Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial

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BACKGROUND: The objective was to evaluate efficacy and safety of rapid, large-dose intravenous (IV) administration of ferric carboxymaltose compared to oral iron in correcting iron deficiency anemia due to heavy uterine bleeding.

STUDY DESIGN AND METHODS: In a randomized, controlled trial, 477 women with anemia, iron deficiency, and heavy uterine bleeding were assigned to receive either IV ferric carboxymaltose (≤1000 mg over 15 min, repeated weekly to achieve a total calculated replacement dose) or 325 mg of ferrous sulfate (65 mg elemental iron) prescribed orally thrice daily for 6 weeks.

RESULTS: Compared to those assigned to ferrous sulfate, more patients assigned to ferric carboxymaltose responded with a hemoglobin (Hb) increase of 2.0 g/dL or more (82% vs. 62%, 95% confidence interval for treatment difference 12.2-28.3, p < 0.001), more achieved a 3.0 g/dL or more increase (53% vs. 36%, p < 0.001), and more achieved correction (Hb = 12 g/dL) of anemia (73% vs. 50%, p < 0.001). Patients treated with ferric carboxymaltose compared to those prescribed ferrous sulfate reported greater gains in vitality and physical function and experienced greater improvement in symptoms of fatigue (p < 0.05). There were no serious adverse drug events.

CONCLUSIONS: In patients with iron deficiency anemia due to heavy uterine bleeding, rapid IV administration of large doses of a new iron agent, ferric carboxymaltose, is more effective than oral iron therapy in correcting anemia, replenishing iron stores, and improving quality of life.

BACKGROUND: Heavy uterine bleeding affects women from adolescence through late reproductive years, affecting 3% to 6% of the 60,000,000 women of reproductive age in the United States.1-4 Although pharmacologic treatment is effective in some and hysterectomy definitive in all,5 women seeking care commonly report symptom duration in years.5,6 Quality-of-life deficits, both physical and emotional, are significant.7 Anemia is a common and often severe complication that is potentially treatable with iron therapy.8 Little information is available, however, to assist medical decision-making in managing the anemia of heavy uterine bleeding. Specifically, evidence is lacking on the contribution of anemia to menorrhagia-related quality-of-life deficits, the benefit of iron replacement therapy to outcomes of direct importance to patients, and the comparative efficacy and safety of oral and intravenous (IV) iron agents.

Although short-term oral administration of ferrous salts has been repeatedly shown to correct iron deficiency

ABBREVIATION: CHr = reticulocyte hemoglobin content.

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TRANSFUSION **,** **
anemia in adherent patients without ongoing blood loss,
the clinical utility of oral iron therapy in managing anemia in
patients with heavy uterine bleeding has not been
established. Since oral iron absorption is limited even in
iron-deficient patients, ongoing blood losses prevent
definitive management of iron deficiency anemia by oral
iron agents in this setting. A high incidence of adverse
gastrointestinal effects, incomplete adherence to pre-
scribed therapy, and the likely need for long-term
administration of high iron doses present additional sig-
nificant barriers to treatment with oral iron. Evidence to
support use of IV iron therapy in this patient population is
similarly lacking. Currently available IV iron agents pose
significant safety and practical challenges. Iron dextran
administration risks life-threatening anaphylaxis and
requires administration of a test dose with resuscitation
medication and resources on hand. Currently available
non–dextran-containing IV iron agents, on the other
hand, are not Food and Drug Administration approved
except in patients with chronic kidney disease and must
be given in small doses over multiple administrations to
avoid precipitating hypotension, cramping, and nausea.

A novel IV iron agent, ferric carboxymaltose, is a non–
dextran-containing investigational drug designed to be
administered in large doses by rapid IV injection. The
ability to safely inject a single dose as large as 1000 mg in
as little as 15 minutes, without a test dose, makes ferric
carboxymaltose a potentially ideal candidate for treating
anemia associated with heavy uterine bleeding. We con-
ducted a randomized, controlled trial to evaluate whether
IV ferric carboxymaltose is more effective than oral ferrous
sulfate in the management of anemia associated with
heavy uterine bleeding.

