Effects of Ferric Citrate in Patients with Nondialysis-Dependent CKD and Iron Deﬁciency Anemia

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ABSTRACT

Iron deﬁciency anemia is common and consequential in nondialysis-dependent CKD (NDD-CKD). Efficacy and tolerability of conventional oral iron supplements are mixed; intravenous iron administration associates with ﬁnite but important risks. We conducted a randomized double-blind clinical trial in adults with NDD-CKD and iron deﬁciency anemia to compare the safety and efﬁcacy of oral ferric citrate (n=117) and placebo (n=115). The primary end point was the proportion of patients who achieved a ≥1.0 g/dl increase in hemoglobin at any time during a 16-week randomized period. Patients who completed the 16-week period could also participate in an 8-week open-label extension period. Signiﬁcantly more patients randomized to ferric citrate achieved the primary end point (61 [52.1%] versus 22 [19.1%] with placebo; P<0.001). All secondary end points reached statistical signiﬁcance in the ferric citrate group, including the mean relative change in hemoglobin (0.84 g/dl; 95% conﬁdence interval, 0.58 to 1.10 g/dl; P<0.001) and the proportion of patients who achieved a sustained increase in hemoglobin (≥0.75 g/dl) over any 4-week period during the randomized trial; 57 [48.7%] versus 17 [14.8%] with placebo; P<0.001). Rates of serious adverse events were similar in the ferric citrate (12.0%) and placebo groups (11.2%). Gastrointestinal disorders were the most common adverse events, with diarrhea reported in 24 (20.5%) and 19 (16.4%) and constipation in 22 (18.8%) and 15 (12.9%) patients treated with ferric citrate and placebo, respectively. Overall, in patients with NDD-CKD, we found oral ferric citrate to be a safe and efﬁcacious treatment for iron deﬁciency anemia.

Anemia and iron deﬁciency are frequent, interrelated, and important problems associated with nondialysis-dependent CKD (NDD-CKD).1,2 Anemia is associated with mortality and cardiovascular events, decrements in physical health and quality of life, and the need for blood transfusion.3 The treatment of anemia in NDD-CKD has been challenged of late due to evolving concerns regarding the safety of erythropoiesis stimulating agents (ESAs),4 heightening interest in an “iron ﬁrst” approach, as recommended by clinical practice guidelines.5

The importance of iron deﬁciency in NDD-CKD is primarily related to its role as a cause of anemia, but severe iron deﬁciency also impairs several homeostatic processes up to and including production of ATP through oxidative phosphorylation. Patients experience fatigue, dyspnea, and cognitive impairment as part of wide-ranging signs and symptoms.6 Epidemiologic and bone marrow biopsy studies have estimated the prevalence of iron
deficiency in NDD-CKD at 48%–98%. Conventional (over-the-counter) iron preparations have demonstrated mixed efficacy in NDD-CKD along with frequent adverse gastrointestinal effects. Despite a relatively high prevalence of anemia, relatively few patients with stages 4–5 CKD are treated with intravenous (IV) iron, owing to associated risks including anaphylactoid reactions, concerns regarding the need for multiple venous cannulations in patients who may require creation of arteriovenous fistula for hemodialysis, and a variety of logistic hurdles.

Ferric citrate functions as an intestinal phosphate binder, and has been approved by the US Food and Drug Administration and other major regulatory agencies for the treatment of hyperphosphatemia in patients on dialysis. Prior studies in patients receiving dialysis and a phase 2 study in patients with NDD-CKD found ferric citrate to increase transferrin saturation, serum ferritin, and hemoglobin. The current phase 3 trial was designed to evaluate the safety and efficacy of ferric citrate for treatment of iron deficiency anemia in patients with NDD-CKD (stages 3–5).

RESULTS

Enrollment
We enrolled 234 patients (117 randomized to ferric citrate and 117 to placebo) starting in October of 2014, and completed the last patient’s final visit in January of 2016. The disposition of trial participants is shown in Figure 1 (Consolidated Standards of Reporting Trials diagram). One patient randomized to placebo did not receive study drug, and one received drug but did not have a postbaseline laboratory assessment.

Baseline Characteristics
Table 1 shows selected baseline demographic and clinical data for patients by randomized treatment group. Baseline characteristics of patients randomized to ferric citrate and placebo were generally well balanced.

