Effect of Intravenous Iron Sucrose in Peritoneal Dialysis Patients Who Receive Erythropoiesis-Stimulating Agents for Anemia: A Randomized, Controlled Trial

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Although iron therapy is essential to optimize use of erythropoiesis-stimulating agents (ESA), randomized, controlled trials have heretofore been unavailable to evaluate reliably the efficacy of intravenous iron as an adjuvant to ESA treatment in peritoneal dialysis (PD) patients. In a multicenter trial, patients who had anemia, PD-dependent chronic kidney disease, stable ESA therapy, and a broad range of iron status (ferritin ≤500 ng/ml, transferrin saturation ≥25%) were randomly assigned to receive either 1 g of iron sucrose intravenously in three divided doses (300 mg over 1.5 h on days 1 and 15, 400 mg over 2.5 h on day 29) or no supplemental iron. No serious adverse drug events occurred after intravenous iron administration. The primary end point, peak hemoglobin increase, was higher (1.3 ± 1.1 versus 0.7 ± 1.1, mean ± SD; P = 0.0028), and anemia intervention (transfusion, increase in ESA dose, or intravenous iron therapy not called for in protocol) occurred later (P = 0.0137) and less often in intravenous iron–treated patients compared with untreated control subjects (one of 66 [1.3%] versus five of 30 [16.7%]). Among patients who did not require intervention, iron-treated patients showed a calculated net ESA dose decrease compared with untreated control subjects. Baseline iron status did not predict responsiveness to intravenous iron therapy. Intravenous iron sucrose is an effective adjunct to ESA therapy in anemic patients with PD-dependent chronic kidney disease and is administered safely as 300 mg over 1.5 h or 400 mg over 2.5 h. Evidence of iron deficiency at baseline is not required to demonstrate intravenous iron efficacy.


Among patients with peritoneal dialysis–dependent chronic kidney disease (PD-CKD), anemia is nearly universal, and use of erythropoiesis-stimulating agents (ESA) is the standard of care. Anemia management in PD-CKD, however, is commonly complicated by iron deficiency. Failure of oral iron supplementation to correct iron deficiency anemia or prevent negative iron balance in patients with PD-CKD is well described (1,2). The alternative, intravenous iron administration, has shown evidence of efficacy in a series of small studies (1–6). The lack of randomized controlled trials (RCT) in PD-CKD, however, leaves the usefulness of intravenous iron as an adjuvant to ESA in these patients untested and uncertain.

Confirmation of adjuvant efficacy requires demonstration that, in ESA-treated patients, the proposed adjuvant serves to increase hemoglobin (Hb) without an increase in ESA dose, to decrease ESA doses without changing Hb, or to prevent red cell transfusions or ESA dose increase. For testing the hypothesis that an adjuvant is effective in ESA-treated patients, a clinical trial should include three design elements: The ESA dose should be stable before and after randomization to reduce trial outcomes to a single primary end point (change in Hb); patients should be randomly assigned to either adjuvant treatment or no adjuvant treatment to isolate adjuvant effect, if any; and trial duration should be long enough, at least 12 wk, to permit observation of the complete Hb response. To our knowledge, no previous trial has been designed specifically to examine adjuvant efficacy of intravenous iron in ESA-treated patients with PD-CKD.

Iron status tests often are used to trigger intravenous iron therapy. In a small, single-arm interventional trial, the sensitivity of transferrin saturation (TSAT) <20% or ferritin <100 ng/ml to predict responsiveness to intravenous iron in anemic patients with PD-CKD was reported as low (7). Detailed information in larger numbers of patients with PD-CKD is needed to elucidate the relationship between baseline levels of iron status tests and likelihood of response to an intravenous iron challenge.

Accordingly, we conducted a 12-wk RCT in anemic patients with PD-CKD and compared treatment of anemia with ESA together with intravenous iron sucrose to treatment with ESA alone. We assessed the adjuvant efficacy of intravenous iron,
determined the safety of iron sucrose given at 300- and 400-mg doses, and evaluated the relationship between baseline iron indices and likelihood of response to intravenous iron challenge.

