Ferumoxytol as an Intravenous Iron Replacement Therapy in Hemodialysis Patients

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Background and objectives: Intravenous iron is a key component of anemia management for chronic kidney disease (CKD). Ferumoxytol is a unique intravenous iron product that can be administered as a rapid injection in doses up to 510 mg.

Design, setting, participants, & measurements: This was a randomized, open-label, controlled, multicenter Phase 3 trial to evaluate the safety and efficacy of intravenous ferumoxytol compared with oral iron. Anemic patients with CKD stage 5D on hemodialysis and on a stable erythropoiesis-stimulating agent regimen received either two injections of 510 mg of ferumoxytol within 7 d ($n = 114$) or 200 mg elemental oral iron daily for 21 d ($n = 116$). The primary efficacy endpoint was the change in hemoglobin from baseline to day 35. Safety was closely monitored.

Results: Ferumoxytol resulted in a mean increase in hemoglobin of 1.02 ± 1.13 g/dl at day 35 compared with 0.46 ± 1.06 g/dl with oral iron ($P = 0.0002$). Twice as many ferumoxytol-treated patients than oral iron-treated patients achieved a ≥1 g/dl hemoglobin increase at day 35 ($P = 0.0002$). There was a greater mean increase in transferrin saturation (TSAT) with ferumoxytol compared with oral iron at day 35 ($P < 0.0001$). The larger hemoglobin increase after ferumoxytol compared with oral iron at day 35 persisted after adjustment for baseline hemoglobin, TSAT, and serum ferritin. Overall adverse event rates were comparable between groups.

Conclusions: In patients on hemodialysis, rapid intravenous injection of 510 mg of ferumoxytol led to significantly greater hemoglobin increases compared with oral iron, with comparable tolerability.

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Anemia is highly prevalent in the chronic kidney disease (CKD) population and is nearly universal in patients with CKD stage 5D on hemodialysis (HD) (1,2). Iron deficiency is a common cause of anemia in CKD patients (3,4) and may be the result of poor iron absorption, blood loss, and increased erythropoiesis after use of erythropoiesis-stimulating agents (ESAs) (5,6). The intravenous (IV) route is recommended for iron replacement therapy in HD patients because oral iron is associated with intolerance and limited efficacy (7–9), since oral iron may be poorly absorbed (10). IV iron is typically given as a 1 g course for the treatment of iron deficiency (9).

IV iron formulations generally consist of an iron core surrounded by a stabilizing carbohydrate shell to encapsulate the bioactive iron, to ensure release of iron within the cells of the reticuloendothelial system, and to limit side effects (11). The first-generation iron dextrans had the advantage of permitting administration of larger doses of iron by slow infusion over several hours, but the risk of anaphylaxis, consequent requirement of a test dose, and other side effects have led to a decline in use in most developed countries (12). Second-generation iron formulations such as iron sucrose and iron gluconate are associated with a lower incidence of allergic reactions compared with iron dextrans, but are administered only in small doses because of dose-related side effects such as hypotension (13,14).

Ferumoxytol is a novel iron oxide nanoparticle with a polyglucose sorbitol carboxymethylether coating designed to minimize immunological sensitivity. It is isotonic, and *in vitro* data suggest that it contains less free iron than other IV iron preparations (15–17). It is perhaps these physicochemical characteristics that permit the rapid administration of larger doses of ferumoxytol compared with the currently available iron preparations. Clinical studies have demonstrated that doses up to 510 mg of ferumoxytol administered by IV injection in as little as 17 sec were well tolerated (18,19). Consequently, a 1-g therapeutic course of IV iron was administered using two rapid injections of ferumoxytol over an interval of less than 1 wk in CKD patients (20). Furthermore, because the molecular weight of ferumoxytol (approximately 750 kD) is above the permeability cutoff of standard HD membranes, it is not removed from plasma by dialysis (18,21) and can therefore be administered any time during the HD procedure.

This report describes a Phase 3 clinical study of the efficacy and safety of ferumoxytol compared with oral iron in patients

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on HD receiving a stable ESA regimen, and the factors that affect hemoglobin response to IV iron in the current era of anemia management.

Materials and Methods

Ferumoxytol

Ferumoxytol injection (AMAG Pharmaceuticals, Inc., Lexington, Massachusetts) is a sterile liquid with a neutral pH and is formulated with mannitol for isotonicity; each milliliter contains 30 mg of iron (15).

