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Diagnostic value of iron indices in hemodialysis patients receiving epoetin

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Diagnostic value of iron indices in hemodialysis patients receiving epoetin.

Background. Iron deficiency remains a common cause of hyporesponsiveness to epoetin in hemodialysis patients. However, considerable controversy exists regarding the best strategies for diagnosis and treatment.

Methods. As part of a multicenter randomized clinical trial of intravenous versus subcutaneous administration of epoetin, we made monthly determinations of serum iron, total iron binding capacity, percentage transferrin saturation, and serum ferritin. If a patient had serum ferritin <100 ng/mL or the combination of serum ferritin <400 ng/mL and a transferrin saturation <20%, he/she received parenteral iron, given as iron dextran 100 mg at ten consecutive dialysis sessions. We analyzed parenteral iron use during the trial, the effect of its administration on iron indices and epoetin dose, and the ability of the iron indices to predict a reduction in epoetin dose in response to parenteral iron administration.

Results. Eighty-seven percent of the 208 patients required parenteral iron to maintain adequate iron stores at an average dose of 1516 mg over 41.7 weeks, or 36 mg/week. Only two of 180 patients experienced serious reactions to intravenous iron administration. Two thirds of the patients receiving parenteral iron had a decrease in their epoetin requirement of at least 30 U/kg/week compared with 29% of patients who did not receive iron ($P = 0.004$). The average dose decrease 12 weeks after initiating iron therapy was 1763 U/week. A serum ferritin <200 ng/mL had the best positive predictive value (76%) for predicting a response to parenteral iron administration, but it still had limited clinical utility.

Conclusions. Iron deficiency commonly develops during epoetin therapy, and parenteral iron administration may result in a clinically significant reduction in epoetin dose. The use of transferrin saturation or serum ferritin as an indicator for parenteral iron administration has limited utility.

The availability of recombinant human erythropoietin (epoetin) has markedly altered the treatment of the anemia of chronic renal failure and greatly reduced the need for transfusions in these patients. A number of clinical circumstances may lead to decreased responsiveness to epoetin, the most important of which is iron deficiency. Considerable emphasis has been placed on the recognition and treatment of iron deficiency in epoetin-treated chronic renal failure patients, yet controversy exists regarding the best strategies for diagnosis and management [1]. Several investigators have suggested that serum ferritin is the most useful marker of iron deficiency in an otherwise normal population [2]. However, serum ferritin is elevated in chronic renal failure and inflammatory states, and the usual thresholds for the diagnosis of iron deficiency may not be applicable under these circumstances [3]. The other readily obtainable marker of iron deficiency, serum transferrin saturation, may also have decreased reliability in patients with chronic renal failure [4]. Several other diagnostic tests, including serum transferrin receptors, red blood cell protoporphyrins, percentage of hypochromic red cells, and reticulocyte hemoglobin concentration, have demonstrated some utility, but require specialized equipment and are not widely available [1].

We have recently completed a study comparing intra-

[1] Investigators, support personnel and centers are listed in the **Appendix**.

Key words: anemia, parenteral iron, serum ferritin, transferrin saturation, recombinant human erythropoietin.

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venous to subcutaneous epoetin administration in hemodialysis patients [5]. As part of the protocol, we obtained monthly serum irons, total iron binding concentrations, and serum ferritins and used a specific algorithm for parenteral iron administration. Using this database, we have analyzed the diagnostic accuracy of the commonly used iron parameters and the influence of parenteral iron administration on epoetin requirements.

METHODS

As part of a multicenter, randomized clinical trial of intravenous versus subcutaneous administration of epoetin (Epogen®; Amgen, Thousand Oaks, CA, USA), we have collected monthly data on serum iron parameters, including serum iron, total iron binding capacity (TIBC), percentage transferrin saturation (TS%), and serum ferritin. The main study was designed to compare the intravenous to subcutaneous administration of epoetin in terms of the average weekly dose required to maintain a target hematocrit of 30 to 33% for 26 weeks. The study was a parallel group design, and after randomization, patients underwent dose reductions until their hematocrits were less than 30% for two consecutive weeks. Then doses were gradually increased until the hematocrits were once again greater than 30%. The hematocrit was then maintained in the target range of 30 to 33% for 26 weeks using a specific dosing algorithm. The design and results of the main study have previously been reported [5].

The management of oral and parenteral iron administration was as follows during the study. Patients entering the study were required to have a transferrin saturation >20% and a serum ferritin >100 ng/mL. Patients were prescribed oral iron, Niferex-150® (Central Pharmaceuticals, Inc./Schwarz Pharma, Inc., Mequon, WI, USA) one capsule twice daily, but oral iron therapy was not specifically monitored. To avoid prolonged periods of iron deficiency and to minimize epoetin doses, we required frequent measurements of iron status and prescribed liberal parenteral iron replacement. Monthly midweek, predialysis determinations of serum iron, TIBC, and serum ferritin were obtained. If a patient had a serum ferritin <100 ng/mL or the combination of a serum ferritin <400 ng/mL and a transferrin saturation <20%, he/she received parenteral iron. The parenteral iron was given as iron dextran (INFeD®; Schein Pharmaceutical, Inc., Florham Park, NJ, USA) 100 mg at ten consecutive dialysis sessions.