Materials and Methods

Study Design

This was an open-label, phase 3, randomized, multicenter trial that was conducted in adherence to the Declaration of Helsinki. Anemic patients who had PD-CKD and required iron supplementation, met all inclusion and exclusion criteria, and had given informed consent were enrolled into the study at 21 study sites. We randomly assigned patients into study groups when they met criteria for randomization, including ESA therapy (darbepoetin or epoetin-α) without dose change for 8 wk, and no parenteral or oral iron for at least 4 wk. Enrolled patients who were not immediately eligible for randomization underwent monthly laboratory examination for up to 6 mo, followed by randomization upon meeting inclusion criteria (Figure 1). Thus, enrollment served to increase the pool of patients who were available for randomization, and randomization could occur as early as 1 d or as late as 180 d after enrollment.

Inclusion Criteria for Enrollment. Criteria for enrollment were distinct from criteria for randomization. Patients were eligible for enrollment when they were older than 18 yr, were able to give informed consent, underwent PD and ESA therapy, and evidenced anemia (Hb < 9.5 g/dl and ≤ 12.5 g/dl). In Mexican study sites, because of the severity of prevalent anemia, previous ESA use was not required and lower Hb was permitted for enrollment (Hb < 8.5 g/dl and ≤ 12.5 g/dl); initiation of ESA after enrollment was permitted, but stable ESA dose for 8 wk was required before randomization.

Exclusion Criteria for Enrollment. Patients were excluded from enrollment when they had a history of known sensitivity to iron sucrose (patients with intolerances to other forms of iron were permitted to participate); chronic or serious infection, malignancy, or major surgery in the month before enrollment; blood transfusion within the week before enrollment; clinically significant bleeding within 3 mo before enrollment; concomitant severe diseases of the liver or cardiovascular system or severe psychiatric disorders or other conditions that, in the opinion of the investigator, made participation unacceptable; pregnancy or lactation; current treatment for asthma; anticipated surgery that would have required hospitalization during the study period other than vascular access or peritoneal catheter placement; anticipated dialysis or renal transplantation during the study; administration of an investigational drug within 30 d of enrollment; chronic alcoholism or drug abuse within the past 6 mo; and known hemochromatosis or hemosiderosis.

Criteria for Randomization. Patients were eligible for randomization when they continued to meet the enrollment criteria and met the following additional criteria: Hb ≥ 9.5 and ≤ 11.5 g/dl; TSAT ≤ 25%; ferritin ≤ 500 ng/ml; stable ESA dose for at least 8 wk; and no iron therapy after enrollment or for at least 4 wk before randomization. In Mexican study sites, because of the severity of prevalent anemia, we permitted a lower limit of Hb for randomization (Hb ≥ 8.5 and ≤ 11.5 g/dl).

Criteria for Premature Withdrawal. Premature withdrawal was required when ESRD treatment modality change to renal transplant or hemodialysis (HD) or an intervention for management of anemia was required. We defined an anemia intervention as a red blood cell transfusion, an increase in ESA dose, or iron administration that was not included in the study protocol. We specified that intervention was required when the Hb fell below 9.5 g/dl during enrollment (8.0 g/dl in Mexico) or below 8.5 g/dl after randomization (8.0 g/dl in Mexico). Of course, patients 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 patient at any time if withdrawal was believed to be in the best interest of the patient. In the analysis of efficacy and safety, we included data for each patient up to the time of withdrawal.

Treatment

Patients in the intravenous iron treatment arm received iron sucrose intravenously in divided doses over a 28-d period as a 300-mg infusion in 250 ml of 0.9% NaCl given over 1.5 h on days 1 and 15 (approximately 3.3 mg/min) and a 400-mg infusion over 2.5 h (approximately 2.7 mg/min) on day 29. Patients received ESA at the same dose as before randomization, unchanged throughout the study period (days 1 to 71). Patients in the ESA only treatment arm received ESA at the same dose as before randomization, unchanged throughout the study period (days 1 to 71).

Randomization Method for Assigning Treatment Group. We first identified patients as new to PD (≤3 mo) or established PD (>3 mo). We then independently stratified new and established patients by Hb level (11.5 to 10.5 versus 10.4 to 9.5 g/dl; for sites in Mexico, 9.4 to 8.5). Within each resulting combination of strata, we then randomly assigned patients in a 2:1 ratio to study treatment group A (ESA + intravenous iron) or B (ESA alone).

