patients with CKD has also evolved over time. In the pre-ESA era, repeated transfusions led to severe iron overload. However, after the approval of ESA in 1989 and its spectacular rise to glory, iron deficiency became common, leading to recommendations by clinical practice guidelines to administer intravenous iron to replenish iron stores and improve response to ESA.<sup>2</sup> Unexpectedly, ESAs suffered a major setback after the publication of four randomized clinical trials in patients on dialysis and patients with CKD, which showed that targeting hemoglobin (Hb) >13.0 g/dl with ESA may cause harm, including cardiovascular events, access thrombosis, and possibly, mortality.<sup>1,3–6</sup> In response to these findings, the Food and Drug Administration (FDA) changed the black box warning for administering ESAs,<sup>7</sup> and changes in clinical practice guidelines and the dialysis payment systems followed suit, with the intent to curtail ESA use.<sup>8</sup> These changes led to a progressive decrease in ESA use, but there was a parallel increase in intravenous iron use in an attempt to further reduce ESA-dosing requirements.<sup>9</sup> This is consistent with Kidney Disease Improving Global Outcomes clinical practice guidelines that recommend using intravenous iron for anemia in dialysis to increase Hb concentration or decrease ESA dose.<sup>10</sup> Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) confirmed the increasing use of intravenous iron in patients on dialysis.<sup>9</sup> Indeed, the mean serum ferritin has increased from 640 to 826 ng/ml from August of 2010 to January of 2012, and the percentage of patients with ferritin >1200 ng/ml also increased from 8.6% to 18% of patients.<sup>11</sup> Unfortunately, excessive intravenous iron administration is not without risks. All intravenous iron formulations have the potential to cause hypotension and anaphylactoid reactions and promote infection, oxidative stress, and endothelial dysfunction. More

importantly, recent DOPPS data showed an increase in mortality and hospitalization rates in patients whose monthly intravenous iron dose was  $>300$  mg.<sup>12</sup> Furthermore, because intravenous iron bypasses the physiologic controls that regulate intestinal iron absorption, it may lead to iron overload. A recent magnetic resonance imaging study showed that 84% of patients on hemodialysis receiving ESA and intravenous iron supplementation have hepatic iron overload.<sup>13</sup> That is why a number of recent editorials have raised concern about the potential harm from the current trend in intravenous iron use in patients on dialysis.<sup>14,15</sup> To recap, ESA and iron supplementation are necessary for treating the anemia of CKD, but high doses of either may not be safe.

The notion that a single drug has the capacity to control serum phosphate and at the same time, reduce ESA and intravenous iron use is appealing. Ferric citrate (FC), a new iron-based phosphate binder that was approved by the US FDA for clinical use in patients on dialysis in September of 2014, may just do that. In a recent phase 3 randomized clinical trial, in which 292 patients on hemodialysis were assigned to FC and 149 patients on hemodialysis were assigned to active control (AC) with sevelamer carbonate and/or calcium acetate and followed for 52 weeks, the phosphate-binding ability of FC was found to be similar to that of AC.<sup>16</sup> For secondary outcomes, the study evaluated the capacity of FC to replenish iron stores and reduce intravenous iron and ESAs use.

In this issue of *JASN*, Umanath *et al.*<sup>17</sup> provide details about changes in serum iron parameters and Hb levels throughout the 52-week period and examined the monthly changes in intravenous iron and ESA use during that trial. FC was supplied as 1-g tablets, each containing 210 mg ferric iron. The median daily dose was eight pills per day (about 2000 mg elemental iron). Intravenous iron was permitted during the study at the discretion of the treating physician but only if serum ferritin was  $\leq 1000$  ng/ml and transferrin saturation (TSAT) was  $\leq 30\%$ . Umanath *et al.*<sup>17</sup> reported that, over 52 weeks, the mean serum phosphorus was not significantly different between the two groups. However, treatment with FC resulted in significantly higher serum ferritin and TSAT levels compared with AC (change in ferritin,  $114.1 \pm 29.35$  ng/ml;  $P < 0.001$ ; change in TSAT,  $8.62\% \pm 1.57\%$ ;  $P < 0.001$ ). Also, subjects receiving FC required less intravenous iron than controls over 52 weeks (median [interquartile range] dose =  $12.9$  [1.0–28.9] versus  $26.8$  [13.4–47.6] mg/wk;  $P < 0.001$ ). Overall, 22% of subjects in the FC group did not receive any intravenous iron during the trial compared with 9% of subjects in the AC group. An important finding was that the cumulative ESA dose over 52 weeks was lower with FC than AC (median [interquartile range] dose =  $5303$  [2023–9695] versus  $6954$  [2664–12,375] units/wk;  $P = 0.04$ ). Subjects treated with FC experienced fewer gastrointestinal and hepatobiliary serious adverse events compared with subjects on AC. Umanath *et al.*<sup>17</sup> concluded that FC not only controls serum phosphate but simultaneously, provides a source of maintenance iron that leads to reduction in intravenous iron and ESA use while maintaining Hb levels in patients on dialysis. Similar results were also reported in patients

