The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients

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Background. Administration of safe and effective iron therapy in patients with chronic kidney disease is a time consuming process. This phase II clinical trial studied ferumoxytol, a semi-synthetic carbohydrate-coated iron oxide administered by rapid intravenous injection to anemic chronic kidney disease patients (predialysis or undergoing peritoneal dialysis).

Methods. Inclusion criteria included hemoglobin ≤ 12.5 g/dL and transferrin saturation $\leq 35\%$. Twenty-one adult patients were randomized to receive ferumoxytol in a regimen of 4 doses of 255 mg iron in 2 weeks or 2 doses of 510 mg iron in 1 to 2 weeks. Ferumoxytol was administered at a rate of up to 30 mg iron/sec.

Results. The maximum hemoglobin response following ferumoxytol administration occurred at 6 weeks, increasing from a baseline of 10.4 ± 1.3 g/dL to 11.4 ± 1.2 g/dL ($P < 0.05$). Ferritin increased from a baseline of 232 ± 216 ng/mL to a maximum of 931 ± 361 ng/mL at 2 weeks ($P < 0.05$), while the baseline transferrin saturation increased from $21 \pm 10\%$ to $37 \pm 22\%$ at 1 week ($P < 0.05$). Seven adverse events in 5 patients during this trial were deemed possibly related to ferumoxytol, none serious. These events included constipation, chills, tingling, a gastrointestinal viral syndrome, delayed pruritic erythematous rash, and transient pain at the injection site.

Conclusion. Although larger studies are required, this small study demonstrates that ferumoxytol can be safe and effective in increasing iron stores, is associated with an increased hemoglobin response, and is well tolerated at a rapid infusion rate.

Providing adequate bioavailable iron to patients with chronic kidney disease (CKD) is necessary to ensure an efficient response to erythropoietic hormone therapy [1]. Additionally, there are data supporting a significant

hemoglobin response in this population with parenteral iron therapy alone [2]. Oral iron administration is relatively ineffective in supporting erythropoiesis in CKD patients [3–5], and many patients have gastrointestinal intolerance of these compounds. As a result, intravenous iron is commonly used to achieve and maintain adequate iron levels in this patient population.

Until recently, iron dextran was the only intravenous iron preparation available in the United States [6]. Adverse reactions have been reported in 4.7% to 43% of patients administered intravenous iron dextran [7–9]. Most of these reactions are mild, with 38% of patients given a total dose infusion exhibiting delayed reactions of arthralgia, myalgia, and fever. Some patients experience anaphylactoid-type reactions (defined as dyspnea, wheezing, chest pain, hypotension, urticaria, or angioedema), which can be serious and life threatening [9].

Comparative data on the safety of the currently available parenteral iron preparations are difficult to evaluate since information on the number of patients treated, the specific product and dosage regimen utilized, previous exposure to other iron preparations, and current diagnoses are often not available. Reports are typically retrospective, and neither blinded nor comparative. A recent retrospective analysis concluded that the rate of adverse drug events was lowest in patients receiving a low-molecular-weight iron dextran preparation compared to a higher-molecular-weight iron dextran or sodium ferric gluconate [10].

Newer parenteral iron preparations such as sodium ferric gluconate and iron sucrose are effective and considered safer [11, 12], but require multiple and/or relatively time-consuming administration regimens. Currently, in the United States, according to the Food and Drug Administration labeling, intravenous iron replacement is generally given as a slow infusion of 125 mg sodium ferric gluconate over 10 minutes or 100 to 200 mg of iron sucrose over approximately 5 minutes. These delivery modes incur significant expense for supplies, such

as tubing and infusate, costly nursing time, and patient inconvenience. To achieve iron repletion with these newer agents, commonly a total dose of 1 g of iron requires 5 to 10 sessions over an extended period of time.