For our post hoc analysis, because there is no generally accepted absolute standard for the diagnosis of iron deficiency, particularly in epoetin-treated patients, we developed a functional definition. Patients were defined as having functional iron deficiency if, after receiving a course of parenteral iron, they were able to have a reduction in their weekly epoetin dose of at least 30 U/kg/week in the subsequent 12 weeks while maintaining the target hematocrit of 30 to 33%. This definition was based on the epoetin dosing algorithm for the main study, which required weekly hematocrits, and if the hematocrit was outside the target range for two consecutive weeks during the maintenance period, the epoetin dose was altered by 30 U/kg/week. Therefore, a decrease in epoetin dose reflected an increase in hematocrit to >33% in the previous two weeks. This definition allowed us to examine the value of serum ferritin and transferrin saturation determinations in predicting the hematologic response to parenteral iron administration.

Table 1. Clinical characteristics of patients

N	208
Age *years*	60.2 ± 12.9
Male %	98.6
Diabetic %	42.8
Length of dialysis *hours*	3.80 ± 0.36
Years on dialysis	3.70 ± 3.93
Years on epoetin	2.17 ± 1.51
Serum albumin *g/dL*	3.8 ± 0.4
Serum aluminum *μg/L*	21.8 ± 16.9
Serum iron *μg/dL*	70.1 ± 41.7
Total iron binding capacity *μg/dL*	238.2 ± 67.3
Transferrin saturation %	28.3 ± 10.7
Serum ferritin *ng/mL*	301 ± 223

Statistical methods

Changes in iron indices following parenteral iron were analyzed using the one sample *t* test. The percentage of patients having a reduction in their epoetin dose of at least 30 U/kg/week following a course of parenteral iron compared with those receiving no iron was analyzed using Fisher's exact test. This analysis was repeated using a decrease of 60 U/kg/week as the threshold for response. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. SAS® (version 6) was used for all analyses [6]. Results are reported as means ± SD.

RESULTS

Iron use

The clinical characteristics of the patients at entry into the study are summarized in Table 1. Two hundred eight patients were randomized to receive either the subcutaneous ($N = 107$) or intravenous ($N = 101$) route of epoetin administration. Although all the patients were prescribed oral iron, parenteral iron was required at some time during the study by 180 (87%) patients to maintain iron parameters within our specific target range. Thirty-one percent of the randomized patients required a single course. Twenty-four percent required two courses, and 32% required three courses of ten 100 mg doses of parenteral iron. The average total amount of intravenous iron administered per patient was 1516 ± 1173 mg. The average time in the study was 41.7 ± 17.3

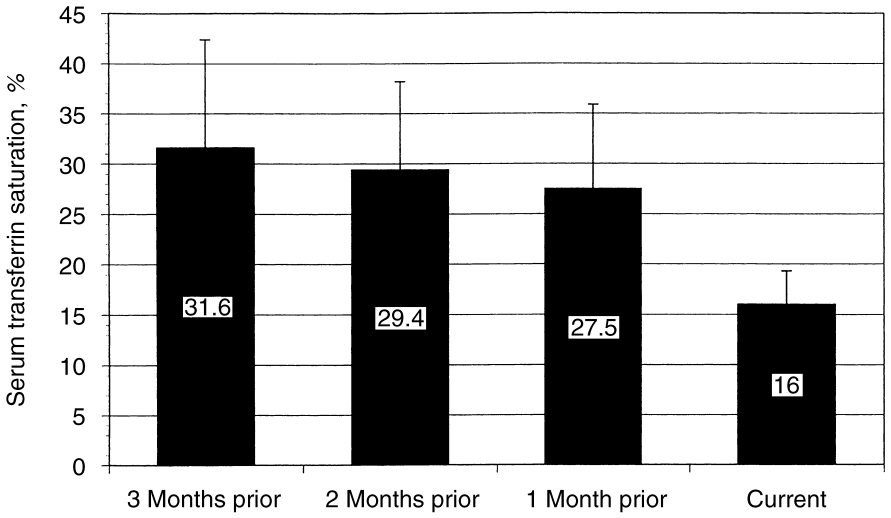

Fig. 1. Values for transferrin saturation in the three months prior to the first value <20%. Values in bars are means, and error bars are standard deviations. $P < 0.001$, comparing current month to all prior months.

week. The 180 patients receiving parenteral iron received a total of 3588 doses of iron dextran. Only two of these 180 patients (1.1%) had serious adverse reactions that precluded subsequent administration of parenteral iron dextran. Both patients experienced hypotensive episodes shortly after the iron infusion was completed. Because the patients were on hemodialysis at the time, it is possible that the events were unrelated to the iron dextran. However, the patients' physicians did not feel it was safe to rechallenge the patients. Since we did not specifically require reporting of minor reactions, we cannot comment on their frequency.