Study Design and Conduct

This was a randomized, controlled, open-label, multicenter Phase III trial comparing the safety and efficacy of IV ferumoxytol to oral iron treatment in patients on HD with iron deficiency anemia (ClinicalTrials.gov identifier: NCT00233597). The protocol was approved by a central institutional review board, and where required, by individual institutional review boards. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. All patients gave written informed consent. The study was conducted in the United States between October 2005 and April 2007.

The sample size estimate of 230 patients was based on a 1:1 randomization of patients to ferumoxytol or oral iron, a mean treatment difference in hemoglobin of 0.6 g/dl (SD of 1.2 g/dl), 90% power to detect a difference using a two-sample *t* test, a 5% Type I error, and a 25% dropout rate.

Inclusion criteria included the following: ≥18 yr of age, on HD for at least 90 d, hemoglobin ≤11.5 g/dl, transferrin saturation (TSAT) ≤30%, serum ferritin ≤600 ng/ml, and stable (±25%) dose ESA therapy for at least 10 d before dosing. The ESA dose was required to remain constant during the study. Exclusion criteria included pregnancy or breast feeding, causes of anemia other than CKD, use of another investigational drug or device within 30 d, iron therapy within 10 d, recent blood transfusion, active infection, or allergy to iron products or multiple drug classes.

Eligible patients were randomized in a 1:1 ratio using a telephone-based system (ClinPhone Interactive Voice Response System, East Windsor, New Jersey) to receive either IV ferumoxytol or oral iron. Ferumoxytol was administered as two 510 mg IV injections over 17 sec, each at a rate of 1 ml (30 mg iron)/s, during sequential dialysis treatments (within 5 ± 3 d). Each dose was injected at any time after 60 min (±15 min) into the HD session once hemodynamic stabilization was achieved. Patients randomized to oral iron took 200 mg of elemental iron daily as Ferro-Sequels (50 mg of ferrous fumarate per tablet; Inverness Medical Innovations, Inc., Waltham, Massachusetts) for 21 d.

Laboratory tests and clinical evaluations were performed during screening visits on day −10 and day −5, before study drug dosing, and at days 21 and 35 after the initial dose. All laboratory tests were performed at a central laboratory (MedTox Laboratories, Inc., St. Paul, Minnesota).

After completion of the randomized study at day 35 and at the discretion of the site investigator, patients in either group, who once again met the study entry criteria (including at least one hemoglobin measurement ≤11.5 g/dl and the iron targets noted earlier), had the opportunity to receive two doses of 510 mg ferumoxytol in an optional, nonrandomized readmission phase. The schedule of ferumoxytol administration and assessments in the readmission phase was the same as in the randomized phase.

Statistical Analyses

Efficacy analyses were conducted on the intent-to-treat (ITT) population (all randomized patients, whether or not they received study drug). Baseline laboratory values were the day −10 and day −5 average. The primary efficacy endpoint was the change in hemoglobin from baseline to day 35. Other efficacy endpoints included the proportion of patients achieving a ≥1 g/dl increase in hemoglobin at day 35; change in hemoglobin at day 21; and change in TSAT, serum ferritin, serum iron, total iron binding capacity (TIBC), and reticulocyte hemoglobin content (CHr) at day 21 and 35. In the event that any postdose laboratory parameter was missing, the analysis assumed no change from baseline and a value of zero was imputed for the change from baseline. Treatment differences were assessed using a two-sided, two-sample *t*-test or χ^2 test. An analysis of covariance model was used to compare day 35 hemoglobin change treatment differences when adjusted for baseline hemoglobin, TSAT, and ferritin. The relationship between hemoglobin change and these baseline parameters was examined by linear regression analysis.

The population for the safety analysis included all patients who were randomized and received at least one dose of study drug. Safety assessments included adverse event monitoring, vital sign assessments, and clinical laboratory evaluations. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 8.0 and the site investigator assigned relatedness to treatment. In the oral iron group, vital signs were collected at baseline; within 15 min before initiation of dialysis; and at 60, 65, 70, 80, 90, and 120 min into dialysis on days 0, 7, 14, 21, and 35. In the ferumoxytol group, vital signs were collected at baseline; within 15 min before initiation of dialysis; at 15 min predose; at 5, 10, 20, 30, and 60 min postdose; and at days 21 and 35. Hypotension was defined as a decrease in systolic blood pressure (BP) of >20 mmHg and to <90 mmHg, or a decrease in diastolic BP of >15 mmHg and to <50 mmHg.

