Ferumoxytol for Treating Iron Deficiency Anemia in CKD

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ABSTRACT

Iron deficiency is an important cause of anemia in patients with chronic kidney disease (CKD), but intravenous iron is infrequently used among patients who are not on dialysis. Ferumoxytol is a novel intravenous iron product that can be administered as a rapid injection. This Phase III trial randomly assigned 304 patients with CKD in a 3:1 ratio to two 510-mg doses of intravenous ferumoxytol within 5 d or 200 mg of elemental oral iron daily for 21 d. The increase in hemoglobin at day 35, the primary efficacy end point, was 0.82 ± 1.24 g/dl with ferumoxytol and 0.16 ± 1.02 g/dl with oral iron (P = 0.0001). Among patients who were not receiving erythropoiesis-stimulating agents, hemoglobin increased 0.62 ± 1.02 g/dl with ferumoxytol and 0.13 ± 0.93 g/dl with oral iron. Among patients who were receiving erythropoiesis-stimulating agents, hemoglobin increased 1.16 ± 1.49 g/dl with ferumoxytol and 0.19 ± 1.14 g/dl with oral iron. Treatment-related adverse events occurred in 10.6% of patients who were treated with ferumoxytol and 24.0% of those who were treated with oral iron; none was serious. In summary, a regimen of two doses of 510 mg of intravenous ferumoxytol administered rapidly within 5 d was well tolerated and had the intended therapeutic effect. This regimen may offer a new, efficient option to treat iron deficiency anemia in patients with CKD.


Anemia develops early during chronic kidney disease (CKD), affects virtually all individuals with stage 5 CKD (GFR <15 ml/min per 1.73 m²),1–3 and is associated with increased cardiovascular morbidity and decreased quality of life.4,5 Iron deficiency is a common cause of anemia in CKD; the estimated prevalence ranges from 25 to 70%.2,6–9 The causes include decreased intake or absorption of iron; iron sequestration as a result of inflammation; blood loss; and increased iron use for red blood cell production in response to erythropoiesis stimulating agents (ESA).10–12 Inadequate production of erythropoietin by the kidney and/or insufficient response to erythropoietin as a result of inflammation contributes to anemia during later stages of CKD.13,14 Appropriate management of anemia in CKD often requires both iron and ESA.15,16 Oral iron therapy has limitations as a result of impaired absorption and gastrointestinal adverse effects that may affect patient compliance.17–19 Intravenous administration overcomes these limitations. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend intravenous iron for patients who have CKD stage 5D and are on hemodialysis and either oral or intravenous iron for patients who are on peritoneal dialysis or...
have CKD stages 1 to 5 and are not on dialysis.\textsuperscript{20} The therapeutic course of intravenous iron typically used in clinical practice is 1 g.\textsuperscript{20–22}

The available intravenous iron formulations in the United States include iron dextran, iron sucrose, and sodium ferric gluconate.\textsuperscript{21–24} With iron dextran, up to 1 g can be administered at one time via a slow infusion, but life-threatening anaphylaxis can rarely occur.\textsuperscript{25–27} Iron sucrose and sodium ferric gluconate seem to have a lower incidence of anaphylaxis\textsuperscript{28–30} but can be safely given in small dosages (\(\leq 200\) mg) (necessitating five to eight visits for the administration of 1 g) or as an infusion of larger dosages.\textsuperscript{21,22,31–33} This is impractical in the outpatient setting and may partly account for suboptimal iron replacement in patients who have stages 1 through 5 CKD or are on home dialysis.\textsuperscript{34–36}

Ferumoxytol is a superparamagnetic iron oxide nanoparticle with a polyglucose sorbitol carboxymethylether coating. Ferumoxytol is isotonic, and preliminary data suggest that it contains less free iron than other intravenous iron preparations.\textsuperscript{37} These physicochemical properties may explain why ferumoxytol can be given rapidly at relatively high dosages.\textsuperscript{38,39} In addition, ferumoxytol appears quickly in circulating red blood cells, suggesting ready bioavailability for erythropoiesis.\textsuperscript{40} This report describes a Phase III clinical trial of ferumoxytol for intravenous iron replacement in patients with CKD stages 1 to 5.