Diagnostic studies

A transferrin saturation <20% has been advocated as a diagnostic threshold for iron deficiency [7]. Seventy-nine percent of patients had a transferrin saturation <20% at some time during the study. Most of the measurements of transferrin saturation occurred with a concomitant low serum ferritin concentration indicative of iron deficiency, but 21% occurred with a serum ferritin >400 ng/mL. Twelve percent of the low transferrin saturations occurred with a serum ferritin <100 ng/mL. Thirty-four percent had a value of 100 to 199 ng/mL. Twenty-one percent were 200 to 299 ng/mL, and 10% were 300 to 399 ng/mL. A serum ferritin <100 ng/mL, a value frequently cited as diagnostic of iron deficiency in patients with chronic renal failure [7], was noted in 36% of patients at some time during the study. In the majority of patients (73%) with a serum ferritin <100 ng/mL, the simultaneously measured value for transferrin saturation was ≥20%, including 31% with a transferrin saturation >28%. In this study, mean corpuscular volume (MCV) was an insensitive index of iron deficiency. Only 5% of the patients with a serum ferritin <100 ng/mL or the combination of a transferrin saturation <20% and serum ferritin <400 ng/mL had an MCV below the lower limit of normal (≤80 fL).

We examined the rate of change in the commonly used diagnostic indices. Figure 1 summarizes the values for transferrin saturation in the three months prior to the first value <20%. In this analysis, patients who had received any parenteral iron in the eight weeks prior to the transferrin saturation value of <20% were excluded. Similarly, Figure 2 summarizes the values for serum ferritin in the three months prior to the first value <200 ng/mL. The values for transferrin saturation and serum ferritin changed rapidly, with the largest changes occurring in the month just prior to the abnormal value. The changes in iron parameters in response to parenteral iron are summarized in Table 2. Only patients who had repeat determinations of iron parameters at least one month after the completion of a ten-dose course of parenteral iron are included in this analysis. Data were available on 136 of the 180 patients receiving parenteral iron, although three of these did not have follow-up serum ferritin values. Serum ferritin, TIBC, and transferrin saturation, but not serum iron, changed significantly within a month of administration of parenteral iron. Table 3 shows the values for transferrin saturation and serum ferritin just prior to starting parenteral iron and their effects on the response of these parameters to parenteral iron. If patients were stratified by their serum ferritin values prior to starting iron, those with serum ferritins greater than 300 ng/mL did not have a significant increase in their transferrin saturation or serum ferritin in response to parenteral iron, although the apparent lack of response may be due to the small sample size.

Hematologic response to parenteral iron and accuracy of diagnostic studies

During the maintenance phase of our study, epoetin doses were adjusted to maintain a target hematocrit of

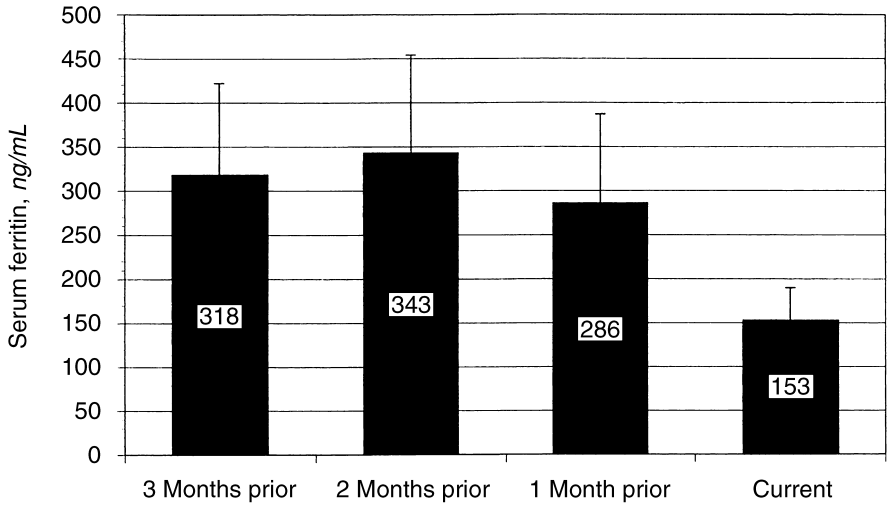

Fig. 2. Values for serum ferritin in the three months prior to the first value <200 ng/mL. Values in bars are means and error bars are standard deviations. $P < 0.001$, comparing current month to all prior months.