The efficacy and safety endpoints in the readmission phase were identical to those in the randomized phase. Because the optional readmission phase was neither randomized nor powered to demonstrate efficacy, the efficacy endpoints were examined for exploratory purposes only. The day 35 hemoglobin measurement was used as the readmission baseline value if the patient entered the readmission phase within 2 to 8 d of the final study visit; otherwise a new laboratory measurement was taken at the time of readmission.

Results

Disposition and Demographics

Two-hundred-thirty patients were randomized (114 to ferumoxytol and 116 to oral iron); of these 102 (89.5%) ferumoxytol- and 99 (85.3%) oral iron-treated patients completed the study (Figure 1). Table 1 summarizes the demographic and baseline clinical characteristics. Baseline characteristics were similar except for more men in the oral iron group compared with the ferumoxytol group (62.9% *versus* 50.0%, $P = 0.04$). Mean baseline laboratory measures were similar between the two treatment groups.

Extent of Exposure

In the randomized phase, 104 of 110 patients (94.5%) in the ferumoxytol group received two complete doses (1.02 g), and six patients (5.5%) received one complete dose (510 mg). Four patients did not receive ferumoxytol because of protocol violation ($n = 1$), adverse event ($n = 1$), or other reasons ($n = 2$). The median time for injection of ferumoxytol was 25 s (range 7 to 60 sec). The mean cumulative dose in the oral iron group was 3765 mg, on the basis of pill count estimates.

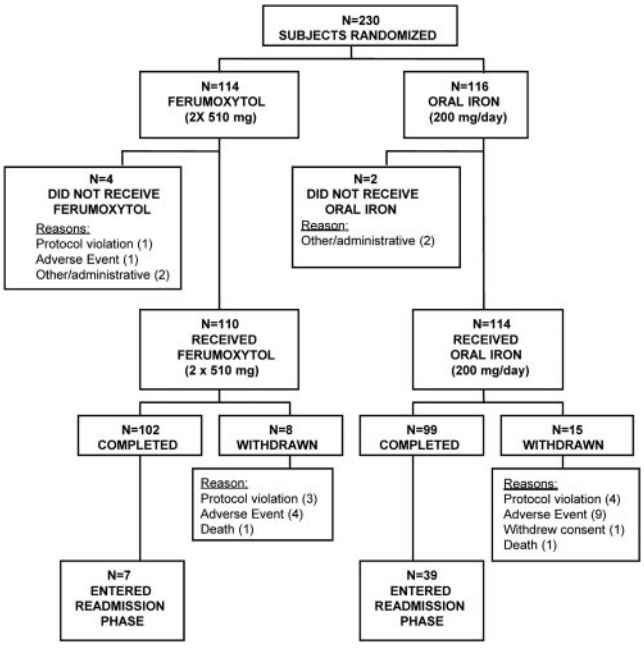

Figure 1. Patient flow diagram.

Efficacy in the Randomized Phase

Ferumoxytol treatment led to improvements across all efficacy endpoints compared with oral iron (Table 2). For the primary endpoint, ferumoxytol produced a significantly greater increase in hemoglobin at day 35 compared with oral iron, with increases of 1.02 ± 1.13 g/dl in the ferumoxytol group and 0.46 ± 1.06 g/dl in the oral iron group ($P = 0.0002$); results were similar at day 21. Twice as many patients in the ferumoxytol group achieved a ≥1 g/dl increase in hemoglobin at day 35 compared with the oral iron group (49.0 *versus* 25.0%, $P = 0.0002$). Mean increase in TSAT was significantly greater with ferumoxytol compared with oral iron at both day 21 (6.22 *versus* 1.39%, $P = 0.0015$) and day 35 (6.44 *versus* 0.55%, $P < 0.0001$). Serum ferritin levels significantly increased in the ferumoxytol group but declined in the oral iron group at both day 21 (357 *versus* −38 ng/ml, $P < 0.0001$) and day 35 (234 *versus* −59 ng/ml, $P < 0.0001$). Likewise, compared with oral iron, ferumoxytol resulted in greater increases in CHr (at days 21 and 35, $P < 0.0001$ for each test) and greater decreases in TIBC (at days 21 and 35, $P < 0.0001$ for each test). Although the increases in serum iron after ferumoxytol were greater than oral iron at both days 21 and 35, these differences did not reach statistical significance.

