CLINICAL
INVESTIGATION

Ferric citrate in end-stage kidney disease as a phosphate binder and source of iron: a review of clinical trials

Hyperphosphatemia is highly prevalent among patients with end-stage kidney disease and is a major risk factor for cardiovascular disease and mortality. The contemporary management of hyperphosphatemia consists of oral phosphate binders for maintenance of normal serum phosphorus levels. Although several phosphate binders are currently available, limitations related to tolerability, safety, effectiveness, cost and pill burden have prompted the development of newer agents. Ferric-based compounds have been recognized to reduce phosphate absorption since the 1930s. In this manuscript, we review the recently available data on the use of ferric citrate with a focus on human studies that have led to its approval as a phosphate binder by the US FDA.

Keywords: binders • hyperphosphatemia • iron

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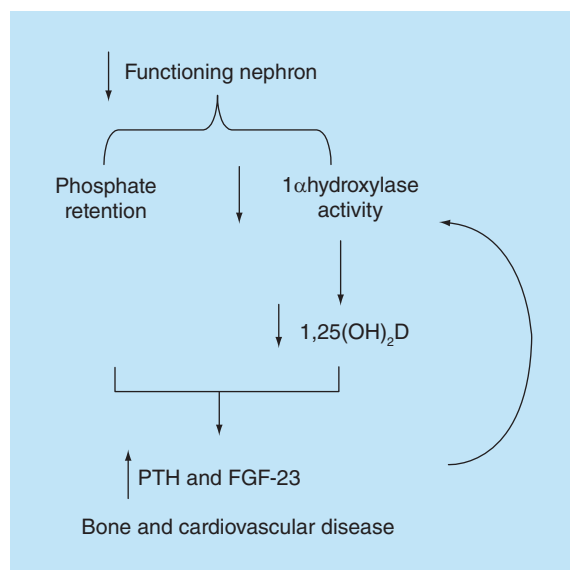*Author for correspondence:
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Chronic kidney disease (CKD) is recognized as a highly prevalent condition in USA and worldwide [1] and it carries significant risk of morbidity and mortality [2]. Common manifestations of advanced CKD include abnormalities of mineral and bone metabolism (MBD) [3,4]. CKD-associated MBD was defined in 2006 to include a wide range of abnormalities in serum levels of phosphorus, calcium, vitamin D, and PTH, in addition to abnormalities in bone turnover, and vascular calcification [5]. This definition takes into account the complexity of MBD as a systemic disorder and acknowledges the important role of abnormal phosphorus metabolism in its development (Figure 1). Under normal conditions phosphate metabolism is tightly regulated by the kidney through its excretion. As such, hyperphosphatemia is highly prevalent in patients with end-stage kidney disease (ESKD) [6–8]. Other factors in addition to reduced clearance by the kidney contribute to hyperphosphatemia in ESKD. These include a high protein intake [9] and insufficient clearance of phosphorus by dialysis. For example, in the setting of normal dietary phosphorus intake (~1000 mg per day) it is estimated that 4200 mg of phosphorus will be absorbed weekly [10]. Estimating that dialysis will remove on average 3171 mg of phosphorus per week [11], phosphorus will accumulate in ESKD at a rate of 150 mg per day resulting in unacceptably high positive phosphorus balance.

In addition to bone disease, hyperphosphatemia has long been associated with increased morbidity and mortality [12–14]. A recent meta-analysis indicated serum phosphorus levels >5.5 mg/dl are associated with significant mortality in patients with ESKD [15]. Thus, in patients with ESKD, contemporary guidelines target normal or near normal levels of serum phosphorus [16,17]. The agents currently available and utilized in the treatment of patients with ESKD are effective but have significant limitations. The available data suggest that phosphate binders, irrespective of agent, are the major contributor to the high pill burden in patients with ESKD [18]. For example, KDOQI guidelines recommend limiting the total dose of calcium-based phosphate binders to 1500 mg of elemental calcium per day to prevent hypercalcemia and minimize risk

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Figure 1. Chronic kidney disease-associated mineral and bone disorder.