Ferumoxytol (Advanced Magnetics, Cambridge, MA, USA) is an investigational, semi-synthetic carbohydrate-coated, magnetic iron oxide preparation. It is one of a class of compounds originally developed as magnetic resonance imaging (MRI) contrast agents, and is administered for MR angiography as a rapid intravenous bolus [13, 14]. Ferumoxytol was designed to minimize potential immunologic reactions, such as those seen with commercially available iron dextran products, and to minimize free iron during dosing.

The purpose of this open label study was to evaluate the safety and efficacy of ferumoxytol in stimulating hemoglobin synthesis in anemic CKD patients on stable dosing regimens of erythropoietic hormones.

METHODS

Subjects were recruited from 3 centers in the United States for this prospective open-label phase 2 dose escalation study. The primary purpose of the study was to evaluate the safety of 2 dose regimens in this patient population, while a secondary purpose was to gather exploratory data on efficacy to permit the design of larger studies. The study was conducted in accord with the Declaration of Helsinki and approved by an Institutional Review Board for each site. After granting informed consent, each subject had screening laboratory tests, a medical history, and a physical examination performed to establish a baseline and confirm inclusion criteria and exclusion criteria. Patients included had been diagnosed with CKD and could be on peritoneal dialysis therapy but not hemodialysis. Other inclusion criteria included an age of 18 years or greater, hemoglobin level less than or equal to 12.5 g/dL, and a transferrin saturation of 35% or less.

Exclusion criteria included women who were pregnant or lactating, the use of parenteral or oral iron therapy in the previous 2 weeks, transfusions or active bleeding in the previous 2 months, major surgery within the previous month, active infections, inflammatory conditions, multiple drug sensitivities, autoimmune disease, immunodeficiencies, androgen therapy within the past 12 weeks, iron overload (transferrin saturation 50% or greater, serum ferritin 800 ng/mL or greater), severe hyperparathyroidism (parathyroid hormone greater than 1500 pg/mL), serum AST or ALT greater than 2 times the upper limit of normal, and receipt of an investigational drug in the previous 30 days.

Patients were allowed, but not required, to be on erythropoietic hormone therapy and the dose was allowed to be modified in accordance with each site's established protocol for therapy.

Serum aluminum and parathyroid hormone concentrations and occult blood in the stool were determined at screening. Serum chemistries, prothrombin time, and activated partial thromboplastin times were obtained prior to drug administration, and repeated one week following completion of the dosing regimen. A complete blood count and measures of body iron status (serum iron, total iron binding capacity, transferrin saturation, ferritin, and transferrin) were obtained at screening and weekly for 8 weeks following the first dose, using routine clinical chemistry and hematology testing

The study drug, ferumoxytol (Advanced Magnetics, Inc.), is a superparamagnetic iron oxide (magnetite) nanoparticle coated with a semi-synthetic carbohydrate designed to minimize immunologic sensitivity. The drug has an average colloidal particle size of 30 nm by light scattering and a molecular weight of 750 kD. Ferumoxytol is a sterile liquid formulated to contain 30 mg/mL of elemental iron and 44 mg/mL of mannitol. It is isotonic and neutral pH.

Patients were to receive either 4 intravenous doses of ferumoxytol at 255 mg of iron (group 1) or 2 intravenous doses of ferumoxytol at 510 mg of iron (group 2). All patients in group 1 were dosed and evaluated for safety prior to enrolling any patients in group 2. Group 1 doses were given every 2 to 3 days, while group 2 doses were administered one week apart. An intravenous line (butterfly) was placed into a peripheral vein and 0.9% NaCl was infused to keep the vein open. The appropriate dose of ferumoxytol was administered by intravenous injection into the peripheral vein at a rate of 1 mL/sec (30 mg/sec) (i.e., 9 seconds for the 255 mg dose or 17 seconds for the 510 mg dose). A 10 to 20 mL normal saline intravenous flush was given after drug administration.