Ferric Citrate Dosing
The average daily dose of ferric citrate and placebo was 5.0 and 5.1 tablets, respectively, over the 16-week randomized period and 7.9 and 9.4 tablets, respectively, during weeks 12 through 16. All patients started on three tablets of ferric citrate at the start of the open-label extension; average daily doses of ferric citrate during weeks 20 through 24 were 4.7 tablets in the group that continued on ferric citrate and 6.1 tablets in the group that switched from placebo to ferric citrate.

Efficacy Assessment during the Randomized Period
Figure 2A shows the mean hemoglobin concentration by study week. The mean relative change in hemoglobin (ferric citrate versus placebo) at week 16 was 0.84 g/dl (95% confidence interval [95% CI], 0.58 to 1.10 g/dl; P<0.001). Patients randomized to ferric citrate were significantly more likely to achieve the primary end point (≥1 g/dl increase in hemoglobin at any time during the randomized trial period) (61 of 117 [52.1%] versus 22 of 115 [19.1%]; P<0.001; Figure 2B). The time to first hemoglobin increase ≥1 g/dl is shown in Figure 2C. Patients randomized to ferric citrate were significantly more likely to experience a sustained increase in hemoglobin (57 of 117 [48.7%] versus 17 of 115 [14.8%]; P<0.001; Figure 2D). Consistent

Figure 1. Consolidated Standards of Reporting Trials diagram.

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effects of ferric citrate on the primary efficacy end point were observed across all predefined subgroups (age, sex, race, CKD stage, and baseline hemoglobin concentration; Figure 2E). Five of 117 (4.3%) patients randomized to ferric citrate and ten of 115 (8.7%) patients randomized to placebo experienced treatment failure due to sustained hemoglobin <9.0 g/dl.

**Iron Parameters**

Figure 3, A and B show the mean transferrin saturation and ferritin concentration over time. Mean relative changes (ferric citrate versus placebo) in transferrin saturation and ferritin at week 16 were 18.4% (95% CI, 14.6% to 22.2%; \( P = 0.001 \)) and 170.3 ng/ml (95% CI, 144.9 to 195.7 ng/ml; \( P = 0.001 \)), respectively.

**Parameters of Mineral Metabolism**

Figure 4 shows the mean serum phosphate concentrations over time during the randomized period. Ferric citrate significantly reduced serum phosphate (relative change from baseline to week 16: \( -0.21 \text{ mg/dl; 95\% CI} -0.39 \text{ to} -0.03 \text{ mg/dl; } P = 0.02 \)) and significantly increased serum bicarbonate (relative change from baseline to week 16: 1.2 mmol/l; 95% CI, 0.1 to 2.4 mmol/L; \( P = 0.03 \)). Detectable serum aluminum levels (lower limit of detection 11 \( \mu \text{g/L} \)) were sparse and were unrelated to study drug or the duration of exposure. Table 2 shows baseline and week 16 values for parathyroid hormone (PTH), and c-terminal and intact fibroblast growth factor 23 (FGF23).

**Adverse Events during the Randomized Period**

A full listing of treatment-emergent adverse events (AEs) with a frequency of at least 5% in either treatment group is shown in Table 3. A more comprehensive listing of treatment-emergent serious AEs and AEs is provided in Supplemental Tables 1 and 2. Gastrointestinal disorders were the most commonly observed AEs, with diarrhea reported in 24 (20.5%) and 19 (16.4%) and constipation in 22 (18.8%) and 15 (12.9%) patients treated with ferric citrate and placebo, respectively. Serious AEs occurred in 14 (12.0%) patients in the ferric citrate group and 13 (11.2%) patients in the placebo group. Treatment-emergent death occurred in two (1.7%) patients treated with ferric citrate and zero patients treated with placebo. None of the deaths or serious AEs were thought to be drug-related.

**Laboratory Tests of Special Interest during the Randomized Period**

Transferrin saturation \( \geq 70\% \) was observed in 21 (17.9%), serum ferritin \( \geq 700 \text{ ng/ml} \) in one (0.9%), and serum phosphate <2.0 mg/dl in two (1.7%) patients treated with ferric citrate, compared with zero patients treated with placebo.