**RESULTS**

Between May 2004 and August 2006, 304 patients were randomly assigned, 228 to ferumoxytol and 76 to oral iron. The rate of study completion was 91\% in the ferumoxytol group and 83\% in the oral iron group. Demographic and baseline clinical characteristics of the study population were similar in the two groups (Table 1), as were hemoglobin and iron indices. The majority of patients had transferrin saturation (TSAT) <20\% (90.4\% ferumoxytol, 94.7\% oral iron), and the 75th percentile was 14\% in the ferumoxytol group and 13\% in the oral iron group. There were 23 protocol violations related to starting ESA or changing the dosage, 6.1\% ferumoxytol and 11.8\% oral iron.

**Efficacy**

Ferumoxytol significantly increased hemoglobin at days 21 and 35, compared with oral iron (Table 2). At day 35, the mean increase in hemoglobin was 0.82 \(\pm\) 1.24 g/dl (8.2 \(\pm\) 12.4 g/L) with ferumoxytol and 0.16 \(\pm\) 1.02 g/dl (1.6 \(\pm\) 10.2 g/L) with oral iron (\(P < 0.0001\) for treatment difference), and 39.0\% of the ferumoxytol group achieved a \(\geq 1\) g/dl (\(\geq 10\) g/L) increase in hemoglobin (versus 18.4\% with oral iron). The increases in ferritin, TSAT, and iron were also significantly greater with ferumoxytol compared with oral iron.

Among both patients on and not on ESA, ferumoxytol resulted in a significantly greater increase in hemoglobin compared with oral iron (Figure 1). In the subgroup not on ESA, mean hemoglobin increase at day 35 was 0.62 \(\pm\) 1.02 g/dl (6.2 \(\pm\) 10.2 g/L) with ferumoxytol (\(n = 145\)) versus 0.13 \(\pm\) 0.93 g/dl (1.3 \(\pm\) 9.3 g/L) with oral iron (\(n = 43\); \(P = 0.0045\) for treatment difference). Among ESA-treated patients, hemoglobin increased by 1.16 \(\pm\) 1.49 g/dl (11.6 \(\pm\) 14.9 g/L) with ferumoxytol (\(n = 83\)) versus 0.19 \(\pm\) 1.14 g/dl (1.9 \(\pm\) 11.4 g/L) with oral iron (\(n = 33\); \(P = 0.0010\)). In the ferumoxytol group, 29.7 and 55.4\% of patients who were not on ESA and were on ESA, respectively, achieved a \(\geq 1\) g/dl (\(\geq 10\) g/L) increase in hemoglobin at day 35 compared with 14.0 and 24.2\% of oral iron–treated patients.

In the nonrandomized readmission phase of the study, 22 patients who had received ferumoxytol during the randomized phase received a second course of ferumoxytol, and 40 from the oral iron group received a first course of ferumoxytol. The readmission baseline mean hemoglobin was 9.91 and 9.95 g/dl (99.1 and 99.5 g/L) in the original ferumoxytol and oral iron treatment groups, respectively. At day 35, the mean increase in hemoglobin among all patients in the readmission phase was 0.64 \(\pm\) 0.83 g/dl (6.4 \(\pm\) 8.3 g/L). The increase was 0.55 \(\pm\) 0.89 g/dl (5.5 \(\pm\) 8.9 g/L) among patients previously treated with ferumoxytol and 0.69 \(\pm\) 0.80 g/dl (6.9 \(\pm\) 8.0 g/L) among patients previously treated with oral iron.

**Safety**

A total of 292 patients who received study drug (217 ferumoxytol and 75 oral iron) were included in the safety analysis. Ferumoxytol was generally well tolerated, with 35.5\% of patients reporting adverse events, compared with 52.0\% of oral iron.