Safety monitoring during drug administration included measurement of blood pressure, heart rate, respiratory rate, and oral temperature prior to drug administration, and repeated at 15, 30, and 60 minutes after ferumoxytol administration, as well as at weekly visits for 8 weeks thereafter, along with evaluation for adverse events. Adverse events were defined as illnesses, signs, or symptoms that appeared or worsened after the implementation of study procedures; evaluated as serious or not serious; as mild, moderate, or severe; as definitely, probably, possibly, unlikely, or definitely not related to drug administration.

Primary efficacy outcomes included changes from baseline of hemoglobin, transferrin saturation, and serum ferritin levels. The time to maximum response was evaluated, as well as epoetin alfa and darbepoetin alfa dosing regimens in the 4 weeks prior to and 8 weeks post ferumoxytol administration. Safety data were gathered and adverse events noted and evaluated for their association

Table 1. Subject demographic and baseline clinical values

	Dose groups		
	4 × 255 mg (N = 10)	2 × 510 mg (N = 11)	Total (N = 21)
Gender	4M/6F	5M/6F	9M/12F
Age	68.9 ± 10.4 (51–86)	58.0 ± 17.8 (28–78)	63.2 ± 15.4 (28–76)
Race (white/black/Hispanic)	9/1/0	7/3/1	16/4/1
Serum creatinine *mg/dL*	5.5 ± 4.2 (1.5–15.4)	3.2 ± 1.6 (0.6–6.0)	4.3 ± 3.3 (0.6–15.4)
Hemoglobin *g/dL*	10.9 ± 1.3 (8.8–12.6)	10.0 ± 1.3 (8.3–12.7)	10.4 ± 1.3 (8.3–12.7)
Ferritin *ng/mL*	252 ± 259 (74–782)	266 ± 215 (2–637)	232 ± 216 (2–782)
Transferrin saturation %	20.2 ± 7.3 (14–36)	21.0 ± 9.8 (3–35)	21 ± 10 (3–47)
GFR *mL/min/1.73m^2*	15 ± 14 (4–38)	31 ± 31[a] (10–117)	23 ± 25[a] (4–117)
CKD stage 1/2/3/4/5	0/0/1/4/5	1/0/2/6/2	1/0/3/10/7

GFR, glomerular filtration rate, as estimated by the Modification of Diet in Renal Disease formula, (http://www.hdcn.com/calcf/gfr.htm). Values are given as mean ± standard deviation. The range is stated in parentheses.

[a]One patient with membranous nephropathy had a creatinine of 0.6 and GFR of 117. If this patient is excluded, the 2 × 510 group averages 23 ± 14 (10–53) and the combined group is 19 ± 12 (4–53).

with ferumoxytol. Efficacy data were evaluated for each individual dosing group as well as the combination of both groups.

Statistics

All results are expressed as mean ± standard deviation. Changes from baseline for the hematologic and iron parameters were examined over time using one-way repeated measures analysis of variance (ANOVA), with post-hoc Dunnet's test.

RESULTS

Twenty-one patients enrolled and completed this study, 18 of whom were predialysis CKD patients and 3 patients (all in group 1) who were receiving chronic peritoneal dialysis therapy. Of the 21 patients, 20 had a history of hypertension, 14 with diabetes, and 2 with polycystic kidney disease. The 10 patients in group 1 (4 × 255 mg iron) received 40 doses of ferumoxytol and the 11 patients in group 2 (2 × 510 mg iron) received 22 doses of ferumoxytol. All patients completed dosing as planned. Patient demographics and baseline clinical characteristics are presented in Table 1. Group 1 patients had a higher hemoglobin (10.9 g/dL) at baseline than group 2 (10.0), but this difference was not statistically significant.