**DISCUSSION**

We found that among patients with NDD-CKD and iron deficiency anemia, ferric citrate effectively repleted iron stores and partially corrected anemia. A treatment effect was seen as early as 1–2 weeks after start of treatment. The response was
Figure 2. Ferric citrate improves hemoglobin response. (A) Mean hemoglobin concentration by study week (P<0.001). (B) Proportion of patients with ≥1 g/dL increase in hemoglobin at any time during the randomized trial period (primary efficacy end point) (P<0.001). (C) Time to first hemoglobin increase ≥1 g/dL (P<0.001). (D) Proportion of patients with sustained increase in hemoglobin during the randomized period (P<0.001). (E) Forest plot of differences in proportion of patients achieving primary efficacy end point by prespecified subgroups (all P>0.10). P values refer to comparisons between treatment groups.
durable and achieved without the use of ESAs. The erythropoietic response with ferric citrate was consistent with that observed previously in patients on dialysis and in an earlier trial in NDD-CKD. Despite the frequency of iron deficiency in this population, most patients go untreated. Studies comparing oral to IV iron in this population have generally found greater efficacy for IV iron. However, to truly understand oral iron efficacy, it would require parallel group testing against placebo or, to a lesser extent, comparison to no iron treatment; few such studies exist in NDD-CKD. In contrast, among patients receiving hemodialysis, three randomized clinical trials found no demonstrable efficacy for oral iron. IV iron has better defined efficacy, but its use in NDD-CKD is limited by documented and perceived risks and the inconvenience of administering IV iron in the outpatient setting.

The cause of iron deficiency anemia in NDD-CKD is usually a combination of relative erythropoietin deficiency and iron deficiency. Whereas anemic patients receiving dialysis usually require ESAs (and supplemental iron) due to the severity of erythropoietin deficiency, patients with NDD-CKD differ in that they have greater relative erythropoietin production. The relative preservation of erythropoietin production at earlier stages of CKD suggests that anemia may be treated in this population by effectively correcting iron deficiency as an initial step. Indeed, clinical practice guidelines suggest a trial of iron supplementation for adult patients with CKD (including ESRD) and anemia not on iron or ESA therapy.

This trial included patients intolerant of, or with inadequate response to, oral iron supplements. However, the efficacy of ferric citrate as a treatment for iron deficiency anemia in CKD does not appear to be limited to patients who have failed prior treatment with oral iron supplements. Results here were consistent with a phase 2 trial of ferric citrate in NDD-CKD in which ferric citrate was prescribed as a phosphate binder and in which patients achieved a robust hematologic response; patients enrolled in the earlier trial had no eligibility criterion regarding prior treatment with oral iron and had less prominent iron deficiency (i.e., higher baseline transferrin saturation and ferritin). The current trial focused on ferric citrate as a means of correcting iron deficiency, with mineral metabolism a secondary focus. We observed significant relative reductions (ferric citrate versus placebo) in serum phosphate, PTH, and c-terminal and intact FGF23. Average serum phosphate concentrations were maintained within a range recommended by clinical practice guidelines and episodes of hypophosphatemia were rare. The reduction in serum phosphate, although modest, was comparable to that seen in another trial of phosphate binders in a similar population. Reductions in c-terminal and intact FGF23 induced by ferric citrate are of uncertain clinical significance. However, elevated serum concentrations of FGF23 have been associated with incidence and progression of CKD, left ventricular hypertrophy, heart failure, cardiovascular events, and all-cause mortality in patients with CKD, and animal studies.

Table 2. Effects of ferric citrate on PTH and FGF23

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ferric Citrate</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PTH (IQR), pg/ml</td>
<td>103 (67, 171)</td>
<td>84 (58, 173)</td>
<td>92 (62, 168)</td>
</tr>
<tr>
<td>Median c-FGF23 (IQR), RU/ml</td>
<td>364.0 (198.2, 601.2)</td>
<td>232.5 (136.5, 397.4)</td>
<td>305.8 (176.6, 484.4)</td>
</tr>
<tr>
<td>Median i-FGF23 (IQR), RU/ml</td>
<td>134.0 (89.6, 233.1)</td>
<td>105.0 (66.7, 180.1)</td>
<td>134.3 (83.1, 201.9)</td>
</tr>
</tbody>
</table>

c-FGF23, c-terminal fibroblast growth factor 23; i-FGF23, intact fibroblast growth factor 23.
models support a causal role of FGF23 in the development of left ventricular hypertrophy.\textsuperscript{28} Adverse effects were generally modest. Gastrointestinal effects were most common, as expected, with nominally higher rates of diarrhea and constipation in ferric citrate–treated patients. Nearly one in five patients treated with ferric citrate experienced a transient increase in the transferrin saturation to >70%. We believe that the transient increases in transferrin saturation reflect the fact that the blood draws were not timed relative to drug intake. As described by Kobune \textit{et al.},\textsuperscript{29} transferrin saturation can rise to >60% within 2–3 hours after intake of an oral iron dose. In future studies, it will be important to specify that laboratory draws for transferrin saturation be obtained before daily dosing.