Table 2. Effect of parenteral iron on iron indices

Laboratory measurement	Value just prior to initiating parenteral iron	Value at least one month after completing course of parenteral iron	*P* value
Serum iron *μg/dL* ($N = 136$)	54.9 ± 40.1	57.9 ± 28.5	0.43
Total iron binding capacity *μg/dL* ($N = 136$)	248 ± 68	229 ± 64	<0.001
Transferrin saturation % ($N = 136$)	22.4 ± 12.6	25.9 ± 11.6	0.008
Serum ferritin *ng/mL* ($N = 133$)	200 ± 147	319 ± 185	<0.001

30 to 33%. Therefore, the expected response of iron-deficient patients receiving parenteral iron during this phase would be a decrease in the epoetin dose necessary to maintain the target hematocrit. Figure 3 summarizes the changes in average weekly epoetin dose following a course of parenteral iron. The weekly dose began to fall in the fourth week after beginning iron administration, continued to fall over the next several weeks, and reached the maximum decrease by the 12th week after the initiation of therapy. At week 12, the mean decrease in epoetin dose was 1763 ± 3841 U/week.

To determine the diagnostic accuracy of our iron parameters, we examined the ability of different values to predict a response to parenteral iron administration. Using the data from patients who received parenteral iron during the maintenance phase of our study, we have developed a functional definition of iron deficiency. Only patients receiving parenteral iron during the 26-week maintenance phase of the study were included in this analysis, since it was the only phase of the study in which hematocrit was maintained in the target range of 30 to 33%. Patients were defined as having functional iron deficiency if after receiving a course of parenteral iron, they were able to have a reduction in their weekly epoetin dose of at least 30 U/kg/week in the subsequent 12 weeks, while maintaining the target hematocrit of 30 to 33%. A dose change of 30 U/kg/week was the minimal change allowed by this dosing algorithm and corresponded to 32% of the average dose (95 U/kg/week) in the group receiving epoetin subcutaneously and 21% of the average dose (140 U/kg/week) in the group receiving epoetin intravenously. Forty of 60 (67%) of those patients receiving parenteral iron during the maintenance phase of the study had a decrease in their epoetin dose, while only 6 of 21 (29%) patients not receiving parenteral iron had a similar decrease ($P = 0.004$ by Fisher's exact test). If a more restrictive definition of a response to parenteral iron as a change in dose of at least 60 U/kg/week was used, 24 of 60 (40%) patients receiving parenteral iron responded. Only 2 of 21 (10%) patients not receiving parenteral iron had a spontaneous change in their epoetin dose of this magnitude ($P = 0.01$).

Using this functional definition of iron deficiency, we have examined the diagnostic accuracy of different thresholds for serum ferritin and transferrin saturation in predicting the response to parenteral iron (Table 4). The conventional tests of diagnostic accuracy, sensitivity, and specificity could not be used since parenteral iron was administered to a selected group of study patients, those with a serum ferritin <100 ng/mL or the combination of a transferrin saturation <20% and a serum ferritin <400 ng/mL. Table 4 lists the number of true positives, patients whose iron parameters fell below the threshold value and who had reduction in epoetin dose after parenteral iron administration, and true negatives, patients whose iron parameters exceeded a threshold value and who did not have a reduction in epoetin dose after parenteral iron administration. We also calculated the positive pre-

Table 3. Effect of parenteral iron on iron parameters stratified by baseline values

		Transferrin saturation				Serum ferritin			
	N	Prior to iron	One month after iron	Change	*P*	Prior to iron	One month after iron	Change	*P*
Serum ferritin									
<100 ng/mL	47	27.3 ± 11.8	29.7 ± 9.7	2.4 ± 15.3	0.28	78 ± 17	216 ± 87	138 ± 90	<0.001
100–199 ng/mL	35	19.7 ± 10.1	25.0 ± 11.1	5.3 ± 10.1	0.004	153 ± 29	297 ± 155	143 ± 152	<0.001
200–299 ng/mL	28	22.3 ± 17.6	25.3 ± 15.5	3.0 ± 22.6	0.50	244 ± 29	364 ± 165	120 ± 155	<0.001
300–399 ng/mL	14	17.2 ± 4.7	20.8 ± 7.4	3.6 ± 9.1	0.16	349 ± 28	409 ± 164	59 ± 173	0.22
≥400 ng/mL	10	19.7 ± 7.6	19.2 ± 7.2	−0.5 ± 8.8	0.88	589 ± 130	615 ± 286	26 ± 335	0.81
Transferrin saturation									
<20%	77	15.3 ± 4.0	23.2 ± 11.2	7.9 ± 11.7	<0.001	233 ± 135	356 ± 177	124 ± 167	<0.001
>20%	59	31.6 ± 14.0	29.5 ± 11.4	−2.1 ± 17.4	0.35	157 ± 153	270 ± 185	113 ± 152	<0.001