Hematologic parameters and measures of iron status are presented in Table 2, including baseline and maximal values, and the time in weeks at which the peak response was observed. Since the 2 dosing groups received the same total iron dosage, they were also combined to form 1 group for statistical analysis. Changes in iron status as reflected in ferritin and transferrin saturation (Figs. 1 and 2) were maximal after 1 to 2 weeks, as was the reticulocyte count, while hemoglobin and hematocrit peaked later, at 5 to 6 weeks. Nine patients exhibited transient ferritin values over 1000 (4 in group 1, 5 in group 2). At 8 weeks after dosing was completed, 2 patients still had ferritin values greater than 1000, while the other 7 patients had ferritin values that had decreased toward baseline. The mean maximal change in hemoglobin concentration (at 6 weeks after ferumoxytol administration) was 1 g/dL (Fig. 3). Although the 2 groups had different baseline hemoglobin values, the hemoglobin response was parallel and equivalent in magnitude. Among the individual patients, 8 patients in each group exhibited an increase in hemoglobin of greater than 0.5 g/dL. The maximum increase in reticulocyte count was seen at 2 weeks.

In the 4-week period prior to ferumoxytol administration, 13 of the subjects received stable hematopoietic hormone therapy (10 subjects received epoetin alfa, 3 patients received darbepoetin alfa), while 8 subjects did not receive either treatment (Table 3). In the 8 weeks after ferumoxytol dosing, 15 patients had their dosing regimens unchanged, 4 patients had their mean weekly doses decreased, and 2 patients had increases in their mean weekly doses, 1 from 2000 to 3450 units (with no change in hemoglobin concentration after ferumoxytol therapy) and 1 from 10,000 to 20,000 units (with a maximal change in hemoglobin post-ferumoxytol therapy of 0.7 g/dL, less than the mean change in the 2 dosing groups). In patients receiving epoetin alfa, the pre-ferumoxytol mean weekly dosage was 9650 units, compared with the mean weekly dose post-ferumoxytol dosage of 9100 units, not statistically different. The mean weekly darbepoetin dosage decreased from 30 μg to 27.8 μg after ferumoxytol administration, not statistically different.
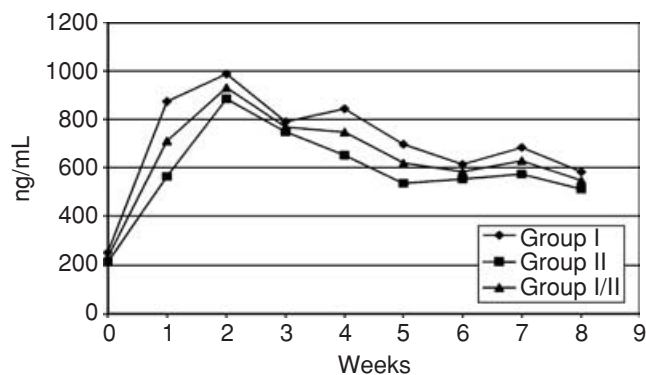
Table 2. The hematologic and iron indices responses to ferumoxytol compared with baseline

	Group	Baseline	Peak	Time to peak
Hematocrit %	4 × 255 mg (N = 10)	33.9 ± 3.3	36.3 ± 2.2	6 weeks
	2 × 510 mg (N = 11)	30.3 ± 3.4	33.5 ± 3.8	5 weeks
	Total (N = 21)	32.0 ± 3.8	34.8 ± 3.4[a]	5 weeks
Hemoglobin g/dL	4 × 255 mg (N = 10)	10.9 ± 1.3	11.8 ± 0.7	4 weeks
	2 × 510 mg (N = 11)	10.0 ± 1.3	11.0 ± 1.4	6 weeks
	Total (N = 21)	10.4 ± 1.3	11.4 ± 1.2[a]	6 weeks
Reticulocyte count %	4 × 255 mg (N = 10)	1.8 ± 0.6	2.1 ± 1.0	2 weeks
	2 × 510 mg (N = 11)	1.7 ± 0.9	2.6 ± 1.4	2 weeks
	Total (N = 21)	1.74 ± 0.8	2.36 ± 1.3	2 weeks
Ferritin ng/mL	4 × 255 mg (N = 10)	252 ± 259	988 ± 353[a]	2 weeks
	2 × 510 mg (N = 11)	212 ± 177	885 ± 378[a]	2 weeks
	Total (N = 21)	232 ± 216	931 ± 361[a]	2 weeks
Transferrin saturation %	4 × 255 mg (N = 10)	20 ± 7	40 ± 8[a]	1 week
	2 × 510 mg (N = 11)	22 ± 12	35 ± 14[a]	2 weeks
	Total (N = 21)	21.3 ± 10	37.2 ± 22.1[a]	1 week