Relationship between Hemoglobin Response and Baseline Laboratory Values

The statistically significant increase in hemoglobin after ferumoxytol compared with oral iron at day 35 persisted after adjustment for baseline hemoglobin ($P = 0.0003$), TSAT ($P = 0.0001$), and serum ferritin ($P = 0.0001$), and there were no significant interactions. The relationship between the hemoglobin response at day 35 and baseline hemoglobin, TSAT, and serum ferritin quartiles are shown in Table 3 and Figure 2. These results are only provided for descriptive purposes because the study was not powered for subanalysis. Among ferumoxytol-treated patients, regression analysis revealed a trend for an inverse relationship between the hemoglobin increase at day 35 and baseline hemoglobin ($R^2 = 0.04$, $P = 0.34$) and baseline serum ferritin ($R^2 = 0.04$, $P = 0.37$), but not with baseline TSAT ($R^2 = 0.00$, $P = 0.87$). For patients at all levels of baseline TSAT, ferumoxytol resulted in a mean hemoglobin increase of approximately 1 g, including patients with baseline TSAT levels between 21 and 30% (Figure 2b). Among patients treated with oral iron, there was no relationship between the hemoglobin response and baseline hemoglobin, TSAT, or serum ferritin.

Efficacy in the Readmission Phase

Among the 46 patients who entered the optional readmission phase (39 previously treated with oral iron and seven with ferumoxytol), baseline hemoglobin levels at re-entry were 10.71 ± 0.83 g/dl and 11.01 ± 0.59 g/dl, respectively. At day 35 of the readmission phase, hemoglobin increased from the readmission baseline by 0.78 ± 0.86 g/dl in patients previously treated with oral iron and by 0.96 ± 0.69 g/dl in patients previously treated with ferumoxytol.

Safety in the Randomized Phase

Seven individuals who did not receive study drug were excluded from the safety analysis. Of the 110 patients included in the safety analysis for the ferumoxytol group, 54 (49.1%) experienced a total of 121 adverse events. In the oral iron group, 64 (56.6%) of the 113 patients included in the safety analysis experienced a total of 152 adverse events. Adverse events considered to be related to treatment by the investigator were less frequent in the ferumoxytol group (8.2%) compared with the oral iron group (15.9%). The frequency of serious adverse events was similar in the ferumoxytol (12.7%) and oral iron groups (12.3%). Within each group, most serious adverse events were reported in single patients except for hypotension (in two patients in the ferumoxytol group) and cellulitis and chronic obstructive pulmonary disease exacerbation (each in two patients in the oral iron group). One (0.9%) ferumoxytol-treated patient had a serious adverse event of hypotension that was considered related to treatment and resolved within a few minutes without sequelae; no oral iron-treated patient had serious adverse event systolic considered related to treatment. There was one (0.9%) death in the ferumoxytol group and three (2.7%) deaths in the oral iron group, none of which were considered related to treatment. There was no meaningful decrease in mean systolic BP after initial administration of ferumoxytol or oral iron (Figure 3).

Safety in the Readmission Phase

In the readmission phase, the overall incidence of all adverse events was 48.0%, which was comparable to the rate of adverse events in each prior treatment group in the randomized phase. In the readmission phase, one patient (1%) who had received oral iron during the randomized phase of the study developed a serious adverse event of hypotension after ferumoxytol that

Table 1. Baseline demographics and clinical characteristics (ITT Population)

	Ferumoxytol 2 × 510 mg $n = 114$	Oral Iron 200 mg/d $n = 116$
Age, mean ± SD (yr)	59.5 ± 14.3	60.8 ± 13.0
Gender, *n* (%) male	57 (50.0)	73 (62.9)
Race, *n* (%)		
African American	69 (60.5)	67 (57.8)
Caucasian	37 (32.5)	40 (34.5)
Asian	6 (5.3)	2 (1.7)
other/missing	2 (1.8)	7 (6.0)
Cause of kidney disease, *n* (%)		
diabetes	49 (42.9)	49 (42.2)
hypertension	39 (34.2)	40 (34.5)
glomerular disease	11 (9.6)	7 (6.0)
other/missing	15 (13.2)	20 (17.2)
Laboratory values, mean ± SD		
hemoglobin (g/dl)	10.59 ± 0.67	10.69 ± 0.57
TSAT (%)	15.71 ± 7.21	15.91 ± 6.29
ferritin (ng/ml)	341 ± 159	358 ± 172

TSAT, transferrin saturation.

resolved without sequelae. Among patients who received ferumoxytol during the randomized phase, there was no increase in the number of or change in pattern of adverse events after a second 1.02-g course of ferumoxytol treatment. There were no deaths during the readmission phase.