MATERIALS AND METHODS

This was an open-label, Phase 3, randomized, active-
control clinical trial with two parallel treatment groups
conducted at 79 sites in the United States and five in
Mexico. Eligible patients were 18 years or older with
anemia, defined as a hemoglobin (Hb) level of 11.0 g/dL
or less, and heavy uterine bleeding, defined as at least one
of the following: inability to control flow with tampons
alone, use of more than 12 pads per period or four
tampons per day, passage of clots, or persistence of flow
longer than 7 days. Additional eligibility criteria included
use of adequate birth control, serum transferrin satura-
tion of 25% or less, and serum ferritin level of 100 ng/mL
or less. Exclusion criteria included red blood cell (RBC)
transfusion or parenteral iron administration within the
prior 8 weeks or anticipated need for blood transfusion
during the study, existing disorders of erythropoiesis,
hemochromatosis, initiation of hormonal therapy poten-
tially affecting uterine bleeding in the 8 weeks before
study entry, use of erythropoiesis-stimulating agents
within the prior 12 weeks, postmenopausal patients
without an endometrial biopsy within the prior 6 months,
malignancy, endometrial hyperplasia with atypia, alcohol
or drug abuse, myelosuppressive therapy, evidence of
chronic viral infection (hepatitis B surface antigen, hepa-
titis C virus antibody, or human immunodeficiency virus),
a serum transaminase level of greater than 1.5 times the
upper limit of normal, or a serum creatinine level of more
than 2.0 mg/dL.

The first subject was enrolled in May 2005, and the
last completed the study in April 2006. We randomly
assigned patients in a 1:1 ratio to receive either IV ferric
carboxymaltose (Injectafer, American Regent, Inc., Shirley,
NY) or oral ferrous sulfate. Randomization was stratified
by Hb level (9.6-11.0, 8.1-9.5, or ≤8.0 g/dL) and by degree
of uterine bleeding during the past 28 days (mild/modu-
rate, severe, or very severe) as judged by the investi-
gator and presence or absence of a poor response to prior
oral iron therapy. Treatment group and subject number
were assigned by blocked randomization using an inter-
active voice response system as previously described by
Van Wyck and colleagues.

All subjects provided written informed consent. The
study protocol was approved by local ethics committees.
The study was conducted in accordance with good clinical
practice guidelines and the Declaration of Helsinki.

A priori rules required premature withdrawal if a
safety intervention for management of anemia was given.
We defined an anemia safety intervention as an RBC
transfusion, initiation of epoetin alfa or darbepoetin alfa,
iron administration not included in the study protocol, or
a new medication or procedure to decrease degree of
uterine bleeding. With the exception of oral iron supple-
ments, medication prescribed before enrollment was
continued throughout the study. Subjects who wished to
withdraw from the study could do so at any time without
the need to justify the decision, and investigators could
withdraw a subject at any time if it was felt to be in the best
interest of the subject. In the analysis of efficacy and
safety, we included data in each patient up to the time of
withdrawal.

Ferric carboxymaltose was supplied as 10-mL single-
dose vials, containing 500 mg of elemental iron in a solu-
tion of sterile water for injection (50 mg/mL). We
 calculated the total iron dose needed to correct anemia and
 replenish iron stores using a modified Ganzoni for-
mula and administered the total dose in separate injec-
tions on Study Day 0 and, if needed, Days 7 and 14.

Patients assigned to oral iron received ferrous sulfate
as 325-mg tablets (65 mg of elemental iron) with instruc-
tions to take 1 tablet by mouth three times daily with 8
ounces of tap water, 1 hour before meals from Day 0 until
Day 42. We monitored adherence to prescribed therapy
and provided repeated counseling at each visit if less than
100% adherence was noted.

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Our hypothesis was that IV ferric carboxymaltose would be more effective than oral ferrous sulfate in the correction of iron deficiency anemia secondary to heavy uterine bleeding. We chose ferrous sulfate as the comparator because administration of a ferrous salt is the accepted standard of care for treatment of iron deficiency anemia in this patient population.