[a] $P < 0.05$ compared with baseline value. None of the values for group 1 were different from those of group 2.
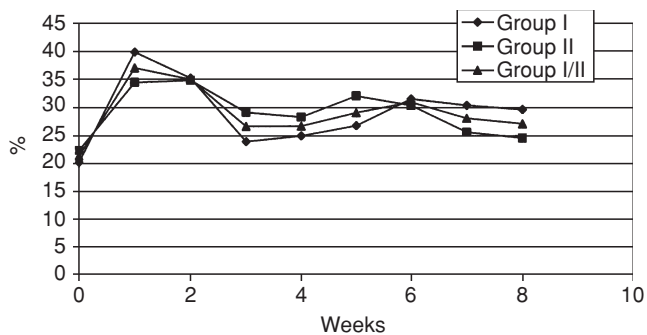
Fig. 1. TSAT response to ferumoxytol.

Fig. 2. Ferritin response to ferumoxytol.

The only statistically significant change in vital signs was a decrease of the mean heart rate in the 4 × 255 mg dose group from 73 to 68 following ferumoxytol dosing. Routine serum chemistry values (apart from ferritin and transferrin saturation) were unchanged in the postdose observation period. There were a total of 7 nonserious adverse events in 5 patients that were deemed possibly related to ferumoxytol; no adverse event was considered to be definitely or likely related, and none led to discontinuation of dosing. These included solitary instances of mild constipation a day later (group 1), mild chills an hour after dosing (group 2), mild tingling a day after dosing (group 1), moderate gastrointestinal upset of presumed viral etiology a day after dosing (group 1), mild delayed pruritic, erythematous rash 3 days after dosing (group 2), and mild pain at the injection site that resolved after reinsertion of the intravenous line in a different site (group 2). No adverse event led to discontinuation of dosing.

DISCUSSION

Ferumoxytol was effective in rapidly increasing measures of body iron status (ferritin and transferrin saturation), in both dosing groups, with a maximal effect seen at 1 to 2 weeks. These increases demonstrate that the
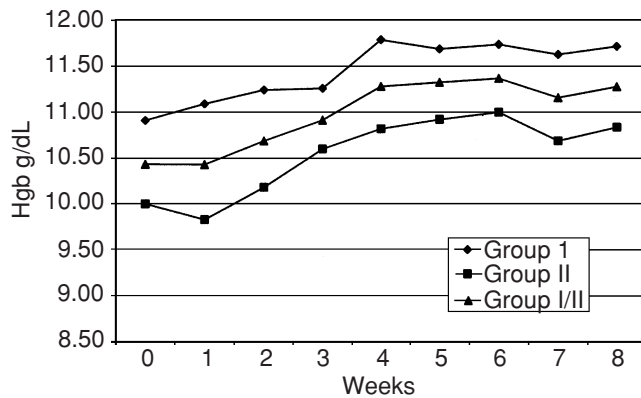
Fig. 3. Hemoglobin response to ferumoxytol.

iron contained in ferumoxytol is bioavailable, and is used to promote increased hemoglobin synthesis and reticulocytosis. Ferumoxytol administration was effective in stimulating erythropoiesis without a significant increase in dosage of hematopoietic hormone therapy, and in patients who had "normal" body iron stores (as evidenced by the mean serum ferritin concentration of 232 ng/mL and mean transferrin saturation of 21%). For the combined groups there was a mean increase in hemoglobin of 1 g/dL, maximally manifested at 6 weeks, while for the individual dosing groups there was a similar and parallel change. This is in keeping with the concept of functional iron deficiency, seen frequently in patients with chronic kidney disease, and which is responsive to exogenous iron.