Discussion

The results of this study provide insight into two key areas: (1) the efficacy profile, safety profile, and potential convenience of ferumoxytol, a novel IV iron designed to minimize immunological sensitivity and permit administration of large doses as an injection; and (2) the factors that affect the hemoglobin response to IV iron in the current era of anemia management. Hemodialysis patients randomized to two 510 mg injections of ferumoxytol demonstrated a significantly greater increase in hemoglobin levels compared with oral iron, as well as significantly greater increases in serum ferritin, TSAT, and CHr. The superior hemoglobin response to ferumoxytol compared with oral iron persisted after adjustment for baseline hemoglobin, TSAT, and ferritin levels. Ferumoxytol was well tolerated and was associated with fewer adverse events than treatment with oral iron. The therapeutic response, tolerability, and convenience of administering a 1 g course of IV iron with just two injections makes ferumoxytol a potentially attractive treatment option for anemic HD patients.

In the United States, the prevalence of iron deficiency in HD patients receiving ESA therapy is as high as 90% (5). Iron deficiency leads to inefficient erythropoiesis and is a common cause of ESA resistance (22). Treatment of iron deficiency is therefore an essential component of appropriate anemia management in HD patients. Intravenous iron therapy replaces iron lost during the HD procedure, enables efficient erythropoiesis, and ameliorates ESA resistance in the setting of iron deficiency, thereby optimizing the use and effects of ESA therapy (7,23–26). The Kidney Disease Outcomes Quality Initiative anemia guidelines recommend IV administration as the preferred route of iron delivery in HD patients on ESA therapy and recommend that the goal of therapy should be to achieve and maintain TSAT >20%, CHr >29 pg/cell, and serum ferritin >200 ng/ml (9). Consequently, most HD patients in the United States receive IV iron to treat iron-deficiency anemia.

Oral iron is a suboptimal choice for iron replacement therapy in HD patients from the point of efficacy, safety, and tolerability (7–9). Claims from studies that have suggested that oral iron may be efficacious in HD patients, at least in a subgroup of patients (27), have been fraught with methodological weaknesses such as their observational nature and selection bias. We compared the hemoglobin increase at 5 wk after two 510 mg doses (1.02 g total dose) of ferumoxytol given within 1 wk with oral iron. Subjects in the control arm of this study were prescribed 200 mg/d for 21 d, resulting in a total cumulative dose of 4200 mg. Given that the absorption of oral iron is incomplete (approximately 40%) (6), and patients may not be fully compliant with daily oral iron dosing, this cumulative dose would ensure that at least 1 g of iron would be absorbed; this would represent a comparable dose of bioavailable iron to that administered in the ferumoxytol treatment arm. Despite most oral iron-treated patients being at least 80% compliant, the hemoglobin increase with ferumoxytol was twice as high as with oral iron, and twice as many patients achieved a hemoglobin increase of 1 g/dl or greater with ferumoxytol compared with oral iron. Likewise, indices of iron stores showed a significantly greater increase after ferumoxytol compared with oral iron, suggesting durability of the response. Furthermore, patients who did not respond satisfactorily to oral iron had a favorable therapeutic response to ferumoxytol in the readmis-

Table 2. Changes in hemoglobin and serum iron indices after ferumoxytol or oral iron therapy (ITT Population)[a]