The primary efficacy endpoint was the proportion of subjects with a Hb increase of 2.0 g/dL or more after treatment. Secondary measures of efficacy included change in Hb from baseline by visit; the proportion of subjects attaining a Hb level of more than 12.0 g/dL (correction of anemia); the proportion achieving an increase in Hb of 3.0 g/dL or more; time to achieve the primary outcome; peak Hb increase from baseline; time to peak Hb increase; maximum increase in ferritin, transferrin saturation, reticulocyte count, or reticulocyte Hb content (CHR); number of subjects requiring intervention; time to intervention; proportion of subjects with a Hb increase of 2.0 g/dL or more combined with a ferritin increase of 160 ng/mL or more; and proportion of patients with improved quality of life. No patients who received treatment were excluded from analysis.

We used a central laboratory for all analyses of outcomes. We used local laboratories and point-of-care testing to determine Hb values needed to qualify for randomization or to calculate total iron dose to be administered.

We assessed the effect of anemia associated with heavy uterine bleeding on health-related quality of life using the SF-36 v217 and the Fatigue Linear Analog Scale Assessment.18 Patients were randomly assigned on Day 0, and the quality-of-life questionnaires were self-administered on Days 0, 14, 28, and 42.

To assess safety, we monitored blood pressure and recorded adverse events before, during, and after each administration of IV iron. The reporting, recording, assessment of possible drug-related hypersensitivity, and grading of adverse events was conducted as described previously.15

We based estimates of statistical power and sample size on findings from previous studies.19,20 using a two-sided Fisher’s exact test and a 5% significance level. Given 390 enrolled patients, we estimated that the study would have at least an 85% power to detect a 25% IV ferric carboxymaltose treatment effect compared to oral ferrous sulfate. We evaluated the time to achieve secondary endpoints using Kaplan-Meier survival curves and examined for treatment group differences using the log-rank test incorporating a life table approach.

We used Fisher’s exact test to determine the effect of treatment assignment on the proportion of patients achieving the primary endpoint and to assess between-group differences in categorical baseline characteristics (sex, race). To assess the effect of treatment on between-group differences in the change from baseline in secondary endpoints, including laboratory findings, SF-36 scale scores, SF-36 summary scores, and fatigue linear analogue scores, we used repeated measures analysis, assigning significance at the 5% significance level. To evaluate within-group differences we used paired t tests. We used linear regression with Pearson’s correlation to examine the relationship between baseline serum phosphate and change in serum phosphate.

**RESULTS**

A total of 477 subjects were randomly assigned to receive IV ferric carboxymaltose or oral ferrous sulfate (Fig. 1). Completion rates exceeded 90% in both groups. Reasons for study discontinuation are listed in Table 1. Baseline characteristics were similar between the two treatment groups (Table 2). Approximately 70% of patients in each group reported a history of oral iron use at the time of enrollment. More than 50% of patients in each group were judged to have severe or very severe uterine bleeding.

Adherence, defined as milligrams received as a percentage of milligrams prescribed, was greater among patients assigned to IV iron compared to those assigned to oral iron (mean percent adherence, 99.9 ± 1.2% vs. 90.3 ± 2.5%, mean ± 95% confidence interval [CI], p < 0.001). Dose reductions due to adverse drug events were seen in one patient receiving IV ferric carboxymaltose and 27 patients receiving oral ferrous sulfate. Of 129 patients in the oral iron group who showed less than 100% adherence unrelated to adverse events, 121 received counseling about the importance of taking the prescribed treatment from study personnel.