Figure 1. Chronic kidney disease-associated mineral and bone disorder. As CKD advances, the kidney is prone to phosphate retention and suffers a reduced capacity to activate vitamin D. Collectively, these events lead to increased PTH levels. Another factor that plays an important role in mineral and bone disorder is the phosphaturic agent, FGF-23.
CKD: Chronic kidney disease; PTH: Parathyroid hormone.

of vascular calcification [19,20]. Despite this restriction, the recommended dose of calcium acetate will generate a pill burden up to 12 capsules a day. For the most commonly used phosphate binder, sevelamer, two consecutive studies, reported the mean daily maintenance dose as 4.9 g per day [21] and 6.9 g per day [22]; the equivalent of six to nine tablets per day. The high pill burden of phosphate binders has been postulated to play a role in the high nonadherence rates reported in patients with ESKD in need of phosphate binders [23]. Additional limitations with respect to currently available phosphate binders include their potential to affect bioavailability of other drugs and vitamins [24–26]. As such, there is a continued need for effective and safe phosphate binders.

Ferric compounds were initially noted to bind phosphorus in animal and human studies conducted several decades ago [27–30]. More recently, ferric compounds have been shown to effectively bind phosphorus in normal and uremic animals [31,32]. The preclinical experience led to the development of iron-based phosphate binders, including ferric citrate and sucroferric oxyhydroxide [33–36]. The latter (sucroferric hydroxide) has been reviewed elsewhere [37], thus this review is focused on ferric citrate. Specifically, several clinical trials have recently demonstrated the safety and efficacy of the compound in patients with ESKD [33–35] leading to its subsequent approval by the FDA as a

phosphate binder in ESKD in 2014. In addition, ferric citrate has been recently approved in Taiwan for control of hyperphosphatemia in ESKD and in Japan for control of hyperphosphatemic in CKD. In this manuscript, we review the data on ferric citrate as an effective phosphate binder for individuals with ESKD. In our review of the literature, we have identified seven studies evaluating the use of ferric citrate. Here we summarize results of four of these studies, the majority of which were conducted in USA (to avoid redundancy or duplication). We also include several posthoc analyses based on these studies.

Chemistry & mechanism of action

Ferric citrate (Auryxia, Keryx Biopharmaceuticals, Inc., NY, USA) is composed of iron in the trivalent state (Fe^{3+}) in combination with citrate ($C_3H_5O(COO)_3^{3-}$). It is available as 1 g tablets containing 210 mg of elemental ferric iron. Phosphorus binds to the ferric ion (dissociated from ferric citrate) and precipitates as ferric or ferrous phosphate. This is subsequently excreted in the stool [31]. In addition to the iron content and phosphate binding capacity, the citrate moiety, if absorbed, is converted to bicarbonate by the liver [38]. This has potential benefits for the treatment of metabolic acidosis associated with ESKD [39]. This is in contrast to use of ferric sulfate where large doses of sulfate can worsen metabolic acidosis in kidney disease [40]. Similar limitations have surrounded the potential development of ferric ammonium chloride as a phosphate binder. In addition, the use of ammonium could potentially associate with increased ammonia levels in the setting of abnormal liver function raising concerns about its safety [41]. These concerns have limited the potential development of ferric-based compounds as phosphate binders and focused development on ferric citrate.

Although iron overload is a well-recognized condition, the potential for iron toxicity by ferric citrate is likely limited due to the tight regulation of iron absorption in the gastrointestinal tract. The duodenum is the main site for iron absorption where iron is actively transported. Ferric ion (Fe^{3+}) is first reduced to ferrous iron (Fe^{2+}) on the surface of the duodenal mucosal cell by cytochrome b. This ferrous iron is then absorbed by the mucosal cell where most of it remains until the mucosal cell is shed. Normally, transfer of intracellular iron to the circulation occurs under the regulation of the hormonehepcidin [42]. Hepcidin binds to the iron exporter ferroportin inducing its degradation, and this reduces the transfer of iron from enterocytes to the circulation. This system tightly regulates gastrointestinal absorption of iron to meet physiologic needs, thus iron absorption is reduced in the face of iron repletion

In addition to the normal regulation of iron transport, there is evidence to suggest that hepcidin levels are increased in ESKD and this may further reduce the absorption of iron in this patient population [43]. Hence, the potential for iron overload via ferric iron absorption in ESKD is low.