Treatment Group	Baseline	Day 21	Change at Day 21	*P* for Day 21 Change[b]	Day 35	Change at Day 35	*P* for Day 35 Change[b]
Hemoglobin (g/dl)							
Ferumoxytol	10.59 ± 0.67	11.41 ± 1.23	0.71 ± 1.07	0.0067	11.72 ± 1.20	1.02 ± 1.13	0.0002
Oral iron	10.69 ± 0.57	11.09 ± 1.07	0.35 ± 0.90		11.22 ± 1.22	0.46 ± 1.06	
TSAT (%)							
Ferumoxytol	15.71 ± 7.21	22.00 ± 12.17	6.22 ± 12.12	0.0015	22.31 ± 13.33	6.44 ± 12.59	<0.0001
Oral iron	15.91 ± 6.29	17.08 ± 9.54	1.39 ± 8.88		16.46 ± 9.72	0.55 ± 8.34	
Ferritin (ng/ml)							
Ferumoxytol	340.52 ± 159.07	749.49 ± 301.63	356.66 ± 247.12	<0.0001	601.79 ± 282.95	233.93 ± 206.95	<0.0001
Oral iron	357.56 ± 171.65	316.24 ± 173.51	−37.56 ± 106.98		289.30 ± 165.76	−59.23 ± 106.22	
Serum iron (μg/dl)							
Ferumoxytol	49.49 ± 20.20	60.06 ± 31.54	10.84 ± 31.40	0.1328	58.64 ± 27.88	9.20 ± 27.77	0.0557
Oral iron	48.23 ± 18.73	53.07 ± 24.78	4.87 ± 23.33		51.02 ± 26.28	2.61 ± 21.71	
TIBC (μg/dl)							
Ferumoxytol	322.36 ± 76.78	280.26 ± 67.83	−41.25 ± 57.02	<0.0001	275.67 ± 60.71	−45.88 ± 52.53	<0.0001
Oral iron	313.89 ± 65.84	310.67 ± 65.86	−4.16 ± 46.87		319.62 ± 67.29	4.21 ± 50.26	
CHr (pg)							
Ferumoxytol	31.12 ± 2.62	32.42 ± 2.60	1.32 ± 1.59	<0.0001	32.22 ± 2.69	1.09 ± 1.64	<0.0001
Oral iron	31.57 ± 2.48	31.68 ± 2.42	0.07 ± 1.46		31.56 ± 2.39	0.00 ± 1.46	

[a]Mean ± SD data are presented.
[b]Two-sample *t*-tests evaluated treatment differences in changes from baseline.
TIBC, total iron binding capacity; CHr, reticulocyte hemoglobin content; TSAT, transferrin saturation.

Table 3. Relationship between change in hemoglobin from baseline at day 35 and baseline laboratory values

Quartile	Ferumoxytol		Oral Iron	
	Mean Change	95% CI	Mean Change	95% CI
Baseline hemoglobin (g/dl)				
8.2 to 10.3	1.239	0.791, 1.687	0.681	0.261, 1.101
>10.3 to 10.7	1.462	1.037, 1.887	0.420	0.091, 0.749
>10.7 to 11.2	0.864	0.465, 1.262	0.531	0.142, 0.921
>11.2 to 11.5	0.645	0.181, 1.109	0.208	−0.359, 0.775
Baseline TSAT (%)				
0 to 10	0.978	0.592, 1.365	0.473	−0.046, 0.992
>10 to 14	0.992	0.561, 1.423	0.680	0.313, 1.047
>14 to 21	1.015	0.465, 1.566	0.263	−0.152, 0.679
>21 to 30	1.184	0.697, 1.671	0.459	0.092, 0.826
Baseline serum ferritin (ng/ml)				
8.00 to 207.75	1.370	0.855, 1.886	0.343	−0.118, 0.804
>207.75 to 360.50	0.953	0.533, 1.374	0.323	−0.010, 0.656
>360.50 to 466.25	1.145	0.741, 1.549	0.388	−0.066, 0.842
>466.25 to 599.00	0.709	0.235, 1.183	0.641	0.279, 1.003

CI, confidence interval.

sion phase of the study, comparable to that seen in the ferumoxytol group in the randomized phase. Finally, the statistically significant increase in hemoglobin response to ferumoxytol compared with oral iron persisted after adjustment for baseline hemoglobin, TSAT, and serum ferritin, and there were no significant interactions. These results reaffirm that IV iron should be the administration route of choice in HD patients.

A common view among clinicians is that oral iron is much safer than IV iron because IV iron has been associated with hypersensitivity reactions and hypotension. Because this was a registrational Phase 3 study of an investigational IV iron product, enrolling patients with an allergy to iron products or multiple drug classes was not appropriate. We found that the incidence of adverse events and serious adverse events was similar among patients treated with ferumoxytol and oral iron. Furthermore, with the exception of two episodes of transient but serious hypotension after ferumoxytol administration (one in each phase of the study), the BP pattern after ferumoxytol was virtually identical to that among patients treated with oral iron in the randomized phase. These BP results were consistent with those from a large safety study, which found similar BP patterns after a single rapid IV dose of 510 mg of ferumoxytol or saline placebo in CKD patients on and not on hemodialysis (28).