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**Table 1.** Demographic and baseline clinical characteristics of the study population (intention-to-treat)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ferumoxytol</th>
<th>Oral Iron</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>228</td>
<td>76</td>
</tr>
<tr>
<td>Age (yr; mean (\pm) SD)</td>
<td>65.1 (\pm) 14.3</td>
<td>63.7 (\pm) 11.1</td>
</tr>
<tr>
<td>Male (%)</td>
<td>41.2</td>
<td>31.6</td>
</tr>
<tr>
<td>Race (%)</td>
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<td></td>
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<tr>
<td>white</td>
<td>57.0</td>
<td>60.5</td>
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<tr>
<td>black/African American</td>
<td>34.2</td>
<td>36.8</td>
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<tr>
<td>Asian</td>
<td>6.1</td>
<td>1.3</td>
</tr>
<tr>
<td>other</td>
<td>2.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Stage of CKD (%)</td>
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<td></td>
</tr>
<tr>
<td>1 (GFR (\leq) 90)</td>
<td>0.4</td>
<td>1.3</td>
</tr>
<tr>
<td>2 (GFR 60 to 89)</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>3 (GFR 30 to 59)</td>
<td>36.0</td>
<td>39.5</td>
</tr>
<tr>
<td>4 (GFR 15 to 29)</td>
<td>46.9</td>
<td>47.4</td>
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<tr>
<td>5 (GFR &lt;15)</td>
<td>13.6</td>
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</tr>
<tr>
<td>missing</td>
<td>1.8</td>
<td>0.0</td>
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<tr>
<td>Erythropoiesis stimulating agent use (%)</td>
<td>36.4</td>
<td>43.4</td>
</tr>
</tbody>
</table>

\textsuperscript{aTo convert to SI units, multiply hemoglobin by 10 to obtain g/dl and ferritin by 1 to obtain \(\mu\)g/L.}

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**To convert to SI units, multiply hemoglobin by 10 to obtain g/dl and ferritin by 1 to obtain \(\mu\)g/L.**
patients (Table 3). Most adverse events were mild to moderate in intensity. Adverse events considered treatment related by the investigator were reported in 10.6% of ferumoxytol-treated patients versus 24.0% of oral iron–treated patients. Serious adverse events occurred infrequently (4.6% ferumoxytol and 9.3% oral iron), and none of the serious adverse events was considered treatment related.

Treatment related adverse events are listed in Table 4. Of the three most common treatment-related adverse events in the ferumoxytol group, only dizziness occurred more frequently with ferumoxytol. All other adverse events each occurred in only one or two patients. Hypersensitivity and hypotension were not observed. The greatest mean (median) change in systolic BP (SBP) was 4.4 (2.0) mmHg at 10 min, and only 20% had a decrease in SBP of 10 mmHg at any time after dosing.

There were no clinically meaningful changes in laboratory tests. The mean changes from baseline to day 35 in parameters of interest for safety were minimal, including serum creatinine (change 0.01 mg/dl from baseline), glucose (−3.16 mg/dl), phosphorus (−0.03 mg/dl), aspartate and alanine aminotransferase (<3 μL), γ-glutaryl transferase (<8 μL), and platelet count (−28,000/mm^3).

The incidence of adverse events in the nonrandomized re-admission phase was similar in the 22 patients who received a second course of ferumoxytol (40.9%) and the 40 patients who received ferumoxytol after previous oral iron therapy (37.5%) and was comparable to the rate in ferumoxytol-treated patients in the randomized phase. Only two (3.2%) patients, previously in the oral iron group, had treatment related adverse