Ferric citrate in preclinical studies

Several animal studies demonstrated the efficacy of ferric citrate to bind phosphorus in the gastrointestinal tract. Hsu *et al.* administered 4% ferric citrate to Sprague Dawley rats with and without kidney disease [31]. All 12 normal rats were fed a standard diet with 1.02% phosphate and 0.95% calcium for 2 weeks. Half of them received 4% ferric citrate for the duration of the 2-week study while the controls did not. The rats in both groups consumed similar amounts of food (24 g per day). However, at the end of the study, daily urinary excretion of phosphorus was significantly lower in the rats given ferric citrate (30.7 ± 1.5 mg per day) compared with the control group (75.0 ± 4.0 mg per day) with a p-value < 0.01. This was accompanied by increased stool phosphorus in the ferric citrate treated rats. Serum phosphorus, iron and hematocrit were similar for both groups at the end of 2 weeks. In a second experiment designed to study ferric citrate phosphate binding capacity in a rat model of kidney disease, azotemia was induced by partial nephrectomy. Subsequently, the rats received either no ferric compound, ferric citrate, ferric ammonium citrate or ferric chloride. Food intake was similar for all four groups of animals. In the azotemic rats, all three ferric compounds significantly reduced urinary phosphorus excretion while increasing fecal phosphorus compared with the control group. Serum phosphorus levels were lower in the groups receiving ferric compounds compared with the control group although this did not achieve statistical significance. Additionally, the ferric-treated azotemic rats had higher end of study hematocrit levels compared with controls. These data suggested that ferric compounds were indeed effective phosphate binders in the gut. The increase in hematocrit in the azotemic rats suggested that ferric compounds may also aid anemia management in CKD.

Safety & efficacy of ferric citrate in clinical studies

The first clinical study to evaluate ferric citrate in ESKD was an open-label cross-over study that was conducted in Taiwan [44]. It was designed, by the authors, to evaluate the efficacy of ferric citrate as a phosphate binder compared with calcium carbonate. The study included 55 subjects; 23 women and 22 men with ESKD. Subjects were either administered calcium carbonate or ferric citrate in random order. Patients underwent a 14-day washout period, then a 28-day treatment period, a second 14-day washout period and a second 28-day treatment period. All phosphate binders were withheld during the washout periods. During the treatment periods, patients received either calcium carbonate or ferric citrate at a dose of 1 g three-times a day with meals. The serum phosphorus increased from a baseline concentration of 5.6 ± 1.5 mg/dl to 7.2 ± 1.9 mg/dl prior to calcium carbonate treatment and to 6.7 ± 1.9 mg/dl prior to ferric citrate treatment. Serum phosphorus declined significantly during treatment with both calcium carbonate (7.2 ± 1.9 to 5.2 ± 1.5 mg/dl; p < 0.0001) and ferric citrate (6.7 ± 1.9 to 5.7 ± 1.6 mg/dl; p < 0.0001) although the absolute reduction in phosphorus was larger with calcium carbonate. The short treatment period, low dose and small number of subjects did not allow for sufficient characterization of adverse effects of ferric citrate, but it was generally well tolerated, with mild gastrointestinal adverse events being the most common. Serum ferritin increased during treatment with ferric citrate but not with calcium carbonate. Liver function tests were similar in both treatment arms. This study offered the first evidence that ferric citrate may represent an effective and safe phosphate binder in humans.