Strengths of this study include the placebo control, allowing for valid assessments of safety and efficacy; a patient sample diverse in age, sex, race/ethnicity, and CKD stage; modest rates of study drug discontinuation; and an objective, clinically meaningful primary end point. The major limitation is a focus on laboratory rather than “hard” clinical outcomes. Nevertheless, safety and efficacy need to be established before conducting larger trials to assess higher-level outcomes. Other limitations include the 16-week randomized period; sufficient to capture drug-related adverse effects and to assess efficacy but arguably insufficient to fully assess long-term changes in iron stores. We did not measure C-reactive protein or other markers of inflammation, which can influence hematopoiesis. Among patients randomized to ferric citrate, down titration of ferric citrate at the start of the extension period yielded a rapid reduction in transferrin saturation and ferritin concentrations. More generally, oral rather than IV iron allows the body’s normal iron regulatory processes, mediated through hepcidin, to prevent excess iron accumulation.\textsuperscript{30}

In conclusion, we found oral ferric citrate to be safe and efficacious in the treatment of iron deficiency in NDD-CKD. With the high prevalence of iron deficiency anemia in patients with CKD and the risks and inconvenience of alternative therapies, oral ferric citrate may broaden therapeutic options for iron deficiency anemia in this population.

**CONCISE METHODS**

**Study Setting**

The trial was sponsored by Keryx Biopharmaceuticals, Inc. S.F., G.A.B., and G.M.C. supervised the trial design. An independent medical monitor blinded to treatment assignment periodically reviewed safety data. The sponsor directed trial operations, collected trial data, and analyzed them according to a predefined statistical analysis plan. The protocol was approved by institutional review boards at participating study sites and registered at Clinicaltrials.gov (NCT02268994).

**Study Population**

Adult patients with NDD-CKD (eGFR < 60 ml/min per 1.73 m\textsuperscript{2} by the four-variable Modification of Diet in Renal Disease study equation) and iron deficiency anemia (hemoglobin between 9.0 and 11.5 g/dl inclusive, with ferritin $\leq$ 200 ng/ml and transferrin saturation $\leq$ 25%) intolerant of, or with inadequate response to, oral iron supplements, and with serum phosphate $\geq$ 3.5 mg/dl were eligible for randomization. The proportion of patients with eGFR < 15 ml/min per 1.73 m\textsuperscript{2} (CKD stage 5) was restricted to no more than 20% of randomized patients. Eligible patients could not have received IV iron, ESAs, or blood transfusion within 4 weeks of screening. Oral iron (other than study drug), IV iron, ESAs, blood transfusion, and other phosphate binders were not permitted after screening. A complete list of inclusion and exclusion criteria is available in the Supplemental Appendix.

**Study Design**

This was a phase 3, randomized, double-blind, placebo-controlled multicenter clinical trial, comprised of a 16-week randomized period, followed by an 8-week open-label safety extension period, during which all patients received ferric citrate.

**Intervention and Dosing**

Randomized patients (1:1) were treated with a starting dose of ferric citrate 1 g (each tablet = 210 mg elemental iron) or matching placebo three times daily with, or within 1 hour of, meals or snacks. The dose of ferric citrate or placebo was titrated at weeks 4, 8, and 12 by an additional three tablets daily, aiming to achieve an increase in hemoglobin by $>1.0$ g/dl above baseline. We increased the dose of study drug only if the patient’s serum phosphate was $\geq$ 3.0 mg/dl, reduced the dose of study drug with serum phosphate $<2.5$ mg/dl, and temporarily discontinued study drug with serum phosphate $<2.0$ mg/dl. Patients who completed randomized treatment for 16 weeks could also participate in an 8-week open-label extension, at which time all patients received ferric citrate.