Determination of Efficacy and Safety

Efficacy. We defined the primary efficacy end point as the change from baseline to the highest Hb observed at any time between baseline and either the end of study or withdrawal. We determined sample size for this study on the basis of the hypothesis that the difference in mean peak Hb response between treatment groups would be 0.75 g/dl, assuming a common SD no greater than 1.0 g/dl. To have a 95% power to detect that difference required a minimum of 111 randomly assigned patients (74 in group A, 37 in group B). Secondary end points included the observed increase in TSAT and ferritin after treatment and the time to anemia intervention.

Laboratory Evaluation. Blood samples for laboratory analyses that were obtained at all appropriate visits were analyzed by a central laboratory. We determined hematologic indices and iron indices at enrollment; at completion of the enrollment period; and on days 15, 29, 43, 57, and 71 after initiation of therapy. We determined the baseline Hb as the final Hb values before randomization. We determined routine
clinical chemistry at enrollment and at day 71 or study completion. Iron indices included serum iron, total iron binding capacity, TSAT, and ferritin.

Safety (Adverse Events). We monitored BP and recorded adverse events in all patients before, during, and for 20 min after administration of intravenous iron. We asked all patients to report any untoward medical event at the onset and queried each patient at each study visit. We recorded adverse events from the day of consent through the completion of the study (day 71) or 30 d after the last dose of study drug, whichever was later. Investigators provided the date of onset, severity, the relationship to study drug, the date of resolution (or that the event was still continuing), the action taken, and the outcome of the adverse experience. We did not consider worsening anemia or iron deficiency to be adverse events, because these developments became study end points when anemia intervention was required, as defined above.

We classified potential hypersensitivity reactions by grade as events that occurred from the start of drug infusion to 20 min after the completion of the infusion, according to accepted guidelines (National Cancer Institute Common Toxicity Criteria Version 2.0; http://ctep.cancer.gov/reporting/etc.html). Investigators graded events that lacked accepted terminology as mild (did not interfere with patient’s usual function), moderate (interfered to some extent), severe (interfered significantly), or life-threatening (resulted in a threat to life or an incapacitating disability). A serious adverse event included any experience that was fatal or life-threatening, resulted in or prolonged inpatient hospitalization, resulted in persistent or significant disability or incapacity, or presented a significant hazard to the patient. Investigators judged relatedness to study drug as none, unlikely, possible, or probable.

Statistical Analyses

Primary Efficacy End Point. The principal analysis of the primary end point was the unstratified comparison of the peak Hb increase above baseline between the two study arms (group A versus group B) in the intention-to-treat (ITT) population, using a two-step procedure. In the first step, we used a regression model to identify important covariates (including baseline Hb, TSAT, ferritin, reticulocyte count, study center, age, gender, and race) and potential interactions with covariates (including baseline Hb, TSAT, ferritin, reticulocyte count, and five of 30 patients (16.7%) in group B required anemia intervention, defined by protocol as an increase in ESA dose before randomization. All five patients were excluded from the evaluation of both safety and efficacy. Therefore, the safety-evaluable population included a total of 121 patients who received at least one dose of iron: 75 patients in group A and 46 in group B. The ITT population, which formed the basis for efficacy analysis, included all safety-evaluable patients who had efficacy data after randomization; except for nine patients in group A and eight in group B who were subsequently found to have been randomly assigned despite ESA dose changes within 8 wk before randomization.

Efficacy

Among the 96 patients in the ITT population, there were no significant differences at baseline between patients in group A (n = 66) and those in group B (n = 30), except for TSAT (Table 1). Patients in group B showed a statistically significantly lower mean TSAT value at baseline (16.8%) than those in group A (19.8%).