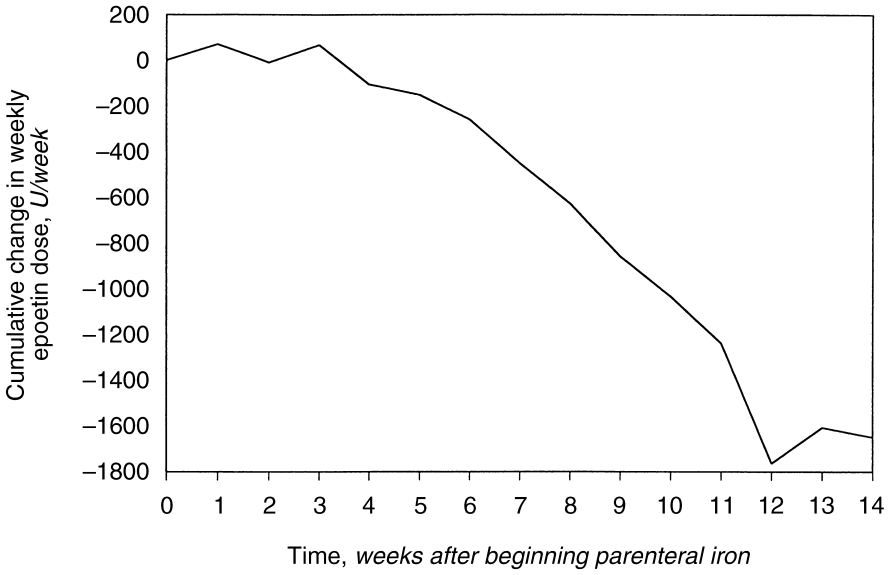

Fig. 3. Changes in epoetin dose after beginning iron therapy.

dictive value, the proportion of patients with a value for the iron parameter below the threshold value who had a reduction in epoetin dose after parenteral administration, and the negative predictive value, the proportion of patients with a value for the iron parameter exceeding the threshold value who did not have a reduction in epoetin dose after parenteral iron administration. Because parenteral iron was not administered to patients with serum ferritins >400 ng/mL, no negative predictive value can be calculated for this value. We summarized the parameters for the two different definitions of functional iron deficiency, either a change in dose of ≥30 U/kg/week or ≥60 U/kg/week. No iron parameter had a positive and negative predictive value exceeding 0.80, a commonly used cutoff for diagnostic utility. A serum ferritin value <200 had the best diagnostic utility with the highest combined positive and negative predictive value at both definitions of functional iron deficiency.

DISCUSSION

In the absence of iron replacement, the development of iron deficiency during epoetin therapy is common [8], and several authors have shown that oral iron is often inadequate to maintain iron stores [9, 10]. In our study, although all patients received oral iron, 87% required parenteral iron at some time during the study to replete their iron stores. The average total dose of iron received per patient was 1516 ± 1173 mg over an average time of 41.7 ± 17.3 weeks, or approximately 36 mg/week. The National Kidney Foundation has recommended administering 25 to 100 mg of parenteral iron weekly as maintenance iron therapy [7]. The actual requirements in our patient population fall at the lower end of this recommendation.

The administration of parenteral iron in the doses utilized in our study (1000 mg over 10 dialysis sessions) results in a rapid response in terms of epoetin dose and iron indices. Epoetin doses begin decreasing within four

Table 4. Diagnostic accuracy of serum ferritin and transferrin saturation in predicting response to parenteral iron

	Epoetin dose change of ≥*30 U/kg/week*				Epoetin dose change of ≥*60 U/kg/week*			
	True positives	True negatives	Positive predictive value	Negative predictive value	True positives	True negatives	Positive predictive value	Negative predictive value
Serum ferritin threshold								
<100 ng/mL	13	16	0.76	0.37	10	30	0.63	0.37
<200 ng/mL	29	11	0.76	0.50	19	19	0.53	0.79
<300 ng/mL	37	3	0.68	0.50	22	5	0.42	0.714
<400 ng/mL	40	0	0.67	NA	24	0	0.40	NA
Transferrin saturation threshold %								
<12	2	17	0.40	0.31	2	33	0.40	0.60
<16	6	13	0.46	0.28	5	28	0.39	0.60
<20	24	6	0.63	0.28	14	12	0.37	0.55
<24	29	4	0.64	0.27	18	9	0.40	0.60
<28	37	4	0.70	0.57	20	8	0.42	0.67

NA is not applicable.

weeks of initiating parenteral iron therapy and continue to fall for the subsequent eight weeks. The average decrease in dose of 1763 U/week in response to parenteral iron administration is 20% of the average maintenance epoetin dose of 8694 U/week [5], indicating that parenteral iron administration results in a clinically significant reduction in epoetin dose. Values for serum iron, total iron binding capacity, transferrin saturation, and serum ferritin reach a new baseline within one month of iron administration. Lynn, Mitchell, and Shepperd examined the rate of change in serum ferritin after 1 g of parenteral iron therapy administered to 15 patients on hemodialysis not receiving epoetin [11]. At one to two months, the average rise in serum ferritin was 228 ng/mL (range 163 to 364) for each gram of iron administered intravenously. Our patients had an average increase in serum ferritin of 152 ng/mL one month after administering 1 g of parenteral iron.