Patients with ESKD typically require different dosages of binders to achieve goal phosphorus levels leading to the frequent titration of phosphate binders in clinical practice. Some patients require high doses of phosphate binders presumably due to nonadherence to a phosphate restricted diet. The safety and tolerability of ferric citrate dose titration, up to a maximum dose of 12 tablets per day, in patients on hemodialysis was explored in 55 subjects with ESKD receiving hemodialysis in USA [34]. Here subjects were enrolled in two periods. Period 1 recruited patients taking six to 15 pills per day of current binder with phosphorus of ≥2.5 mg/dl. Period 2 recruited another group of patients taking ≥12 pills per day of current binder with phosphorus of ≥3.5 mg/dl. Subjects with ferritin ≥1000 ng/ml or transferrin saturation (TSAT) ≥50% at screening were excluded. Previous binders were discontinued and subjects started 4.5 g per day of ferric citrate for the first period or 6 g per day for the second period. Ferric citrate was titrated for 4 weeks to maintain a phosphorus level of 3.5–5.5 mg/dl. Chemistries and complete blood count were obtained weekly and a gastrointestinal questionnaire was administered at drug initiation and final visit. Intravenous (iv.) iron therapy was allowed if the ferritin level was <500 ng/ml and TSAT <30%. During the course of the study, four

serious adverse events were reported, none related to the study drug. Based on the gastrointestinal questionnaire, subjects reported stool discoloration commonly (62%). Other gastrointestinal complaints were reported less commonly including constipation (15%) and bloating (7%). Mean iron parameters at the beginning of the study were: ferritin 554 ± 296 ng/ml, iron 68 ± 21 µg/dl and TSAT 30 ± 7.8%. At the end of study, mean ferritin was 609 ± 340 ng/ml (p = 0.02), iron 75 ± 27 µg per d (p = 0.04) and TSAT was 35 ± 13% (p = 0.001). Mean phosphorus levels were not significantly changed from baseline when on their baseline binder compared with at the end of study when on ferric citrate (5.9 ± 1.4 mg/dl at baseline to 5.4 ± 1.4 mg/dl; p = NS).

A larger dose-ranging and efficacy study of ferric citrate was initiated subsequently in 151 subjects with hyperphosphatemia and ESKD receiving maintenance hemodialysis conducted in the USA [33]. Subjects were randomized in an open-label placebo-controlled study to receive: a fixed-dose of 1, 6 or 8 g of ferric citrate per day for 4 weeks. Subjects were required to have a serum ferritin level <1000 ng/ml, TSAT <50% and serum phosphorus level 3.5–7.9 mg/dl at the screening visit. Subjects underwent a 1–2 week wash out period where current phosphate binders were discontinued. Hyperphosphatemia was required prior to randomization. In this study, mean baseline phosphorus levels were 7.3 ± 1.7 mg/dl, 7.6 ± 1.7 mg/dl and 7.5 ± 1.6 mg/dl in the 1 g, 6 g and 8 g per day groups, respectively. Phosphorus levels decreased in a dose-dependent manner (mean change at end of treatment, -0.1 ± 1.3 mg/dl in the 1 g per day group, -1.9 ± 1.7 mg/dl in the 6 g per day group and -2.1 ± 2.0 mg/dl in the 8 g per day group). As anticipated, the most common adverse event was stool discoloration (19.2%). Ferritin levels increased in the 6 g per day and 8 g per day groups by 90.1 ± 198.6 and 90.2 ± 279.0 ng/ml. Results of this study confirmed that ferric citrate binds phosphorus in a dose-dependent fashion.

Although no major adverse events were reported in association with ferric citrate in any of these studies, the short duration of treatment and the evidence of iron absorption necessitated a larger study of longer duration. Hence, a larger pivotal Phase III study was undertaken to test the long-term safety and confirm the efficacy of ferric citrate [35]. The detailed rationale and design of the study are discussed elsewhere [45]. A schema of the overall study design is shown in Figure 2. Briefly, the study recruited individuals with ESKD who had been receiving either hemodialysis (three-times a week) or peritoneal dialysis (for a minimum of 3 months), who were receiving a phosphate binder (three to 18 tablets a day of calcium carbonate, calcium acetate, lanthanum carbonate or sevelamer)