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**Table 2. Baseline and follow-up hemoglobin and indices of iron stores, intent-to-treat population**

| Parameter | Ferumoxytol (n = 228) | Oral Iron (n = 76) | P
|-----------|-----------------------|-------------------|---
| Hemoglobin (g/dl; mean ± SD) | | | |
| baseline  | 9.96 ± 0.69 | 9.96 ± 0.78 | |
| day 21    | 10.71 ± 1.03 | 10.21 ± 0.80 | |
| day 35    | 10.88 ± 1.27 | 10.15 ± 1.07 | |
| day 35 change from baseline | 0.82 ± 1.24 | 0.16 ± 1.02 | <0.0001
| Hemoglobin ≥1-g/dl increase from baseline (%) | | | |
| day 21    | 32.5 | 15.8 | |
| day 35    | 39.0 | 18.4 | |
| Ferritin (ng/ml; mean ± SD) | | | |
| baseline  | 146.1 ± 173.6 | 143.5 ± 144.9 | |
| day 21    | 703.1 ± 355.6 | 157.6 ± 154.5 | |
| day 35    | 555.7 ± 320.0 | 160.8 ± 161.0 | |
| day 35 change from baseline | 381.7 ± 278.6 | 6.9 ± 60.1 | <0.0001
| Serum iron (μg/dl; mean ± SD) | | | |
| baseline  | 45.0 ± 18.2 | 43.7 ± 18.6 | |
| day 21    | 76.5 ± 35.8 | 52.7 ± 25.2 | |
| day 35    | 68.0 ± 26.2 | 50.1 ± 19.1 | |
| day 35 change from baseline | 22.7 ± 24.3 | 4.4 ± 19.2 | <0.0001
| TSAT (%) | | | |
| baseline  | 11.3 ± 6.1 | 10.1 ± 5.5 | |
| day 21    | 24.1 ± 13.1 | 12.8 ± 8.1 | |
| day 35    | 21.0 ± 10.1 | 11.8 ± 6.7 | |
| day 35 change from baseline | 9.8 ± 9.2 | 1.3 ± 6.4 | <0.0001

*To convert to SI units, multiply hemoglobin by 10 to obtain g/dl, ferritin by 1 to obtain μg/L, and iron by 0.179 to obtain μmol/L.

*Two-sample t test for evaluating a difference between the treatment groups in change from baseline.

*Baseline value is the mean from the day −10 and day −5 values.

*Change from baseline does not equal day 35 minus baseline because it includes imputed value of zero for change from baseline for patients who did not have a value obtained at day 35.

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**Figure 1.** Hemoglobin response by treatment group and ESA use, from baseline to day 21 and day 35. Compared with patients who were randomly assigned to oral iron (OI), ferumoxytol (FER) resulted in a greater increase in hemoglobin during follow-up in patients who were on ESA as well as among patients who were not on ESA.
events (constipation and increased appetite). There were no
treatment related serious adverse events.

DISCUSSION

Although one third of patients initiating dialysis in the
United States have received ESA, many are anemic at initi-
ation (mean hemoglobin 10.1 g/dl [101 g/L]).41 This sug-
gests that current anemia management is suboptimal in pa-
tients with CKD stages 1 to 5. Iron deficiency is
underrecognized,42 and undertreatment may be related to
physicians’ perception that oral iron is neither effective nor
well tolerated and that available intravenous iron prepara-
tions are too cumbersome to be widely used in this popula-
tion. This study demonstrates that a regimen of two 510-mg
doses of ferumoxytol administered as an undiluted injec-
tion in the outpatient office was convenient and well toler-
ated and had the intended therapeutic effect.

Intravenous ferumoxytol, given as two doses of 510 mg
within 1 wk, was more effective than oral iron in raising hemo-
globin in patients with CKD stages 1 to 5. At day 35, the mean
increase in hemoglobin from baseline was four times higher
among patients who were randomly assigned to ferumoxytol
compared with oral iron, and twice as many ferumoxytol-
treated patients achieved a ≥1-g/dl increase in hemoglobin
(39.0 versus 18.4% oral iron). It was not surprising that more
patients did not have a ≥1-g/dl increase in hemoglobin given
that fewer than half of the patients were on ESA therapy (36%
ferumoxytol, 43% oral iron). Among those on ESA, 55% of
ferumoxytol-treated patients had a ≥1-g/dl increase in hemo-
globin at day 35 versus 24% with oral iron. Among patients
initially treated with oral iron in the randomized phase, subse-
quent treatment with ferumoxytol during the readmission
phase led to a mean increase in hemoglobin of 0.69 ± 0.80 g/dl
(6.9 ± 8.0 g/L), confirming persistent iron deficiency despite
oral iron therapy.