Anemia Intervention. One of 66 patients (1.3%) in group A and five of 30 patients (16.7%) in group B required anemia intervention, defined by protocol as an increase in ESA dose, administration of nonprotocol intravenous iron, or red blood cell transfusion. Median time to anemia intervention was significantly shorter among patients without iron treatment than with intravenous iron treatment (34 versus 59 d; Wald \( \chi^2 \) P = 0.0137; Figure 3). Exploratory analysis revealed that ESA dose decreases occurred in selected patients, contrary to study protocol, in response to elevated Hb. Eleven (16.7%) of 66 patients in group A and three (10.0%) of 33 patients in group B experienced Hb >13.0 g/dl. Eight ESA dose decreases occurred in

Results

Patient Disposition

A total of 188 patients were enrolled. Time to randomization did not differ between groups (47.2 ± 45.0 versus 29.8 ± 32.9 d, group A versus group B, mean ± SD). A total of 126 patients were randomly assigned at 27 centers (mean 4.7 patients per center; range 1 to 27) to receive ESA plus iron sucrose (group A: 80 patients) or ESA alone (group B: 46 patients). Of these 126 patients, five were randomly assigned to group A but were discontinued from the study before dosing (Figure 2). Of these five patients, two were lost to follow-up, two were withdrawn as a result of acute adverse events, and one had an unstable ESA dose before randomization. All five patients were excluded from the evaluation of both safety and efficacy. Therefore, the safety-evaluable population included a total of 121 patients who received at least one dose of iron: 75 patients in group A and 46 in group B. The ITT population, which formed the basis for efficacy analysis, included all safety-evaluable patients who had efficacy data after randomization; except for nine patients in group A and eight in group B who were subsequently found to have been randomly assigned despite ESA dose changes within 8 wk before randomization.

Figure 2. Disposition of study patients after screening. We examined safety in the safety-evaluable population and efficacy in the intent-to-treat (ITT) population.
seven (10.6%) of 66 patients in group A, and two dose decreases occurred in two (6.1%) of 33 patients in group B. Median time to ESA dose decrease was no different in group A than in group B patients (33 versus 36 d, respectively; P = 0.5087; Figure 3). However, the magnitude of dose decrease was greater among group A than group B patients. We converted darbepoetin doses if any to epoetin-α equivalents by multiplying by 200, then for each patient, we subtracted actual doses given during the trial from those that would have been given had ESA dosing remained unchanged. We calculated that the resulting epoetin-α dose decrease totaled 260,528 IU in group A and 65,429 IU in group B. Therefore, the net between-group ESA dose difference that was associated with intravenous iron therapy was 195,099 IU, or 2,956 IU per group A patient. We did not calculate added ESA requirements that were incurred as a result of dose increases, because patients with ESA dose increases were withdrawn from the study.

**Hb Response.** Patients in group A showed a higher peak Hb increase, the primary end point, than did those in group B (1.3 versus 0.6; difference 0.7 [95% confidence interval 0.3 to 1.2]; P = 0.0028). Hb increase from baseline was significant at each interval after baseline in group A. We observed no significant increase in Hb at any interval in group B (Figure 4). When compared with patients who were assigned to group B, a greater proportion of patients who were assigned to group A showed an increase in Hb ≥1.0 g/dl (59.1 versus 33.3%; P = 0.0273). Among patients who completed the study, median time to peak Hb response did not differ between groups (48.3 versus 51.4 d). Baseline status, including age, race, gender, Hb, TSAT, and ferritin, showed no significant effect on peak Hb increase or proportion of patients with Hb increase >1 g/dl.

Study site showed no discernible effect on efficacy results, whether all patients among all sites were examined by the *a priori* statistical plan or US patients were compared with Mexican patients by exploratory analysis. When we compared Mexican study patients with those in the United States, we found neither an overall country effect on Hb outcomes between groups A and B nor a selective country effect within either group A or group B. When we removed Mexican sites from analysis, US-only patients showed the relative between-group