and who had demonstrated tolerance to either calcium acetate or sevelamer carbonate. This was a multicenter, international, sequential randomized and controlled trial involving two randomized periods (a 52-week active control period followed by a 4-week placebo control period). The first period consisted of a 2-week washout and only those subjects achieved a serum phosphorus ≥6 mg/dl were allowed to proceed to randomization. Subjects were randomized in the active control period to ferric citrate or active control in a 2:1 ratio. Active control agents selected at the discretion of the investigator and were dispensed by the study and consisted of calcium acetate 667 mg capsules and/or sevelamer carbonate 800 mg tablets. Ferric citrate and active control were titrated to achieve goal phosphorus level 3.5–5.5 mg/dl. Ferric citrate was titrated using a protocol supplied algorithm and active control was titrated guided by the package inserts. The starting dose for ferric citrate was six tablets which were distributed per investigator discretion with meals and snacks. Compliance was assessed by pill counts. The placebo control period extended for 4 weeks after completion of 52-week active control period. During this period subjects who were randomized to ferric citrate during the active control period were rerandomized to remain on ferric citrate or to placebo, and phosphorus levels were monitored every week. All treatment emergent adverse events (serious and nonserious) were monitored and recorded regularly and serious adverse events were reviewed by an independent Collaborative Study Group committee. The primary efficacy outcome of the trial was change in phosphorus levels for ferric citrate versus placebo at the end of the placebo control period (week 56) as compared with baseline (here defined as week 52, the end of the active control period). Oral iron therapy was not allowed for the duration of the study. Intravenous iron was allowed at the discretion of the treating physician, only if serum ferritin was <1000 ng/ml and TSAT was <30%. Use of erythropoiesis-stimulating agents was not dictated by study protocol. Four hundred and forty-one subjects were found to fulfill the inclusion criteria and were randomized at the end of the washout period.

At the end of the placebo-controlled period, serum phosphorus was significantly lower in the ferric citrate group compared with the placebo group (difference -2.2 ± 0.2 mg/dl; p < 0.001) [35]. Throughout the 52-week active control period, serum phosphorus levels were similar for ferric citrate and active control (Figure 3). Specifically serum phosphorus was 5.4 ± 1.6, 5.4 ± 1.7 and 5.3 ± 1.4 mg/dl for ferric citrate, sevelamer carbonate and calcium acetate respectively. Serum parathyroid hormone (PTH) levels were reduced in

both the ferric citrate and active control groups similarly between baseline and the end of the 52 weeks. No deaths were attributed to the study drug. Serious adverse events were reported by 39% of subjects taking ferric citrate and 49% of subjects taking active control. Serious gastrointestinal adverse events were reported in approximately 7% of subjects receiving ferric citrate and 13% of subjects receiving active control. Serious cardiovascular and infectious adverse events occurred less frequently in the ferric citrate group (9.3 and 14.5% for ferric citrate compared with 13.4 and 19.5% for active control). The overall safety of ferric citrate was comparable to the safety of active control (sevelamer carbonate and/or calcium acetate). Mean pill count was 8.8 pills per day for ferric citrate, 7.7 pills per day for calcium acetate and 9.0 pills per day for sevelamer carbonate.

Mean iron parameters were higher for subjects receiving ferric citrate (ferritin = 899 ± 488 ng/ml; TSAT = 39% ± 17%) compared with subjects receiving active control (ferritin = 628 ± 367 ng/ml; TSAT = 30% ± 12% and p < 0.001 for both) at the end of the active control period. Subjects on ferric citrate received less iv. elemental iron with a median dose of 12.95 mg per week versus 26.88 mg per week for active control; p < 0.001. These data were further affirmed in a more detailed analysis [46]. Subjects receiving ferric citrate showed increased ferritin and TSAT as early as week 12 of the study. Ferritin increased by 114.1 ± 29.4 ng/ml (p < 0.001) and TSAT increased by 8.62 ± 1.6% (p < 0.001). TSAT levels plateaued at week 12, and the rate of rise of ferritin decreased after week 24, although it did not meet the statistical definition of a plateau. Notably, cumulative iv. iron dose was significantly lower for the ferric citrate arm (median [inter-quartile range (IQR) dose was 12.9 [1.0–28.9] mg per week) compared with the active control arm (median [IQR] dose was 26.8 [13.4–47.6] mg per week); p < 0.001. Erythropoiesis stimulating agent (ESA) dose was significantly lower in the ferric citrate group compared with active control (median [IQR] dose 5303 [2023–9695] units per week for ferric citrate versus 6954 [2664–12375] for active control); p = 0.04. Thus, ferric citrate use was associated with reduced iv. iron and ESA usage in patients with ESKD on dialysis. Importantly, subjects receiving ferric citrate achieved higher hemoglobin levels than subjects receiving active control (p = 0.04), demonstrating that the reductions in iv. iron and ESA usage did not come at the expense of the control of anemia.