**Efficacy**

A greater proportion of patients assigned to IV ferric carboxymaltose, compared to those assigned to oral iron, achieved the primary endpoint, an increase in Hb level of 2.0 g/dL or more, within 42 days after baseline (82.0% vs. 61.8%; 95% CI of treatment difference, 12.2%-28.3%; p < 0.001). Between-group differences were significant at each study visit (Fig. 2). The proportion of patients meeting the primary endpoint was unrelated to baseline degree of anemia, severity of uterine bleeding, race, age, or history of prior response to oral iron. In patients assigned to the IV ferric carboxymaltose group, the erythropoietic response (Hb, hematocrit, reticulocytes, mean corpuscular volume, mean corpuscular Hb, and CHr) was significantly better as early as Day 7 (Fig. 3); the proportion of patients who achieved an increase in Hb level of 3.0 g/dL or greater was greater at each treatment interval after Day 14 (Fig. 2); the proportion of patients who experienced an increase in Hb level of more than 12.0 g/dL was greater
Serum ferritin increased promptly in the IV ferric carboxymaltose group but increased only slightly in the oral iron group. Differences between groups were significant at each study interval (Fig. 3). Transferrin saturation increased significantly at every interval in both groups but with little between-group difference, because the oral iron treatment group showed a more pronounced increase in serum iron but a less pronounced fall in total iron binding capacity.

After initiation of treatment, patients in both treatment groups showed broad improvement in health-related quality-of-life scores (Fig. 4). Compared to patients assigned to oral iron treatment, patients assigned to IV ferric carboxymaltose showed greater improvement in the physical component summary of SF-36, primarily due to greater responses in Physical Functioning, Vitality, and Role-Physical components. IV ferric carboxymaltose-treated patients also showed improved resolution of fatigue in the linear analog scale assessment.

The clinical course of one of the patients randomly assigned to receive ferric carboxymaltose, illustrated in Fig. 5, is instructive. Patient 42001 received two doses totaling 2000 mg on Days 0 and 7. Despite ongoing heavy uterine bleeding, the initial increase in ferritin reflects incorporation of ferric carboxymaltose into reticuloendothelial iron stores, followed by a decrease in ferritin reflecting mobilization of reticuloendothelial iron concurrent with the erythropoietic response. The patient’s Hb level began to increase on Day 14 from a nadir of 7.3 to 9.1 g/dL.

(72.8% vs. 49.8%, 95% CI of treatment difference, 14.3-31.7; p < 0.001).

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on Day 28; had a definitive surgical procedure been performed on Day 28, this patient would have received a combination of effective medical and surgical therapy without the necessity of blood transfusion therapy. Instead, in the absence of definitive surgical therapy, the heavy uterine bleeding continued and the patient’s Hb level declined to 6.9 g/dL on Day 42. This case illustrates how large doses of IV ferric carboxymaltose can effectively manage iron deficiency anemia in the setting of ongoing, heavy uterine bleeding.

Safety
Among patients evaluated for safety, the mean cumulative per-patient dose of IV ferric carboxymaltose administered was 1568 mg and the mean cumulative dose of oral iron was 7302 mg. There were 483 total injections of IV iron administered: five patients received only one infusion, 197 patients received two infusions, and 28 received three infusions. Of the 230 patients assigned to receive IV iron, 225 (97.8%) received total doses that exceeded 1000 mg, the equivalent amount of iron in 5 blood units.