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**Table 1. Baseline demographic and laboratory values among intention-to-treat patients in intravenous iron and oral iron treatment groups**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Group A (ESA + IV Iron; n = 66)</th>
<th>Group B (ESA Alone; n = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (y)</td>
<td>52.3</td>
<td>55.7</td>
<td>0.9825</td>
</tr>
<tr>
<td>race (white/black/Hispanic/Asian)</td>
<td>27/13/22/4</td>
<td>6/4/17/3</td>
<td>0.0520</td>
</tr>
<tr>
<td>gender (male/female)</td>
<td>42/24</td>
<td>14/16</td>
<td>0.1261</td>
</tr>
<tr>
<td>epoetin-α (IU/wk)</td>
<td>11,681</td>
<td>7,932</td>
<td>0.1012</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>79.2</td>
<td>75.4</td>
<td>0.8341</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>10.6</td>
<td>10.5</td>
<td>0.7821</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>19.8</td>
<td>16.8</td>
<td>0.0043</td>
</tr>
<tr>
<td>ferritin (ng/ml)</td>
<td>167.5</td>
<td>194.2</td>
<td>0.2975</td>
</tr>
<tr>
<td>TSAT &lt; 20% and ferritin &lt; 100 ng/ml (n)</td>
<td>12</td>
<td>5</td>
<td>1.0000</td>
</tr>
<tr>
<td>previous iron intolerance (dextran/gluconate)</td>
<td>2/2</td>
<td>0/0</td>
<td>0.3059</td>
</tr>
</tbody>
</table>

*a*Hb, hemoglobin; IV, intravenous; TSAT, transferrin saturation.
efficacy effects that were seen among all patients combined, but smaller sample sizes \((n/1100547\text{ and }15,\text{ groups }A\text{ and }B,\text{ respectively})\) rendered comparisons not statistically significant.

**Iron Stores and Iron Adequacy for Erythropoiesis, Response to Treatment.** Serum ferritin increased significantly from baseline only in group A, and differences between groups were highly significant (Figure 5). Peak ferritin values attained were higher in group A than in group B \((P < 0.0001)\) and correlated directly with baseline Hb \((P = 0.0409)\) and baseline ferritin \((P = 0.0004)\). TSAT increased in both groups; differences between groups narrowly failed to achieve statistical significance. However, peak TSAT values were significantly higher in group A than in group B \((P = 0.0098)\) and correlated directly with both baseline Hb \((P = 0.0007)\) and baseline ferritin \((P = 0.0120)\).

**Clinical Utility of Baseline Iron Indices.** The clinical utility of baseline iron status tests to discriminate between patients who are iron responsive, defined as a \(\Delta Hb \geq 1.0\text{ g/dl}\) after intravenous iron treatment \(\geq 1\text{ g/dl}\), and those who are iron nonresponsive, defined as a \(\Delta Hb < 1\text{ g/dl}\), was weak. Baseline TSAT and ferritin showed no diagnostic utility at any cutoff value (Figure 6).

**Safety**

**Extent of Exposure.** Among the 75 patients in group A, five had a history of intolerance to an intravenous iron agent (two to iron dextran, two to ferric gluconate, and one to both). Group A patients received 149 doses of iron sucrose as 300 mg over 90 min and 70 doses of iron sucrose as 400 mg over 2.5 h. The mean cumulative per-patient dose of intravenous iron sucrose that was administered in the safety population was 970.9 mg \((95\% \text{ confidence of the mean } 944.4\text{ to }997.5\text{ mg})\).

**Adverse Events.** There were no serious adverse drug events (ADE). Sixty-two patients in group A and 26 patients in group B completed the study. An additional 22 patients \((12\text{ in group }A,\text{ }10\text{ in group }B)\) discontinued for reasons other than intervention (Table 2). Three patients in group A discontinued as a result of adverse events; of these, one experienced an adverse event that was considered study drug related. This patient experienced swelling of the feet and pruritus 30 to 45
min after completing her first 300-mg iron sucrose administration. Hydrocortisone was administered. Symptoms and findings resolved within 2 h. The patient elected to withdraw from the study. The investigator considered the event moderate in intensity and probably related to study drug. A second patient experienced pruritus 18 h after receiving a 400-mg dose of iron sucrose. Diphenhydramine was administered orally. Symptoms resolved within 2 d. The event was considered moderate and related to study drug.

Three episodes of hypotension were recorded, two in group A, including one judged unlikely to be related and one unrelated to study drug, and one in group B. Five patients in group A had a history of intolerance to an intravenous iron product, including three who were intolerant to ferric gluconate (two with pruritic rash and one with hypotension, nausea, vomiting, and diarrhea) and two who were intolerant to iron dextran (one hypotension with back pain and one bronchospasm). The patient with leg swelling described above was one of the two patients with a history of rash after ferric gluconate.