Cost–effectiveness of ferric citrate

The observed reductions in iv. iron and ESA use in ferric citrate-treated subjects may have an economic impact as well. The potential cost–effectiveness of the use of ferric citrate was explored in an abstract during
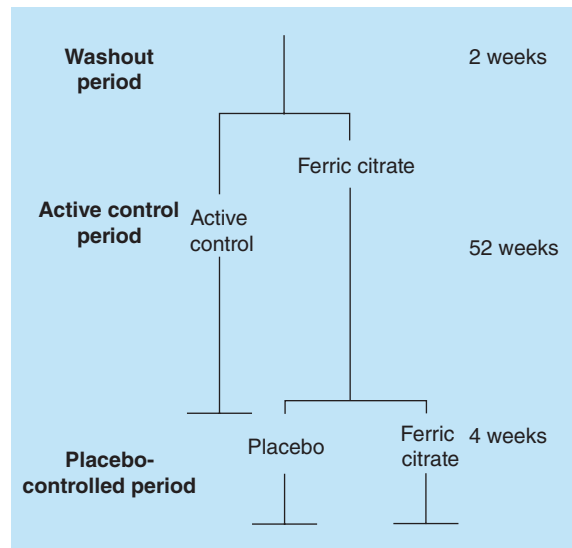

Figure 2. Phase III study.

the clinical meeting for the National Kidney Foundation [47]. In this analysis, the projected use of iv. iron and ESA was evaluated based on data from the Phase III study. To extrapolate patterns of ESA and iv. iron use seen in the study participants compared with the general USA dialysis population, percent differences between groups in this study were mapped to data from the USRDS for 2011. The mean dose of ESA in the ferric citrate group decreased relative to the dose used in active control. Logarithmic curves indicated a predictable pattern upon which projections were based. Similarly, the percent of subjects receiving iv. iron declined during the study more rapidly in the ferric citrate compared with the active control. This trend was projected to continue or the year after the study. Based on this, it was reported that projected use of iv. iron and ESA was significantly lower for individuals using ferric citrate as a phosphate binder compared with USRDS data from 2011. The projected savings were $2101 per patient per year.