### TABLE 2. Demographic and baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intention-to-Treat Population</th>
<th>IV ferric carboxymaltose (n = 228)</th>
<th>Oral ferrous sulfate (n = 225)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>Mean 38.7 ± 7.5</td>
<td>39.5 ± 7.6</td>
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<tr>
<td></td>
<td></td>
<td>Range 18-54</td>
<td>19-53</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td></td>
<td>113 (49.6)</td>
<td>104 (46.2)</td>
<td>0.833</td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td>63 (27.6)</td>
<td>60 (26.7)</td>
<td></td>
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<tr>
<td>Hispanic</td>
<td></td>
<td>46 (20.2)</td>
<td>57 (25.3)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>2 (0.9)</td>
<td>1 (0.4)</td>
<td></td>
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<tr>
<td>Other</td>
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<td>4 (1.8)</td>
<td>3 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>81.5 ± 22.7</td>
<td>84.0 ± 23.5</td>
<td>0.250</td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>162.2 ± 8.3</td>
<td>163.2 ± 8.3</td>
<td>0.175</td>
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<tr>
<td>Past surgery for heavy uterine bleeding</td>
<td></td>
<td>37 (16.2)</td>
<td>32 (14.2)</td>
<td>0.602</td>
</tr>
<tr>
<td>Current medications for heavy uterine bleeding</td>
<td></td>
<td>86 (37.7)</td>
<td>74 (32.9)</td>
<td>0.326</td>
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<tr>
<td>Iron therapy before study</td>
<td></td>
<td>157 (68.9)</td>
<td>157 (69.8)</td>
<td>0.839</td>
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<tr>
<td>Menstrual cycle</td>
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<td></td>
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<tr>
<td>Regular</td>
<td></td>
<td>147 (64.8)</td>
<td>167 (74.2)</td>
<td>0.908</td>
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<tr>
<td>Irregular</td>
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<td>78 (34.4)</td>
<td>53 (23.6)</td>
<td></td>
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<tr>
<td>Continuous</td>
<td></td>
<td>2 (0.9)</td>
<td>5 (2.2)</td>
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<tr>
<td>Missing</td>
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<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td></td>
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<tr>
<td>Degree of uterine blood loss</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate</td>
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<td>98 (43.0)</td>
<td>94 (41.8)</td>
<td></td>
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<tr>
<td>Severe</td>
<td></td>
<td>105 (46.1)</td>
<td>108 (48.0)</td>
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<tr>
<td>Very severe</td>
<td></td>
<td>25 (11.0)</td>
<td>23 (10.2)</td>
<td></td>
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<tr>
<td>Allergy to previous medication</td>
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<td>67 (29.4)</td>
<td>68 (30.2)</td>
<td>0.918</td>
</tr>
<tr>
<td>Baseline laboratory values</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hb (g/dL)</td>
<td></td>
<td>9.4 ± 1.2</td>
<td>9.4 ± 1.2</td>
<td>0.850</td>
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<tr>
<td>MCV (fL)</td>
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<td>76.4 ± 8.2</td>
<td>76.7 ± 8.5</td>
<td>0.647</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td></td>
<td>22.3 ± 3.2</td>
<td>22.5 ± 3.5</td>
<td>0.532</td>
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<tr>
<td>RDW (%)</td>
<td></td>
<td>17.4 ± 2.5</td>
<td>17.4 ± 2.5</td>
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<tr>
<td>Reticulocytes (%)</td>
<td></td>
<td>1.6 ± 1.0</td>
<td>1.6 ± 0.7</td>
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<tr>
<td>CHr (pg)</td>
<td></td>
<td>25.0 ± 3.2</td>
<td>25.0 ± 3.3</td>
<td>0.965</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td>338.4 ± 106.7</td>
<td>341.2 ± 107.5 (N = 223)</td>
<td>0.782</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td></td>
<td>6.9 ± 9.3</td>
<td>6.8 ± 8.8</td>
<td>0.881</td>
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<tr>
<td>Transferrin saturation (%)</td>
<td></td>
<td>5.8 ± 4.0</td>
<td>5.6 ± 3.6</td>
<td>0.577</td>
</tr>
</tbody>
</table>

* Data are reported as means ± SD or number (%).

MCH = mean corpuscular Hb; MCV = mean corpuscular volume; RDW = RBC distribution width.

Fig. 2. Proportion of patients achieving a Hb increase of more than 2.0 g/dL (● = primary endpoint) or 3.0 g/dL (●● = secondary endpoint) according to treatment assignment. Significant between-group differences:

*p < 0.05, **p < 0.01, ***p < 0.001.
No hypotensive or serious drug-related adverse events were reported in either treatment group. There were no deaths. Patients assigned to oral iron therapy were more likely to experience drug-related gastrointestinal complaints, particularly constipation (14.2% vs. 3.0%), diarrhea (4.4% vs. 1.7%), nausea (11.9% vs. 3.5%), and vomiting (3.1% vs. 0.4%), whereas those assigned to IV iron therapy were more likely to report transient fatigue (2.2% vs. 0%), headache (6.5% vs. 4.4%), dizziness (2.2% vs. 0.4%), dysgeusia (2.6% vs. 0.9%), and rash (2.2% vs. 0%). Most reported rashes were described as flushing or maculopapular, occurred during or immediately after iron administration, and resolved within minutes to 3 hours after IV iron administration. One rash was described as urticarial and resolved within 6 hours without treatment. Four patients received a second injection of IV iron after experiencing a rash after the first injection: of these, one experienced a recurrent pruritic rash that resolved within 2 hours. There was no difference between groups in the number of infections reported, and no infection was thought to be related to study drug.