We noted that serum ferritin and transferrin saturation decreased rapidly prior to iron administration in those patients meeting our criteria for parenteral iron administration. In the month prior to the first laboratory determination with a transferrin saturation <20%, the value was 27.6 ± 8.5%, decreasing to 16.0 ± 3.3% in the following month. Similarly, in patients with serum ferritins <200 ng/mL, the values decreased from 286 ± 101 to 153 ± 37 ng/mL within one month. These findings suggest that patients may have transferrin saturation and serum ferritin values that are considered quite adequate and within one month develop values diagnostic of iron deficiency. If routine determinations of iron diagnostic indices are done quarterly, as is common practice, patients may have unrecognized iron deficiency for several months.

The use of parenteral iron in our study was relatively free of adverse events, with only two serious reactions, both hypotensive episodes, out of 3588 (0.04%) doses of iron and 180 (1.1%) patients. Fishbane et al retrospectively reviewed the safety of intravenous iron dextran in 573 hemodialysis patients and found a similar low incidence of adverse events, with 27 patients (4.7%) having adverse reactions [12]. Four (0.7%) had serious reactions, including one cardiac arrest and three hospitalizations, but no deaths. Ten patients (1.7%) had anaphylactoid reactions including the four serious reactions. Hypotension occurred in 0.5%.

Although the importance of iron deficiency as a cause of epoetin hyporesponsiveness in hemodialysis patients is well recognized, considerable controversy surrounds its diagnosis. The "gold standard" for diagnosis in the nonuremic population has been low or absent iron staining on bone marrow aspirates. Several studies have compared the standard serum iron parameters of transferrin saturation and serum ferritin to iron staining of bone marrow samples in hemodialysis patients not receiving epoetin. Most of these studies indicate that serum ferritin correlates well with bone marrow iron staining. Values of serum ferritin from 35 to 300 ng/mL may be indicative of iron deficiency, while serum ferritins >300 ng/mL indicate adequate bone marrow iron content [13–17]. However, Ali et al found that serum ferritin did not correlate with bone marrow iron stores in 36 hemodialysis patients [3]. In their study, performed before the availability of epoetin, serum ferritin was increased in ten marrow-iron-depleted subjects. The subjective nature of the assessment of bone marrow iron content has been highlighted by some authors, who argue that the absence of visible stainable bone marrow iron cannot be equated with depleted iron stores [18]. Furthermore, there are no studies correlating bone marrow iron staining with the response to parenteral iron in patients with chronic renal failure.

Several investigators have correlated the hemoglobin response to parenteral iron administration with iron parameters prior to administration in patients not receiving epoetin. Allegra, Mengozzi, and Vasile found that in 72 hemodialysis patients, no patient with a serum ferritin

>191 ng/mL responded to iron with an increase in hemoglobin, while eight of 27 patients with a serum ferritin of 19 to 191 ng/mL and 14 of 30 with a serum ferritin <19 ng/mL responded [19]. Lynn, Mitchell, and Shepperd examined the response to 1 g of parenteral iron in 31 hemodialysis patients [11]. No patient with a serum ferritin >55 ng/mL had an increase in hemoglobin concentration of >1 g/dL, while 17 of 21 patients with a serum ferritin <55 ng/mL had an increase in hemoglobin concentration of >1 g/dL. This difference was highly significant ($P < 0.001$). Beallo et al found that a serum ferritin <35 ng/mL not only correlated with absent bone marrow iron stores, but also predicted a positive response to parenteral iron [20].

The studies cited previously in this article were performed in patients not receiving epoetin. It has been suggested that the iron levels needed for adequate erythropoiesis in hemodialysis patients may be increased under exogenous epoetin stimulation [1]. Patients may have adequate iron stores, but diminished responsiveness to epoetin administration that can be enhanced by parenteral iron administration. We have examined this phenomenon by developing a functional definition of iron deficiency based on the response of our patients to parenteral iron administration. If patients responded to intravenous iron dextran with a subsequent fall in their epoetin requirements (≥30 U/kg/week) while maintaining a stable hematocrit, they were defined as being functionally iron deficient. In the 26-week maintenance phase of our study, during which epoetin doses were carefully adjusted to maintain our target hematocrit of 30 to 33%, 60 patients received parenteral iron. Sixty-seven percent had a decrease in their epoetin dose of ≥30 U/kg/week in the subsequent weeks. In contrast, only 29% not receiving parenteral iron had a similar spontaneous decrease in their epoetin dose.