There were 11 episodes of peritonitis: Six (8.0%) in group A and five (10.9%) in group B. Of these, four episodes (two in each group) were considered serious; no episode was considered related to study drug. Similarily, there were seven episodes of catheter exit-site infection: Three (4.0%) in group A and four (8.7%) in group B. Post hoc calculations suggested that our study had sufficient power to have an 80% or better chance to detect a two-fold increase in the rate of infection (peritonitis plus exit-site infection) in group A compared with group B.

Table 2. Reason for discontinuation other than anemia intervention, by treatment group

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>Group A (ESA + IV Iron; n = 75)</th>
<th>Group B (ESA Alone; n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients treated (safety assessable)</td>
<td>75 (100%)</td>
<td>46 (100%)</td>
</tr>
<tr>
<td>adverse event related to study drug</td>
<td>1 (1.3%)</td>
<td>0</td>
</tr>
<tr>
<td>adverse event unrelated to study drug</td>
<td>2 (2.7%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>selection criteria/study compliance</td>
<td>3 (4.0%)</td>
<td>3 (6.5%)</td>
</tr>
<tr>
<td>renal transplant</td>
<td>3 (4.0%)</td>
<td>0</td>
</tr>
<tr>
<td>lost to follow-up</td>
<td>1 (1.3%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>patient request unrelated to adverse event</td>
<td>1 (1.3%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>other</td>
<td>1 (1.3%)</td>
<td>3 (6.5%)</td>
</tr>
</tbody>
</table>

Total patients who completed study | 62 (82.7%) | 26 (56.5%)

*Data numbers of patients (% of group total). Each reason is unique to each patient; no patient is listed more than once.

Laboratory Evaluation. There were no significant changes in clinical biochemistry laboratory results, including blood ureas nitrogen, creatinine, albumin, bicarbonate, or phosphorus, at any interval in either treatment group.

Discussion

We report the results of a prospective, randomized, controlled trial in patients with PD-CKD that compared the anemia management efficacy of intravenous iron therapy added to ongoing ESA treatment with that of ESA therapy alone. Our results show that intravenous iron administration increases Hb without an increase in ESA dose, decreases the need for anemia intervention, and replenishes iron stores.

Our trial highlights Hb-targeting bias as an inherent limitation of anemia adjuvant trials. Examination of efficacy of an adjuvant to ESA requires maintaining ESA doses constant before and after randomization to either adjuvant therapy or no-treatment control. We set the lower limit of Hb by design, and when Hb fell below that target, we removed patients from the trial to permit definitive treatment (anemia intervention). We observed an effective, albeit unspecified and off-protocol, upper Hb limit when investigators decreased ESA doses when

Table 3. Reported ADE in group A safety-evaluable patients

<table>
<thead>
<tr>
<th>Adverse Drug Events</th>
<th>Group A (ESA + IV Iron; n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>5 (6.7%)</td>
</tr>
<tr>
<td>constipation</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>diarrhea</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>nausea/vomiting</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>abdominal pain</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Pruritus and swelling</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Discoloration at injection site</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Increased peripheral eosinophil count</td>
<td>1 (1.3%)</td>
</tr>
</tbody>
</table>

*Data are number of patients (% column total). All events were judged nonserious. One patient reported two gastrointestinal adverse drug events.
a high Hb raised safety or reimbursement concerns. The resulting Hb targeting in our anemia adjunct trial, like dose targeting in a dialysis adequacy trial (8), introduces unavoidable bias. Control group patients in our trial were more likely to need ESA dose increases and other anemia interventions and therefore were more likely to be removed from the trial. Greater dropout rates in the no-iron control group, as seen previously in a trial of oral iron versus no-iron treatment in patients with HD-dependent CKD (9), create selective loss (censoring) of patients who are most prone to poor anemia outcomes and leaves the remaining control group patients relatively responsive to ESA and dietary iron. Iron-deficient patients without kidney disease may show increases in both Hb and TSAT despite assignment to treatment with an iron-free placebo (10), presumably because dietary iron intake in healthy individuals is sufficient to provide positive iron balance.