The safety profile of ferumoxytol may have a basis in its unique physicochemical profile. An ideal IV iron formulation should have low immunogenicity, stable binding of the iron to its carrier molecule in serum until it is taken up into the reticuloendothelial system for transfer to transferrin or storage, and no direct release of iron in the serum, thereby avoiding the generation of a free or labile iron pool (11,29). Indeed, ferumoxytol demonstrates several of these properties. Ferumoxytol exhibited extremely low immunogenicity in the rat paw edema test (15). Moreover, a comparison of bleomycin-detectable iron and TSAT in the serum of patients receiving either ferumoxytol, iron gluconate, or iron sucrose showed that ferumoxytol generated the least catalytic free iron for comparable levels of TSAT (16,17). These characteristics, along with an isotonic formulation, may explain in part why 510 mg of ferumoxytol can be administered as a single rapid injection compared with the need for 5 to 10 separate infusions of 100 to 200 mg with other iron preparations in current use (30,31).

The results of this study also provide insight into the factors that affect the hemoglobin response to IV iron in the current era of anemia management. The hemoglobin increase with ferumoxytol therapy was inversely related to the baseline hemoglobin, and in the highest quartile of baseline hemoglobin the mean increase was 0.64 g/dl. This provides reassurance against concerns of an overshoot of target hemoglobin levels after IV ferumoxytol administration, given the current sensitivity surrounding high hemoglobin levels (32,33). More importantly, the hemoglobin response to ferumoxytol was unrelated to the baseline TSAT levels up to 30%, which was the cutoff for entry into the study. This suggests that HD patients with TSAT levels up to 30% (and possibly higher) can benefit from ferumoxytol therapy. Finally, the inverse relationship between serum baseline ferritin levels and the hemoglobin response supports the notion that serum ferritin levels are a marker of inflammation and resistance to ESA or iron therapy (34). Even in the highest serum ferritin quartile of 466 to 600 ng/ml, the 0.70 g/dl increase in hemoglobin after ferumoxytol was notable. Likewise, in the Dialysis Patients' Response to IV Iron at Elevated Ferritin (DRIVE) study, 1 g of ferric gluconate administered to HD patients with hemoglobin levels <11 g/dl, serum ferritin levels of 500 to 1200 ng/ml, and TSAT levels ≤25% resulted in a greater and more rapid increase in hemoglobin with IV iron compared with controls (25). Taken together, these data dem-