Fishbane et al have also used the response to parenteral iron to define iron deficiency in patients receiving epoetin [4]. Forty-seven patients with serum ferritin levels <600 ng/mL were treated with intravenous iron dextran, 1000 mg over 10 dialysis sessions. The target hematocrit range was 30 to 34%. The patients were followed for two months and those whose hematocrit values increased by 5% or who had a 10% decrease in their epoetin dose were classified as having iron deficiency. In results similar to those in the current report, they found that 31 (66%) of these patients responded to parenteral iron.

They have also examined the utility of iron indices in predicting the responses to parenteral iron in patients receiving epoetin [4, 21, 22]. When these authors examined the predictive value of specific serum ferritin and transferrin saturation thresholds, they found that the receiver operating curves demonstrated that none of the indices had a high level of utility (sensitivity and specificity >80%). The best cutoff values for the diagnosis of iron deficiency were a serum ferritin <150 ng/mL (sensitivity of 71% and a specificity of 69%) or a transferrin saturation <21% (sensitivity of 81% and specificity of 63%) [4]. These cutoff values are similar to our finding that a serum ferritin of <200 ng/mL had the best combined positive and negative predictive value, but with limited clinical utility. We were unable to demonstrate clinically useful predictive utility for any cutoff values for transferrin saturation.

We used a parenteral iron algorithm that standardized the administration of iron in response to abnormal iron indices. Several authors have suggested that intravenous iron should be given on a maintenance schedule in hemodialysis patients, with regular weekly, biweekly, or monthly doses [23, 24]. In studies comparing these regimens to oral iron, lower doses of epoetin for similar or high hematocrits were necessary in patients receiving maintenance intravenous iron. However, no studies are available comparing this regimen with regimens similar to ours, where parenteral iron is given in response to abnormal iron indices. In our study, the average reduction in epoetin dose 12 weeks following parenteral iron therapy was 1763 ± 3841 U/week. It is possible that with maintenance iron therapy periods of iron deficiency can be avoided, allowing for sustained reductions in epoetin dose. Our finding that iron parameters may decrease markedly over a period of a month also suggest an advantage for regular maintenance iron therapy, rather than administering it in response to abnormal ferritins or transferrin saturations.

It should be recognized that the major benefit of parenteral iron administration in hemodialysis patients receiving epoetin is the lowering of the epoetin dose. As indicated by our results, although the average dose reduction is clinically significant, 1763 U/week or approximately 20% of the average weekly dose, a significant number of patients do not respond to iron administration with an increased hematopoietic response. Only 66% of patients had a dose reduction ≥30 U/kg/week, and only 40% had a reduction of ≥60 μ/kg/week. It would be useful to have cutoff values of transferrin saturation or ferritin that would predict a positive response to iron, but we and others have not been able to define clinically useful cutoff values [4]. Using our iron dosing algorithm, we administered parenteral iron to 87% of our study population and noted a clinically important epoetin dose reduction in 40 to 66% of patients. Whether it is clinically desirable to administer parenteral iron to a significant minority of patients who may not benefit with a reduction in epoetin dose depends on the risks and economic costs of parenteral iron administration. The risk of a severe acute reaction to parenteral iron dextran has been reported to be 0.7%, although it is probably lower with newer parenteral iron preparations [12, 25]. Several long-term risks associated with iron administration have been proposed, including tissue iron accumulation, increased

free radical generation, increased cardiovascular mortality, and increased infection risk [24]. These risks remain theoretical at the current time and would require large, long-term trials to confirm.

Regarding economic costs, these have not been rigorously assessed. Recently, Besarab et al have published a study comparing two protocols for maintenance iron infusions and demonstrated that from a dialysis facilities perspective, targeting a transferrin saturation of 30 to 50% versus 20 to 30% was cost effective even though it required an increase in monthly maintenance parenteral iron administration from 176 to 501 mg/month [26]. It seems likely that given the poor predictive value of the readily available iron parameters, in order to effect an overall epoetin dose reduction in the hemodialysis population, parenteral iron will need to be administered to a significant percentage of patients who will not respond with an epoetin dose reduction. What the appropriate upper limit of serum ferritin should be to minimize the potential long-term consequences of parenteral iron administration remains to be determined.

Our study shows that the majority of patients receiving epoetin and prescribed the usual doses of oral iron require parenteral iron to maintain adequate iron stores. Changes in iron indices develop rapidly with marked decreases occurring over a period of one month. Therefore, providing parenteral iron in response to abnormal quarterly determinations of iron indices, as is commonly done, may leave patients iron deficient for prolonged periods. Acute adverse reactions to the administration of iron dextran were infrequent, with only 2 of 180 patients experiencing serious reactions. Parenteral iron administration according to our protocol reduces epoetin requirements. Two thirds of the patients had a reduction in their epoetin requirement of at least 30 U/kg/week. The average dose decrease 12 weeks after initiating parenteral iron was 1763 U/week. Analyzing the ability of serum ferritin or transferrin saturation to predict a positive response to parenteral iron indicated that neither of these indices had combined positive and negative predictive values >0.80. A serum ferritin <200 ng/mL was the best value for predicting a response to parenteral iron, but had limited clinical utility.