This study demonstrates that ferumoxytol can be administered as a rapid bolus of 30 mg of iron per second in a concentrated form of 30 mg/mL, and in a dosage of up to 510 mg. In contrast, both iron sucrose and ferric sodium gluconate require a much slower rate of administration and/or much lower dose, mandating a longer period of time and more clinic visits to administer equivalent doses. Thus, ferumoxytol has the advantage of requiring fewer patient visits and a shorter administration time than these commonly used iron therapies, with benefit to the clinician, ancillary staff, and patient.

A preparation of iron dextran, which was recalled by the FDA in 1990, was the first available parenteral iron preparation in the United States. Intravenous infusion rates of 100 to 300 mg/min have been reported [15], although subsequently a maximum rate of 100 mg/minute was recommended [16]. Typical dosages reported ranged from 500 to 3000 mg, although it is not clear how many of the almost 2400 patients actually received (and tolerated) the higher dosages/infusion rates. Since serious adverse reactions to iron dextran may be induced by relatively low doses, it is not possible to accurately describe serious adverse reaction rates in this relatively small cohort.

Iron sucrose has been administered intravenously and undiluted in dosages of 100 to 200 mg (5–10 mL) over a 5-minute period with relative safety, and in a dosage of up to 500 mg diluted in 250 to 500 mL over a 2- to 6-hour dosing duration [3–5, 12, 17–22]. One small, uncontrolled study concluded that a regimen of iron sucrose 500 mg intravenously over a 2-hour duration had an unacceptably high rate of adverse effects (e.g., hypotension requiring hospitalization) [23]. In contrast, a study evaluating the same dosing regimen in peritoneal dialysis patients noted no adverse drug effects [18].

Sodium ferric gluconate has generally been diluted in 100 mL of 0.9% sodium chloride, at a dose of 125 mg, and given intravenously over a 10-minute interval. Recently, experience has been reported with 250 mg and up to 500 mg dosages (not FDA approved), generally given at slower administration rates (up to 5 hours). While one study concluded that this could be done without apparent adverse effects [24], others have noted significant untoward reactions (e.g., severe nausea/vomiting, hypotension, and syncope) in 10% to 30% of patients with this dosing regimen [25, 26]. If our data and experience with ferumoxytol are confirmed in larger cohorts, ferumoxytol would clearly represent an improvement in the logistic aspects of intravenous iron delivery.

All adverse events considered possibly related to ferumoxytol in this open label, uncontrolled study were mild to moderate, and qualitatively similar to other iron preparations. No adverse event was serious, and none were considered definitely or likely related to drug administration. Anaphylaxis and immediate hypotension were not observed in this small study, but the number of exposures is too small to draw any definitive conclusions. Other small studies of ferumoxytol in normal subjects, hemodialysis patients, and patients undergoing cardiovascular MRI have reported nausea and metallic taste, respectively [13; abstract; Jacobs P et al: *J Am Soc Nephrol* 14:27A, 2003].

The current study was of relatively short duration (less than 12 weeks), and, thus, was not designed to address the question of potential chronic toxicities of ferumoxytol. With other parenteral iron preparations, the risks of increased infection rates and oxidative stress have been noted as possible toxicities. A recent review concluded, however, that no studies exist that provide reliable conclusions linking parenteral iron therapy and infection in dialysis patients [27]. While oxidative stress may be linked to cardiovascular morbidity and mortality, careful monitoring and avoidance of excessive serum ferritin levels may minimize this risk [27].