In another posthoc analysis of the seminal Phase III study, Rodby *et al.* [48] extrapolated the hospitalization data from the trial to estimate further healthcare savings. Significantly fewer subjects were hospitalized at least once in the ferric citrate group compared with the active control group (34.6% as compared with 45.6%). This corresponded to absolute risk reduction of 11% (risk reduction of 24%; p = 0.02) and translated to 58 fewer hospitalizations for the ferric citrate arm for the duration of the study. Hospitalization costs were estimated from the 2013 US Renal Data System Annual Data Report and it was estimated that the use of ferric citrate would lead to $867,622 per year of savings in healthcare expenses. This would be in addition to the estimated $2101 per year per dialysis patient in cost
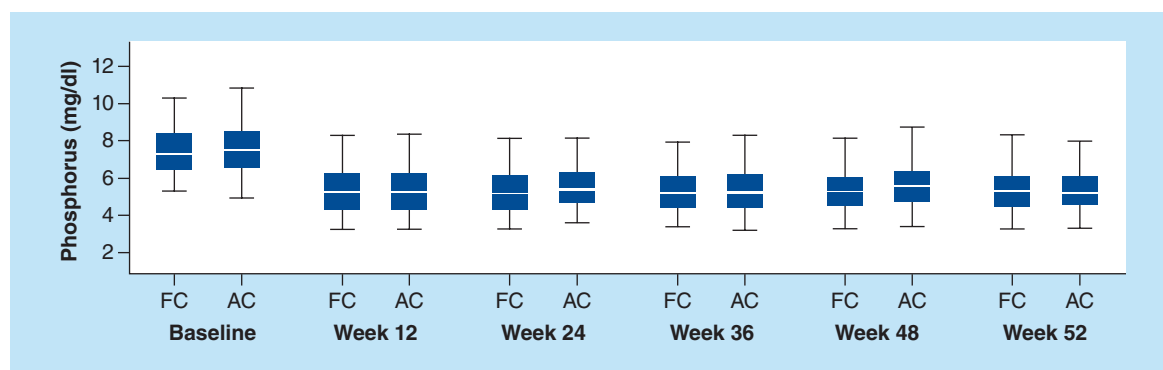
Figure 3. Results of a randomized double-blinded placebo-controlled study of ferric citrate compared with active control (calcium carbonate/sevelamer). Mean phosphorus levels are shown (mg/dl) by study time point. Box plots display 5th, 25th, 50th, 75th and 95th percentiles.
AC: Active control; FC: Ferric citrate.
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savings from the decreased iv. iron and ESA usage. These data are limited as they are based on projections and retrospective data. However, it is indeed possible that the reduced hospitalizations may in part be related to the decrease iv. iron and ESA usage reported with ferric citrate. This hypothesis was raised by several findings. First, fewer serious adverse events were noted in subjects treated with ferric citrate compared with active control. Hospitalizations are known to contribute the greatest proportion of serious adverse events in a clinical trial. Second, the iv. iron and ESA dose were reduced in subjects receiving ferric citrate compared with active control. Use of iv. iron, as opposed to oral iron, may lead has been reported to be associated with to high levels of free nonprotein-bound iron that could induce oxidative stress and increase the risk of infectious complications as it is a key cofactor for many organisms and increase the risk of cardiovascular disease and it may increase the risk of infectious complications as it is a key cofactor for many organisms [49]. Also by reducing the use of iv. iron and ESA the infection risk inherent in any iv. injection is reduced. Consistent with this, high dosages of ESA have been associated with higher morbidity and mortality [50]. As postulated by the authors, significantly fewer subjects were hospitalized at least once in the arm receiving ferric citrate compared with the arm receiving active control (34.6% as compared with 45.6%). This corresponded to risk reduction of 24% (p = 0.02) and translated to 58 fewer hospitalizations for the ferric citrate arm for the duration of the study. Hospitalization costs were estimated from the 2013 US Renal Data System Annual Data Report and it was estimated that use of ferric citrate led to $867,622 of savings in healthcare expenses in the participating study subjects. The possibility that use of ferric citrate may reduce healthcare costs and improve overall quality of life (via reduced

hospital admissions) for patients is exciting as that is a rare combination in healthcare today.

Extended safety study, results from a pragmatic 48-week clinical trial

The safety of long-term use of ferric citrate phosphate binder was further explored in a 48-week extension trial. Subjects from the pivotal 58-week trial who had previously been randomized to either ferric citrate or active control were enrolled [51]. For administrative reasons, 36 subjects from the Phase III study were immediately rolled into this trial, but all others had varying time gaps between completing the first trial and entering the second. All subjects received ferric citrate which was again supplied as 1 g tablets containing 210 mg of ferric iron. Dose titration of ferric citrate was aimed to achieve goal serum phosphorus of 3.5–5.5 mg/dl. One hundred and sixty-eight subjects were enrolled. Of those, two withdrew without receiving the study drug. Of the 166 who received the drug, 125 subjects completed the study on ferric citrate. Sixteen withdrew due to adverse events. Overall, safety data were comparable to that of the Phase III trial. Six subjects (3.6%) died during the duration of the study. Serious infectious adverse events occurred in 30 (18%), serious gastrointestinal events in 9 (5.4%) and serious cardiac events in 18 (10.8%) of the participating subjects. In this study, ferric citrate effectively controlled serum phosphorus levels and improved parathyroid hormone levels. Serum ferritin increased from 710 to 785 n/ml and TSAT increased from 32.4 to 37.7% at week 12 of the study (p < 0.05 for both), but both plateaued thereafter. This led to a statistically significant reduction in iv. iron and ESA use. Notably the percentage of subjects who required no iv. iron increased from 59% at baseline to 71% at week 12 and to 85% at the end of the study period. These data suggest that use of ferric citrate may