Discontinuation of study drug due to adverse events occurred in five patients in the ferric carboxymaltose arm and seven patients in the oral iron arm. Four of the events experienced by subjects assigned to IV ferric carboxymaltose were considered related: two experienced mild rash, one met the protocol stopping rule for ferritin (>800 ng/mL; resolved by Study Day 28), and one experienced injection-site pain and peripheral edema. The fifth patient discontinued after experiencing unrelated noncardiac chest pain and an elevated white blood cell count, whereas all seven patients assigned to oral ferrous sulfate discontinued due to gastrointestinal complaints.

We observed a transient decrease in serum phosphate among patients in both the oral and the IV iron treatment groups. The change from baseline to lowest observed value was greater in the IV ferric carboxymaltose treatment group than in the oral iron group (Table 3). A nadir
phosphate level of less than 2.0 mg/dL occurred in no patient assigned to oral iron but in 157 (70%) of those assigned to IV ferric carboxymaltose. The lowest value of phosphate recorded was 0.9 mg/dL on Day 21 after IV ferric carboxymaltose in a patient whose baseline phosphate was 2.6 mg/dL. Among those who showed a nadir phosphate of less than 2.0 mg/dL, the median time from baseline to nadir by Kaplan-Meier estimate was 15 days and the median time from nadir to first value of 2.0 mg/dL or more was 18 days (p > 0.05). No patient in either treatment group evidenced complaints or findings consistent with hypophosphatemia. Although declines in mean serum potassium and serum calcium were seen in both treatment groups (Table 3), changes in these electrolytes were slight and transient and did not correlate with changes in serum phosphate. Serum creatinine was unchanged in both groups.

**DISCUSSION**

More than 6 million women of reproductive age in the United States are iron deficient, and more than 3 million women have iron deficiency anemia.2,22,23 Our results provide evidence that iron deficiency anemia in these women imposes a formidable disease burden that is rapidly treatable with large dose IV ferric carboxymaltose. Among subjects in this study, baseline physical and mental components of SF-36 scores were comparable to
those seen in patients with chronic depression, congestive heart failure, or chronic kidney disease. After iron administration by either route, patients reported a prompt and broad increase in SF-36 scores and a rapid decrease in fatigue scores. Patients given IV ferric carboxymaltose compared to those given oral ferrous sulfate showed greater improvements in physical component scores and fatigue. However, between-group differences should be regarded with caution for instruments measuring quality-of-life variables.

In an open-label trial, patient-reported outcomes may be affected by awareness of treatment assignment. This would be particularly true of an IV versus oral trial. That said, health-related quality-of-life scores tend to increase with Hb level, regardless of treatment (including erythropoiesis-stimulating agents), and the treatment-related improvement in fatigue specifically that is seen in open-label interventional trials is also seen in trials in which patients are masked to treatment assignment. The differences in quality of life noted here are not only statistically significant, but clinically significant as well. Furthermore, the differences were clinically and significantly different.

Patients who received ferric carboxymaltose administered in one to three doses showed more rapid correction of iron depletion, iron-deficient erythropoiesis, and anemia; greater improvement in health-related quality of life; and fewer adverse gastrointestinal symptoms than did patients assigned to oral ferrous sulfate. These responses were significantly different by Day 14 for the primary outcome (Hb increase > 2g/dL) and by Day 28 for the secondary outcome (Hb increase > 3g/dL), demonstrating the value of IV ferric carboxymaltose in early correction of iron deficiency in women postpartum and in replacing on-going iron losses in women with heavy uterine bleeding.