Previous studies of available intravenous iron preparations
have not shown substantially greater efficacy when compared
with ferrous sulfate 325 mg three times per day.32,33,43 Among
89 patients who were not receiving ESA, sodium ferric glu-
conate (250 mg/wk for 4 wk) was not much more effective than
oral iron (hemoglobin increase 0.4 g/dl [4 g/L] with intrave-
nous versus 0.2 g/dl [2 g/L] with oral iron).43 In a study of
intravenous iron plus ESA in 96 patients with CKD, five doses
of 200 mg of iron sucrose led to an increase in hemoglobin of
1.0 versus 0.7 g/dl with oral iron plus ESA (NS).32 In another
study with 40% of patients on ESA, patients who were treated
with 1 g of intravenous iron sucrose had a 0.7-g/dl (7-g/L)
mean increase in hemoglobin, and 44% had a ≥1-g/dl increase
in hemoglobin, compared with 0.4 g/dl (4 g/L) and 28%, re-
spectively, with oral iron (P = 0.03 for both end points).33
More rapid correction of iron deficiency with ferumoxytol
(within 1 wk) may explain the highly significant difference
between oral and intravenous iron in the ferumoxytol trials not
previously seen with available intravenous iron therapies, but
other factors such as improved bioavailability and study design
may also contribute.

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<tr>
<th>Table 3. Summary of adverse events in the safety populationa</th>
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<tr>
<td>Parameter</td>
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<tr>
<td>Adverse events</td>
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<tr>
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<td>Related serious adverse events</td>
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<td>Events (n) Patients (n [%])</td>
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<td>Related adverse events</td>
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<tr>
<th>Table 4. Treatment-related adverse events</th>
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<tr>
<td>Parameter</td>
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<tr>
<td>Any related adverse event</td>
</tr>
<tr>
<td>Nausea</td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Chills</td>
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<tr>
<td>Rash</td>
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<td>Dysgeusia</td>
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<td>Injection-site swelling</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Abdominal pain upper</td>
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<tr>
<td>Vomiting</td>
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<td>Patients (n [%])</td>
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a Patients who received at least one dose of study drug.
Appropriate therapy of anemia in patients with CKD requires identification and repletion of iron deficiency before initiating ESA. In this study, patients who were not on ESA and were treated with ferumoxytol had a greater increase in hemoglobin at day 35 (0.62 g/dl [6.2 g/L]) than patients who were on oral iron and ESA (0.19 g/dl [1.9 g/L]); by comparison, the increase was 1.16 g/dl (11.6 g/L) among patients who were on ESA and were treated with ferumoxytol. The possibility that some patients could be treated with intravenous iron alone or that appropriate intravenous iron replacement may delay initiation or reduce the dosage of ESA could improve care and reduce costs. Safety concerns with ESA raised by recent clinical trials, which led to a Food and Drug Administration warning in their package insert, further make the case for appropriate intravenous iron therapy.

Ferumoxytol, administered as an intravenous injection in two doses of 510 mg within 5 ± 3 d, was well tolerated, with no reported adverse events of hypotension or hypersensitivity. In fact, the proportion of patients with related adverse events was lower in the ferumoxytol group (10.6%) compared with oral iron (24.0%). There was no increase in the incidence of adverse events among patients who received a second course of intravenous ferumoxytol. In contrast, other intravenous iron preparations administered rapidly or at higher dosages have been associated with a higher rate of adverse events. In non-dialysis-dependent patients with CKD, infusions of 250 mg of sodium ferric gluconate over 1 h resulted in adverse events in 13 (29.5%) of 44 patients, including three serious adverse events (hypotension [4.6%] and anaphylaxis [2.2%]). Iron sucrose as a 500-mg infusion over 3.5 to 4 h caused hypotension in two (6.7%) of 30 patients, and in another study, 200 mg over 2 min was associated with anaphylactoid reactions in seven (1.1%) of 657 patients.