CONCLUSION

Intravenous ferumoxytol in a dosage of up to 510 mg can be given safely as a rapid intravenous bolus. It is effective in providing bioavailable iron to increase body iron stores, as evidenced by improvements in ferritin and

Table 3. Summary of erythropoietin dosing by dose group and time point

Time point Descriptive statistics	Ferumoxytol		
	4 × 255 mg iron	2 × 510 mg iron	Total
Baseline	$N = 10$	$N = 11$	$N = 21$
Mean ± SD	7200.0 ± 8066.4	6272.7 ± 9381.8	6714.3 ± 8574.0
Day 7 (week 1)	$N = 10$	$N = 11$	$N = 21$
Mean ± SD	7000.0 ± 8232.7	4090.9 ± 7435.8	5476.2 ± 7769.3
Change from baseline (mean ± SD)	−200.0 ± 632.5	−2181.8 ± 12944.6	−1238.1 ± 9219.0
Day 14 (week 2)	Not recorded	$N = 9$	$N = 10$
Mean ± SD		6111.1 ± 9360.1	5500.0 ± 9033.9
Change from baseline (mean ± SD)		−1555.6 ± 9043.1	−1400.0 ± 8540.1
Day 21 (week 3)	$N = 10$	$N = 9$	$N = 19$
Mean ± SD	9245.0 ± 8015.3	3888.9 ± 7912.7	6707.9 ± 8215.8
Change from baseline (mean ± SD)	2045.0 ± 5590.5	−2666.7 ± 8000.0	−186.8 ± 7064.9
Day 28 (week 4)	$N = 10$	$N = 11$	$N = 21$
Mean ± SD	7745.0 ± 8219.6	5000.0 ± 8729.3	6307.1 ± 8395.0
Change from baseline (mean ± SD)	545.0 ± 8788.5	−1272.7 ± 8112.8	−407.1 ± 8278.3
Day 35 (week 5)	$N = 10$	$N = 7$	$N = 17$
Mean ± SD	7745.0 ± 8219.6	4428.6 ± 7345.2	6379.4 ± 7814.5
Change from baseline (mean ± SD)	545.0 ± 8788.5	−2000.0 ± 10392.3	−502.9 ± 9252.7
Day 42 (week 6)	$N = 10$	$N = 10$	$N = 20$
Mean ± SD	4745.0 ± 6689.6	3000.0 ± 6342.1	3872.5 ± 6407.1
Change from baseline (mean ± SD)	−2455.0 ± 6479.3	−1500.0 ± 8527.7	−1977.5 ± 7387.4
Day 49 (week 7)	$N = 10$	$N = 9$	$N = 19$
Mean ± SD	4745.0 ± 6689.6	4444.4 ± 6839.4	4602.6 ± 6571.8
Change from baseline (mean ± SD)	−2455.0 ± 6479.3	−555.6 ± 9837.6	−1555.3 ± 8059.3
Day 56 (week 8)	$N = 10$	$N = 6$	$N = 16$
Mean ± SD	6795.0 ± 6467.3	3333.3 ± 8165.0	5496.9 ± 7093.2
Change from baseline (mean ± SD)	−405.0 ± 5019.0	−2333.3 ± 11343.1	−1128.1 ± 7676.8

transferrin saturation, and in raising hemoglobin levels in anemic CKD patients. Compared with other parenteral iron preparations, it may provide efficiencies of time, and perhaps cost, for patients and clinicians. Definitive conclusions, including chronic toxicities, will be drawn based upon the results of larger clinical trials, currently in progress.