The most common adverse event associated with ferric carboxymaltose administration was transient, asymptomatic hypophosphatemia. The effect of treatment for iron deficiency anemia on serum phosphate has not been previously examined. However, selective hypophosphatemia without other electrolyte disorders has been reported in association with accelerated erythropoiesis at the onset of acute hemolytic anemia, resolution of erythropoietic aplastic crisis in hereditary spherocytosis, and reconstitution of hematopoiesis after allogeneic peripheral blood stem cell transplantation. Urinary phosphate is not increased, confirming the absence of a renal effect. Taken together with our findings that the serum phosphate decline in ferric carboxymaltose-treated patients is related to degree of reticulocyte response and that oral iron-treated patients show phosphate changes in the same direction but of lesser magnitude, the evidence suggests that hypophosphatemia after IV ferric carboxymaltose results from cellular uptake of extracellular phosphate in association with rapid expansion of erythropoiesis.

In the patient with hypophosphatemia reported during recovery from stem cell transplantation, paresthesias developed when the phosphate level dropped to 0.4 mg/dL (0.13 mmol/L). We observed no phosphate level less than 0.9 mg/dL. In short, hypophosphatemia after IV ferric carboxymaltose administration for iron deficiency anemia is asymptomatic and reverses spontaneously without specific treatment.

The efficacy of oral iron therapy hinges on the rate of iron losses via heavy uterine bleeding relative to the rate of gastrointestinal iron absorption, which in turn hinges on patient adherence. Our results indicate that oral iron is significantly less effective than IV ferric carboxymaltose therapy in improving Hb levels and repleting iron stores in
patients with heavy uterine bleeding. Adherence is optimized when oral iron agents are provided directly to the patient; when follow-up is frequent; and when counseling, education, and motivation are made available, all unlikely in most clinical practices. Adherence diminishes with increasing doses of elemental iron, duration of treatment, effective bioavailability, baseline gastrointestinal complaints, the presence of drug-related gastrointestinal adverse events, and the provision of a prescription. In the absence of supervision, follow-up, and counseling, non-adherence to oral iron therapy, defined as discontinuation of medication, ranges from 10% after 2 weeks of therapy to 25% after 1 month and 32% after 2 months. Among patients given prescriptions rather than oral iron tablets, nonadherence after 2 months of therapy approaches 40%.7

In patients with heavy uterine bleeding, negative external iron balance from blood loss must be compensated by mobilizing iron from internal stores (measured by the level of serum ferritin) to supply adequate iron for erythropoiesis (measured by the level of transferrin saturation and, ultimately, blood Hb). Large-dose IV iron administration provides sufficient iron to not only correct anemia but also replenish iron stores; in this trial the mean ferric carboxymaltose dose provided the iron required to produce the equivalent of 5 units of blood.21 In contrast, treatment with oral iron for 6 weeks was associated with a suboptimal improvement in anemia and no iron storage increase. The value of an approach with IV ferric carboxymaltose therapy is illustrated in Fig. 5, in which the patient’s Hb level was optimized by Day 28 for a definitive surgical correction, which should have occurred at this time (but did not, with development of blood loss anemia over the subsequent two weeks to Day 42).

In conclusion, this study demonstrates that ferric carboxymaltose can be administered in large doses by rapid IV injection, requires no test dose, is safe, and is more effective than oral iron therapy in correcting anemia, replenishing iron stores, and improving quality of life in patients with iron deficiency anemia associated with heavy uterine bleeding.

CONFLICT OF INTEREST

Dr Van Wyck served as a consultant and as a speaker for American Regent, Inc., a division of Luitpold Pharmaceuticals, Shirley, NY. He was also an investigator for a grant supported by American Regent. Dr Morrison has served as a consultant to Luitpold Pharmaceuticals. Dr Hadley and Dr Jehle have served as research investigators for Luitpold Pharmaceuticals. Dr Mangione served as an employee of Luitpold Pharmaceuticals. Dr Goodnough is a consultant and serves as a speaker for American Regent, Inc., a division of Luitpold Pharmaceuticals, Shirley, NY. He also serves as a consultant and is on the speaker’s bureau for Amgen, Thousand Oaks, CA; Ortho Biotech, Bridgewater, NJ; and Watson Pharmaceuticals, Morristown, NJ.

REFERENCES