In short, in patients who are receiving ESA therapy, Hb targeting bias minimizes differences that are achieved between iron treatment and no-iron control arms. Even with these constraints, however, intravenous iron administration proved effective in our study as an adjunct to ESA therapy. In patients who had PD-CKD and underwent combined ESA and intravenous iron therapy, Hb rose higher, interventions were fewer, and net epoetin dose decrease was greater than in patients who were given ESA therapy alone.

Whether oral iron administration is an effective adjunct to ESA therapy in PD patients is unclear. Failure of oral iron administration to sustain target iron indices in PD patients who undergo ESA therapy is common (1,11). When intravenous iron is administered to PD patients who previously had received oral iron, Hb levels rise and ESA doses either fall or remain unchanged (2,4,6,7). Although intravenous iron agents are more expensive than oral iron agents, the cost of an effective ESA adjunct is offset by sparing of the cost of ESA. In ESA-treated patients, therefore, failure of an inexpensive adjunct may increase the effective cost of anemia management. Although RCT have shown intravenous iron to be superior to oral iron in ESA-treated HD patients (12–14) and patients with CKD (15), RCT in PD patients are currently lacking. Our study provides needed information to guide the design, size, and duration of such a comparative trial.

In HD patients, the iron status tests TSAT and ferritin are useful markers of responsiveness to a 1000-mg intravenous iron challenge (16). In the patients with PD-CKD in this study, characterized by ESA use and moderate iron status (Hb ≤11.5 g/dl, TSAT ≤25%, ferritin ≤500 ng/ml), these tests proved unhelpful (Figure 6). Remarkably, despite the fact that few patients met criteria for iron deficiency at baseline CKD (TSAT <20% and ferritin <100 ng/ml; Table 1), nearly 60% of patients in this study showed a 1-g/dl rise in Hb after intravenous iron administration. This success rate, coupled with the observation that the likelihood of Hb increase seemed to be independent of iron status (Figure 6), confirms that iron deficiency is not required to demonstrate intravenous iron efficacy in patients with PD-CKD (7).

Convenient dosing schedules are important practical determinants of the efficacy of intravenous iron administration in the outpatient treatment setting. The maximum Food and Drug Administration–approved dose for single administration is 100 mg for iron dextran over 2 min and 125 mg of ferric gluconate over 10 min. Iron sucrose is Food and Drug Administration approved for administration of 100 mg over 2 to 5 min, 200 mg over 2 to 5 min, 300 mg over 1.5 h, or 400 mg over 2.5 h. Hypotension, presumably related to bioactive iron release, is a concern whenever intravenous iron is administered too much, too fast (17). Although two episodes of hypotension were recorded in patients who were assigned to group A, neither was considered either serious or likely to have been related to intravenous iron. Iron sucrose has been administered as 1000 mg in two 500-mg doses 1 to 2 wk apart, but the described infusion times of 3.5 to 6 h for each dose may prove inconvenient for many (4,7,18). We also observed two episodes of pruritus after 300- and 400-mg infusions, respectively. Whether these reactions were due to hypersensitivity or were related to rate and total dose of infusion is unclear. Hypersensitivity reactions to nondextran iron agents are less common and less severe than those seen after iron dextran (19).

Because intravenous iron agents have been shown to augment the growth of pathogenic bacteria in vitro (20), we recorded infection rates in patients through 30 d after trial completion or discontinuation. In keeping with previous evidence in patients with PD-CKD (21), we found the rate of infection to be no higher among patients who received intravenous iron than among those who did not. These findings held true for rates of all peritonitis, serious peritonitis, and catheter exit-site infection. We conclude that a 1000-mg intravenous iron challenge poses no discernible infectious risk for patients with PD-CKD.

Conclusion

Results of the first RCT to assess intravenous iron in patients with anemia that is associated with PD-CKD confirm that intravenous iron administration can be an effective adjunct to ESA therapy, even when baseline iron status tests do not suggest iron deficiency. Moreover, administration of iron sucrose as 300 mg over 1.5 h or 400 mg over 2.5 h is well tolerated and provides a practical approach to completing iron repletion expeditiously in the outpatient treatment center.

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References

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