The convenience of providing 1 g of iron as ferumoxytol with two intravenous injections in the outpatient office, instead of with five to eight smaller doses or larger dosages via infusion, could improve the management of anemia in patients with CKD stages 1 to 5 by facilitating compliance. Because ferumoxytol could be administered during routine phlebotomy, it would require fewer venipunctures and intravenous catheter placements than currently available intravenous iron products, potentially preserving veins for future hemodialysis access. The ability to administer ferumoxytol safely at high dosages without dilution or infusion may also save nursing time and the cost of disposables incurred with multiple infusions.

The results of this study emphasize key anemia management principles in patients with CKD stages 1 to 5. First, intravenous iron therapy is more effective than oral iron for increasing hemoglobin levels. Second, for most patients, correction of iron deficiency with intravenous iron is an appropriate first step in anemia management, before initiating ESA therapy. Third, patients on ESA need monitoring for and correction of iron deficiency. Finally, the ability to administer ferumoxytol in dosages up to 510 mg as a rapid intravenous injection could facilitate iron deficiency anemia management in the physician’s office.

**CONCISE METHODS**

**Ferumoxytol**

Ferumoxytol is produced by AMAG Pharmaceuticals, Inc. (Cambridge, MA). It has a colloidal particle size of 30 nm and a molecular weight of 750 kD. Ferumoxytol injection is a sterile liquid with a neutral pH, formulated with mannitol for isotonicity; each milliliter contains 30 mg of iron and 44 mg of mannitol.

**Study Design and Conduct**

This was an open-label, randomized, controlled, multicenter Phase III trial (ClinicalTrials.gov NCT00255424). The protocol received institutional review board approval. All patients gave written informed consent.

Patients were prescreened for anemia up to 8 wk before study drug dosing. Screening visits were undertaken on day −10 (±4 d) and day −5 (±3 d) before study drug dosing. Eligible patients were randomly assigned in a 3:1 ratio to intravenous ferumoxytol or oral iron, using a telephone-based system (ClinPhone, East Windsor, NJ). Ferumoxytol treatment consisted of two 510-mg doses within 5 ± 3 d, administered intravenously at a rate of 1 ml/s (30 mg of iron) in the outpatient office. Oral iron treatment consisted of 200 mg of elemental iron daily for 21 d, as Ferro-Sequels (50 mg of ferrous fumarate plus docusate sodium; Inverness Medical Innovations, Inc., Waltham, MA), two tablets twice daily on an empty stomach. Compliance was monitored at weekly visits and with a formal pill count on day 21. Patients receiving ESA were to be on a stable dosage (and on ≤35,000 U/wk erythropoietin or ≤120 μg of darbepoetin every 2 wk), and patients who were not on ESA were precluded from starting ESA during the study.

Follow-up visits and tests were scheduled for day 21 (±5 d) and day 35 (±5 d) after the initial dose of study drug. Laboratory tests were performed at MedTox Laboratories, Inc. (St. Paul, MN).

**Eligibility Criteria**

Anemic adult patients (≥18 yr) who had CKD stages 1 to 5 and hemoglobin ≤11.0 g/dl (110 g/L), serum ferritin ≤600 ng/ml (600 μg/L), and TSAT ≤30% and were able to provide informed consent were eligible. Exclusion criteria were pregnancy or breastfeeding, causes of anemia other than iron deficiency, malignancy (except nonmelanoma skin cancer or disease-free for ≥2 yr after curative therapy), use of another investigational drug or device within 30 d, recent iron therapy, serum parathyroid hormone >1500 pg/ml (ng/L), active or recent bleeding, recent or anticipated surgery other than vascular access surgery, recent or anticipated blood transfusion, active infection requiring therapy, allergy to intravenous iron, and allergy to two or more drugs.