REFERENCES

1. NATIONAL KIDNEY FOUNDATION: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Am J Kidney Dis* 39(Suppl 1):S1–S266, 2002
2. SILVERBERG DS, IAINA A, PEER G, *et al*: Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. *Am J Kidney Dis* 27:234–238, 1996
3. SILVERBERG DS, BLUM M, AGBARIA Z, *et al*: Intravenous iron for the treatment of predialysis anemia. *Kidney Int* 69:S79–S85, 1999
4. MACDOUGALL IC, TUCKER B, THOMPSON J, *et al*: A randomized controlled study of iron supplementation in patients treated with erythropoietin. *Kidney Int* 50:1694–1699, 1996
5. SILVERBERG DS, IAINA A, PEER G, *et al*: Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. *Am J Kidney Dis* 27:234–238, 1996
6. BURNS DL, POMPOSELLI JJ: Toxicity of parenteral iron dextran therapy. *Kidney Int* 69:S119–S124, 1999
7. FISHBANE S, UNGUREANU VD, MAESAKA JK, *et al*: The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 28:529–534, 1996
8. HAMSTRA RD, BLOCK MH, SCHOCKET AL: Intravenous iron dextran in clinical medicine. *JAMA* 243:1726–1731, 1980
9. AUERBACH M, WITT D, TOLER W, *et al*: Clinical use of the total dose intravenous infusion of iron dextran. *J Lab Clin Med* 111:566–570, 1988
10. CHERTOW GC, MASON PD, VAAGE-NILSEN O, AHLMEN J: On the relative safety of parenteral iron preparations. *Nephrol Dial Transplant* 19:1571–1575, 2004
11. WATSON PHARMA, INC.: Ferrlecit® 2001 package insert, 2001
12. AMERICAN REGENT: Venofer® product package insert, 2005
13. PRINCE MR, ZHANG HL, CHABRA SG, *et al*: A pilot investigation of new superparamagnetic iron oxide (ferumoxytol) as a contrast agent for cardiovascular MRI. *J X Ray Science Technol* 11:231–240, 2003
14. ERSOY H, JACOBS P, KENT CK, *et al*: Blood pool MR angiography of aortic stent-graft endoleak. *AJR Am J Roentgenol* 182:1181–1186, 2004
15. MARCHASIN S, WALLERSTEIN RO: The treatment of iron-deficiency anemia with intravenous iron dextran. *Blood* 23:354–358, 1964
16. WALLERSTEIN RO: Intravenous iron-dextran complex. *Blood* 32:690–695, 1968
17. AL-MOMEN AM, HURAIB SO, MITWALLI AH, *et al*: Intravenous iron saccharate in hemodialysis patients receiving r-HuEPO. *Saudi J Kidney Dis Transplant* 5:168–172, 1994
18. DOMRONGKITCHAIPORN S, JIRAKRANONT B, ATAMASRIKUL K, *et al*: Indices of iron status in continuous ambulatory peritoneal dialysis patients. *Am J Kidney Dis* 34:29–35, 1999
19. PRAKASH S, WALELE A, DIMKOVIC N, *et al*: Experience with a large dose (500 mg) of intravenous iron dextran and iron saccharate in peritoneal dialysis patients. *Perit Dial Int* 21:290–295, 2001

20. AGGARWAL HK, TZIVISKOU E, BELLIZZI V, *et al*: Prolonged administration over six hours of large doses of intravenous iron saccharate (500 mg) prevents severe adverse reactions in peritoneal dialysis patients. *Perit Dial Int* 22:636–637, 2002

21. SCHWENK MH, BLAUSTEIN DA: Rapid, high-dose intravenous iron sucrose therapy in 2 Jehovah's Witness patients with chronic kidney disease. *Clin Nephrol* 62:116–120, 2004

22. BLAUSTEIN DA, SCHWENK MH, CHATTOPADHYAY J, *et al*: The safety and efficacy of an accelerated iron sucrose dosing regimen in patients with chronic kidney disease. *Kidney Int* 63(Suppl 87):S72–S77, 2003

23. CHANDLER G, HARCHOWAL J, MACDOUGALL IC: Intravenous iron sucrose: Establishing a safe dose. *Am J Kidney Dis* 38:988–991, 2001

24. FOLKERT VW, MICHAEL B, AGARWAL R, *et al*: Chronic use of sodium ferric gluconate complex in hemodialysis patients: Safety of higher-dose (≥250 mg) administration. *Am J Kidney Dis* 41:651–657, 2003

25. BASTANI B, JAIN A, PANDURANGAN G: Incidence of side-effects associated with high-dose ferric gluconate in patients with severe chronic renal failure. *Nephrology* 8:8–10, 2003

26. DANDA RS, KIRK LJ, PERGOLA PE: High-dose iron gluconate in chronic kidney disease patients. *Nephrology* 9:47–48, 2004

27. ARONOFF GR: Safety of intravenous iron in clinical practice: Implications for anemia management protocols. *J Am Soc Nephrol* 15:S99–S106, 2004