with CKD not on dialysis who had iron deficiency anemia but were not allowed to receive ESA or intravenous iron.<sup>18</sup> In that 12-week study, FC treatment significantly increased mean TSAT from  $22\% \pm 7\%$  to  $32\% \pm 14\%$ , increased ferritin from  $116 \pm 83$  to  $189 \pm 122$  ng/ml, increased Hb levels from  $10.5 \pm 0.8$  to  $11.0 \pm 1.0$  g/dl, reduced serum phosphate levels from  $4.5 \pm 0.6$  to  $3.9 \pm 0.6$  mg/dl, reduced urinary phosphate, and reduced serum intact FGF-23 levels.

We know that nearly all patients on hemodialysis will develop iron deficiency if iron is not routinely administered. Oral iron agents have previously been deemed inadequate for replenishment and maintenance of iron stores in patients on hemodialysis. However, the fact that FC resulted in increased ferritin and TSAT in patients on dialysis and patients with CKD and sustained reduction in the use of intravenous iron and ESA therapy, as shown by Umanath *et al.*,<sup>17</sup> indicate that FC can be helpful in maintaining iron stores in these patients. In that sense, FC is unique among phosphate binders, because it has the potential to directly and simultaneously improve mineral disorders and anemia of CKD. When prescribed in a mean dose of eight tablets per day, it effectively controls serum phosphate and delivers up to 2000 mg elemental iron per day (compared with about 200 mg elemental iron from oral iron formulations). By contrast, sucroferric oxyhydroxide, although effective as an iron-based phosphate binder, does not seem to significantly increase iron stores, because its active moiety, polynuclear ferric oxyhydroxide, is insoluble and does not release ferric iron for absorption.<sup>19</sup>

How should we incorporate FC into the management of patients on dialysis and patients with CKD with hyperphosphatemia? As discussed, administration of FC to patients on dialysis and patients with CKD achieved many therapeutic goals that we all desire: controlling serum phosphate, increasing iron stores, reducing intravenous iron and ESA use, maintaining/increasing Hb levels, and reducing FGF-23 levels.

Given that iron supplementation is necessary for most patients with CKD, particularly those on hemodialysis who are receiving ESA, the iron absorbed from FC will likely be beneficial in patients with either low or adequate iron stores. In these patients, FC as a source of maintenance iron may afford cost-savings through its sparing effects on ESA and intravenous iron use.<sup>20</sup> The main concern is whether use of FC over long periods of time has the potential to result in iron overload. We are not told what fraction of the 2000 mg elemental iron provided by eight tablets per day of FC is absorbed. Umanath *et al.*<sup>17</sup> claim that the plateau of TSAT at 12 weeks and the reduced rate of increase in serum ferritin at 24 weeks, despite continuing FC exposure, suggest that the absorption of iron is tightly regulated and saturable. However, almost 20% of their patients treated with FC had at least one serum ferritin measurement  $> 1500$  ng/ml compared with about 10% of patients in the AC group. Umanath *et al.*<sup>17</sup> stated that the majority of the high ferritin values was caused by intravenous iron administration and that most resolved by 52 weeks. Although this may be reassuring, longer-term clinical trials will be needed to confirm

these assertions. In the meantime, we should be prudent when prescribing FC to patients who have ferritin levels >1000 ng/ml or TSAT >30% and regularly monitor iron parameters in such patients. Undoubtedly, the effect of this drug on iron parameters will be vigorously debated as it should, with advocates touting the values of iron absorption and the backers of its competitor, sucroferric oxyhydroxide, highlighting its potential risk for iron overload. For now, iron absorption from FC should be considered a plus until future studies determine whether it is too much of a good thing.

## DISCLOSURES

None.

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