**Sample Size**

Sample size was calculated for 3:1 randomization to ferumoxytol/oral iron, to maximize exposure to ferumoxytol for safety assessments.
Assuming a mean treatment difference in hemoglobin between ferumoxytol and oral iron of 0.6 g/dl (SD 1.2 g/dl), 90% power using a two-sample t test (with 5% type I error), and a 25% dropout rate, the final sample size estimate was 304 patients.

Efficacy Analysis

Efficacy was assessed on the basis of changes in hemoglobin and serum iron indices (iron, TSAT, and ferritin) from baseline (average of day −10 and day −5 values). The primary efficacy end point was the mean change in hemoglobin from baseline to day 35. Other efficacy end points included mean change in ferritin and proportion of patients achieving a ≥1-g/dl (10-g/L) increase in hemoglobin. For missing laboratory parameters at day 21 or 35, the analysis assumed no change from baseline (value of zero imputed for the change from baseline). In addition, an analysis of patients with fully evaluable data yielded similar results (data not shown). The primary end point variable, hemoglobin at day 35, was missing for 10% of ferumoxytol and 13% of oral iron treated patients.

Statistical significance of the comparison between treatment groups was assessed using a two-sided, two-sample t test or χ² test, as appropriate. The principal efficacy analyses were conducted using Intention-to-Treat principles, and prespecified efficacy analyses were also stratified by ESA use.

Safety Analysis

Safety was monitored during and for 1 h after ferumoxytol administration and throughout the 35-d study follow-up, by evaluating vital signs, adverse events (by direct observation and interview), and changes in laboratory tests and physical examinations. Patients in the oral iron group had vital signs obtained on days 0, 7, 14, 21, and 35 and in the ferumoxytol group at preadministration and 5, 10, 20, 30, and 60 min after, and at days 21 and 35. Mean arterial pressure was calculated using the formula [(2 × diastolic BP) + systolic BP]/3.

Patients were monitored for hypotension and hypersensitivity reactions (urticaria, rash, pruritus, facial or laryngeal/pharyngeal edema, asthma, or other allergic reactions) after ferumoxytol administration. Hypotension was defined as a decrease in systolic BP of >20 mmHg and to <90 mmHg or a decrease in diastolic BP of >15 mmHg and to <50 mmHg. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 8.0. Relatedness of adverse events to treatment was assessed by site investigators.

Readmission Phase

After completion of the randomized study at day 35 and at the discretion of the site investigator, patients in either treatment group who continued to be anemic and met other study entry criteria were eligible to receive two doses of 510 mg of ferumoxytol in an open-label manner. This optional readmission phase was conducted to examine the safety and efficacy of administering two courses of two doses of 510 mg of ferumoxytol and the response to ferumoxytol in patients who remained anemic after oral iron therapy. Because the readmission phase was neither randomized nor powered to demonstrate efficacy, the efficacy end points were examined for exploratory purposes only.

ACKNOWLEDGMENTS

AMAG Pharmaceuticals, Inc. funded the study, and its employees identified study sites, monitored the study to ensure adherence to good clinical practice, and performed data analyses according to the predefined statistical analysis plan.

We gratefully acknowledge the contribution of members of the Clinical Studies Steering Committee (Drs. W. Kline Bolton, Anatole Besarab, Robert Provenzano, Ajay Singh, and Allen Nissenson), who provided guidance during all phases of the study and critical review of the manuscript.

DISCLOSURES

A.T.K., J.B., L.B., and B.J.G.P. are employees of AMAG Pharmaceuticals, and B.S.S. is a member of the Clinical Studies Steering Committee of AMAG Pharmaceuticals, Inc.

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