eliminate the need for iv. iron, with its attendant risks, in the majority of individuals receiving it.

Conclusion

Ferric compounds have been known to bind phosphorus effectively. In recent years ferric citrate has emerged as an effective phosphate binder in animal studies. Subsequent studies in humans with ESKD receiving dialysis have demonstrated that ferric citrate is an effective and safe phosphate binder that also delivers iron and reduces the need for iv. iron and erythropoiesis-stimulating agents while maintaining hemoglobin levels. These studies led to the approval of ferric citrate by the FDA for the con-trol of serum phosphorus levels in patients with ESKD on dialysis.

Executive summary

- Hyperphosphatemia is prevalent in patients with end-stage kidney disease (ESKD). It is associated with high morbidity and mortality. Lowering serum phosphorus in patients with ESKD is challenging and requires the use of oral phosphate binders often. Several binders are available to control phosphorus in this patient population, but due to adverse events, issues with tolerability and cost, and pill burden, there is a continued need for newer agents. While ferric-based compounds have been known to bind phosphorus for decades, iron-based binders have only recently emerged on the market. In this manuscript, we review ferric citrate; a binder that has been recently approved for use to lower serum phosphorus in USA, Taiwan and Japan.
- Ferric binds phosphorus in the gut after it dissociates from citrate. Considering that iron absorption is tightly regulated in the gut, the likelihood of iron overload with oral agents is believed to be low. The citrate moiety bypasses the many limitations of previously available iron-based products.
- Preclinical data have shown ferric citrate to be an effective phosphate binder in both uremic and normal rats. In addition, in these early studies hematocrit was found to increase in the azotemic rats indicating that ferric citrate may also deliver iron.
- Several clinical studies are subsequently reviewed including the first study from a group in Taiwan. The study showed the ferric citrate does bind phosphorus effectively in patients with ESKD. Subsequent study showed that ferric citrate lowers phosphorus in a dose-dependent fashion. Such studies were followed by a larger Phase III clinical trial that demonstrated the effectiveness of ferric citrate in controlling serum phosphorus levels compared with placebo. The study further demonstrated that ferric citrate was a safe alternative binder when compared with active control (sevelamer carbonate and/or calcium acetate). It is important to note that all these studies excluded individuals with high serum ferritin and transferrin saturation levels.
- Several posthoc analyses were conducted on the Phase III trial, and demonstrated that use of ferric citrate was associated with reduced use of intravenous iron and ESA in the participating subjects. Furthermore, hospitalization rates for the subjects receiving ferric citrate were lower than for the subjects receiving active control. In addition to improved quality of life, these findings were projected to reduce healthcare cost for patients with ESKD significantly. While these data are limited by the retrospective nature, they are exciting.
- Finally results of an extended safety trial are reviewed including the noted adverse events during the trial. Similar to other previously published work, the most common adverse events reported included stool discoloration and gastrointestinal discomfort. Serious adverse events were noted at rates comparable to the group receiving active control.
- To conclude, ferric citrate is a newly approved agent for the control of hyperphosphatemia in patients with ESKD in the USA. It has been shown to be effective at lowering serum phosphorus in ESKD in clinical trials. It also has been shown to associate with reduced use of intravenous iron and ESA in *post hoc* analyses and as such its use may reduce healthcare cost in our patients. These data render ferric citrate an appealing therapeutic option for control of hyperphosphatemia in ESKD.

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