**Figure 4.** Ferric citrate reduced serum phosphate. Mean serum phosphate by study week ($P<0.001$). $P$ value refers to comparisons between treatment groups.
Table 3. Treatment-emergent AEs (reported in 5% or more in either group)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ferric Citrate (n=117), n (%)</th>
<th>Placebo (n=116), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-emergent AE</td>
<td>93 (79.5)</td>
<td>75 (64.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (20.5)</td>
<td>19 (16.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>22 (18.8)</td>
<td>15 (12.9)</td>
</tr>
<tr>
<td>Feces discolored</td>
<td>17 (14.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (11.1)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7 (6.0)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0)</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>8 (6.8)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (4.3)</td>
<td>6 (5.2)</td>
</tr>
</tbody>
</table>

Events occurring during the randomized period (randomization to week 16).

Primary Efficacy End Point
The primary efficacy end point was the proportion of patients achieving an increase in hemoglobin concentration of 1.0 g/dl or more from baseline at any point through the end of the randomized period (week 16). Patients who ceased participation in the trial during the randomized period without having achieved the requisite increase in hemoglobin were considered nonresponders.

Secondary Efficacy End Points
Secondary efficacy end points included mean changes (baseline to 16 weeks) in hemoglobin, transferrin saturation, and ferritin, and the proportion of patients who experienced a sustained treatment effect, defined as a mean change in hemoglobin from baseline ≥0.75 g/dl over any 4-week time period during the 16-week randomized period, provided that an increase of 1.0 g/dl or more had occurred during that 4-week period. The final secondary efficacy end point was the mean change in serum phosphate (baseline to 16 weeks).

Exploratory End Points
We considered changes in serum bicarbonate, intact PTH, and c-terminal and intact FGF23 as exploratory end points.

Laboratory Determinations
All clinical chemistry analyses were performed by a central laboratory (PDP Central Laboratory Services, Highland Heights, KY) using a standard chemistry autoanalyzer. FGF23 was measured in plasma using the second-generation carboxyterminal ELISA (Immunotopics, San Clemente, CA) and in serum using an ELISA against the intact protein (Kainos, Japan).

Sample Size Determination
We anticipated that approximately 14% of patients randomized to placebo and approximately 32% of patients randomized to ferric citrate would achieve the primary efficacy end point. With 230 patients randomized 1:1 to ferric citrate and placebo, we expected the trial to have >90% power to detect the hypothesized difference between the two groups (two-sided α=0.05).

Statistical Analyses
We analyzed efficacy data within a modified intention-to-treat population, including all patients with any study drug exposure and at least one postbaseline laboratory assessment. We used the two-sided chi-squared test to compare the proportion of patients achieving the primary efficacy end point by randomized group, and calculated two-sided 95% CIs for the treatment difference using the normal approximation. We used the same approach for evaluating the difference in proportion of patients who achieved a sustained treatment effect. For the continuous secondary and exploratory efficacy end points, we used a mixed model repeated measures approach with randomized treatment, week, and treatment × week interaction as fixed effects, and patient as a random effect. We conducted sensitivity analyses with analysis of covariance using a last observation carried forward approach. We used the nonparametric Wilcoxon rank sum test for highly skewed variables (i.e., PTH and FGF23). To control the overall type 1 error rate at 5% for the primary and secondary efficacy end points, we employed a closed testing procedure, in which a comparison was eligible for superiority testing only if all previous comparisons (the primary end point comparison and previous secondary end point comparisons, if any) were also significant in favor of ferric citrate. We used the Kaplan–Meier product limit estimate to determine time to first hemoglobin increase from baseline of 1.0 g/dl or more, and compared cumulative incidence curves using the log-rank test. We prespecified the following subgroups to evaluate for effect modification on the primary efficacy end point: age (<65 and ≥65 years of age), sex (women and men), race (black and nonblack), baseline hemoglobin concentration (<10.5 and ≥10.5 g/dl), and CKD stage (stage 3 or 4 and stage 5). We considered two-tailed P values <0.05 statistically significant. We conducted all analysis using SAS version 9.2 or higher (Cary, NC).

DISCLOSURES
J.N., L.L., and K.U. are employees of Keryx Biopharmaceuticals, Inc. S.F., G.A.B., P.E.P., and G.M.C. have received research support from Keryx. No compensation was provided for manuscript preparation.

REFERENCES


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