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APPENDIX

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REFERENCES

1. Fishbane S, Maesaka JK: Iron management in end-stage renal disease. *Am J Kidney Dis* 29:319–333, 1997
2. Guyatt GH, Oxman AD, Ali M, *et al:* Laboratory diagnosis of iron deficiency anemia: An overview. *J Gen Intern Med* 7:145–153, 1992
3. Ali M, Fayemi AO, Franscino J, *et al:* Failure of serum ferritin levels to predict bone-marrow iron content after intravenous iron-dextran therapy. *Lancet* 1:652–655, 1982
4. Fishbane S, Kowalski EA, Imbiano LJ, Maesaka JK: The evaluation of iron status in hemodialysis patients. *J Am Soc Nephrol* 7:2654–2657, 1996
5. Kaufman JS, Reda DJ, Fye CL, *et al:* Subcutaneous versus intravenous administration of erythropoietin in hemodialysis patients. *N Engl J Med* 339:578–583, 1998

6. *SAS/STAT User's Guide* (version 6, vols 1 and 2, 4th ed). Cary, SAS Institute, 1989
7. NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. *Am J Kidney Dis* 30(Suppl):S192–S240, 1997
8. Van Wyck D, Stivelman J, Ruiz J, *et al:* Iron status in patients receiving erythropoietin for dialysis-associated anemia. *Kidney Int* 35:712–716, 1989
9. MacDougall IC, Tucker B, Thompson J, *et al:* A randomized study of iron supplementation in patients treated with erythropoietin. *Kidney Int* 50:1694–1699, 1996
10. Wingard RL, Parker RA, Ismail N, Hakim RM: Efficacy of oral iron therapy in patients receiving recombinant human erythropoietin. *Am J Kidney Dis* 25:433–439, 1995
11. Lynn K, Mitchell T, Shepperd J: Serum ferritin concentration in patients receiving maintenance hemodialysis. *Clin Nephrol* 14:124–127, 1980
12. Fishbane S, Ungureanu V, Maesaka JK, *et al:* The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 28:529–534, 1996
13. Aljama P, Ward M, Pierides A, *et al:* Serum ferritin concentration: A reliable guide to iron overload in uremic and hemodialyzed patients. *Clin Nephrol* 10:101–104, 1978
14. Bell JD, Kincaid WR, Morgan RG, *et al:* Serum ferritin and bone-marrow iron stores in patients on maintenance hemodialysis. *Kidney Int* 17:237–241, 1980
15. Gokal R, Millard P, Weatherall D, *et al:* Iron metabolism in haemodialysis patients. *Q J Med* 191:369–391, 1979
16. Kalantar-Zadeh K, Hoffken B, Wunsch H, *et al:* Diagnosis of iron deficiency anemia in renal failure patients during the post-erythropoietin era. *Am J Kidney Dis* 26:292–299, 1995
17. Moreb J, Popovtzer M, Friedlander M, *et al:* Evaluation of iron status in patients on chronic hemodialysis: Relative usefulness of bone marrow hemosiderin, serum ferritin, transferrin saturation, mean corpuscular, and red cell protoporphyrin. *Nephron* 35:196–200, 1983
18. Cavill I: Diagnostic methods. *Clin Hematol* 11:259–273, 1982
19. Allegra V, Mengozzi G, Vasile A: Iron deficiency in maintenance hemodialysis patients: Assessment of diagnosis criteria and of three different iron treatments. *Nephron* 57:175–182, 1991
20. Beallo R, Dallmann P, Schoenfeld P, Humphreys M: Serum ferritin and iron deficiency in patients on chronic hemodialysis. *Trans Am Soc Artif Int Organs* 22:73–79, 1976
21. Fishbane S, Lynn RI: The utility of zinc protoporphyrin for predicting the need for intravenous iron therapy in hemodialysis patients. *Am J Kidney Dis* 25:426–432, 1995
22. Fishbane S, Galgano C, Langley RCJ, *et al:* Reticulocyte hemoglobin content in the evaluation of iron status of hemodialysis patients. *Kidney Int* 52:217–222, 1997
23. Fishbane S, Frei GL, Maesaka J: Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *Am J Kidney Dis* 26:41–46, 1995
24. Besarab A, Frinak S, Yee J: An indistinct balance: The safety and efficacy of parenteral iron therapy. *J Am Soc Nephrol* 10:2029–2043, 1999
25. Bailie GR, Johnson CA, Mason NA: Parenteral iron use in the management of anemia in end-stage renal disease patients. *Am J Kidney Dis* 35:1–12, 2000
26. Besarab A, Amin N, Ahsan M, *et al:* Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. *J Am Soc Nephrol* 11:530–538, 2000