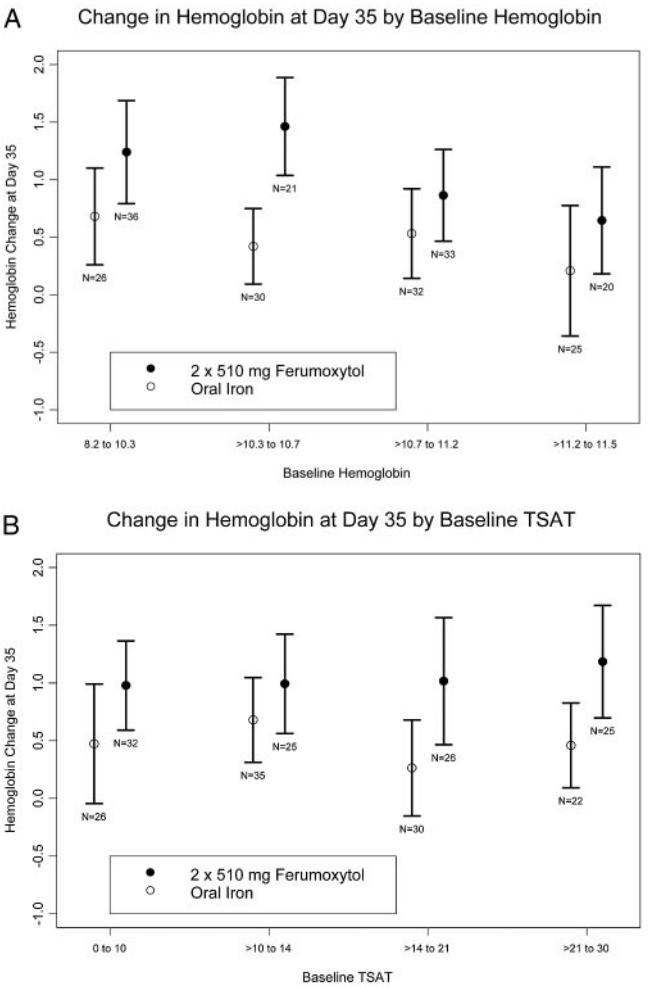

Figure 2. Change in hemoglobin at day 35 by baseline hemoglobin and TSAT. Mean change in hemoglobin from baseline at day 35 stratified by baseline quartiles of (a) hemoglobin and (b) TSAT. Circles represent means and bars represent 95% confidence intervals around the means.

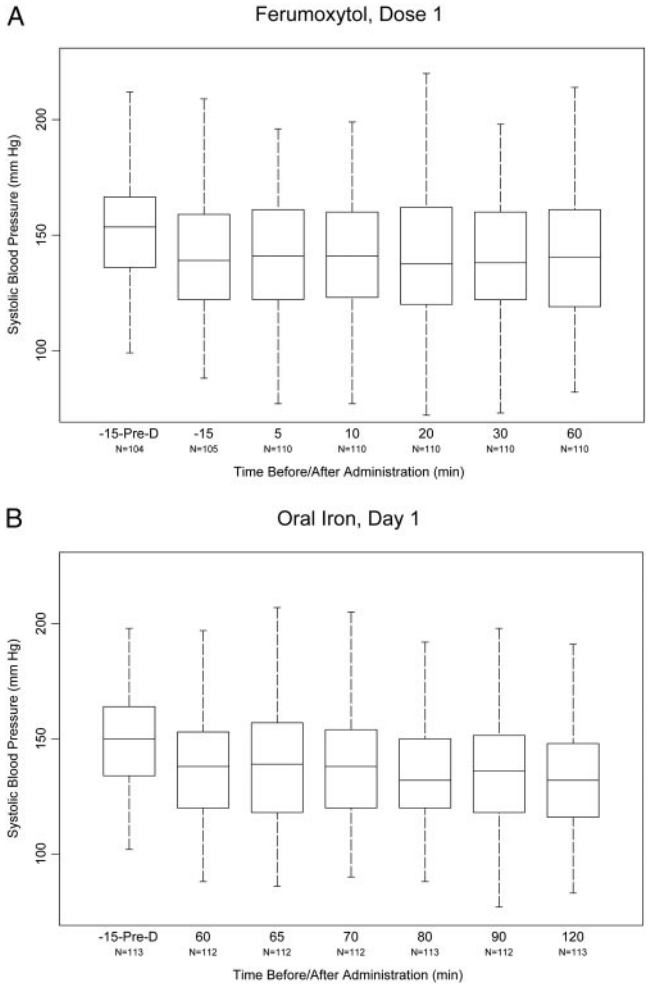

Figure 3. Mean systolic blood pressure measurements after the administration of the first dose of (a) ferumoxytol or (b) oral iron. Boxplots show median (line inside box), 25th, and 75th percentiles (bottom and top of box, respectively), and whiskers extending to values nearest 1.5 times the interquartile range.

onstrate hemoglobin response to IV iron treatment across a wide range of baseline ferritin levels (<200 ng/ml in the study presented here to 1200 ng/ml in the DRIVE study) and should be considered as part of a re-examination of the current IV iron therapy guidelines in CKD patients, especially with respect to baseline ferritin and TSAT levels.

The ability to administer a repletion course of IV iron with fewer doses has potential implications for patient compliance, efficiency of care, and cost in HD patients. Efficient correction of iron deficiency may produce a cost savings by optimizing ESA use (24,26), particularly in patients demonstrating ESA hyporesponsiveness in the setting of iron deficiency. In addition, fewer injections of iron to administer a 1 g therapeutic course may improve patient management through increased compliance and reduced medical errors and would theoretically increase staff efficiency.

Acknowledgments

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Disclosures

Drs. Pereira and Brenner are employees of AMAG Pharmaceuticals, Inc. Dr. Provenzano is a member of the Clinical Studies Steering Committee of AMAG Pharmaceuticals, Inc. Drs. Schiller and Coyne were ferumoxytol study investigators.

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