Predictors of the response to treatment in anemic hemodialysis patients with high serum ferritin and low transferrin saturation

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Treating hemodialysis patients to combat anemia corrects hemoglobin but exacerbates iron deficiency by utilizing iron stores. Patients needing iron should receive this by intravenous (i.v.) means. The Dialysis patients' Response to IV iron with Elevated ferritin (DRIVE) trial investigated the role of i.v. iron in anemic patients with high ferritin, low transferrin saturation, and adequate epoetin doses. We examined whether baseline iron and inflammation markers predict the response of hemoglobin to treatment. Patients (134) were randomized to no added iron or to i.v. ferric gluconate for eight consecutive hemodialysis sessions spanning 6 weeks with epoetin increased by 25% in both groups. The patients started with hemoglobin less than or equal to 11 g/dl, ferritin between 500 and 1200 ng/ml, and transferrin saturation of less than 25%. Significantly, patients with a reticulocyte hemoglobin content greater than or equal to 31.2 pg were over five times more likely to achieve a clinically significant increase in hemoglobin of greater than 2 g/dl. Lower reticulocyte hemoglobin contents did not preclude a response to i.v. iron. Significantly higher transferrin saturation or lower C-reactive protein but not ferritin or soluble transferrin receptor levels predicted a greater response; however their influence was not clinically significant in either group. We conclude that none of the studied markers is a good predictor of response to anemia treatment in this patient sub-population.

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Anemia treatment in the hemodialysis population with erythropoiesis-stimulating agents increases hemoglobin but consumes iron stores, frequently resulting in iron deficiency. Blood loss in the dialysis circuit, laboratory testing, interventional procedures, and gastrointestinal bleeding lead to continuing iron losses.[1] Oral iron therapy is usually ineffective in providing sufficient iron in this population.[1,2] Consequently, the National Kidney Foundation-Kidney Disease Outcome Initiative (NKF-KDOQI) strongly recommends that hemodialysis patients needing iron should be treated with intravenous (i.v.) iron therapy.[1–3]

Serum ferritin and transferrin saturation (TSAT) are routinely utilized in dialysis patients to aid in diagnosing iron deficiency and in guiding iron therapy. Uniformly low TSAT ($<20\%$) and ferritin (<200ng/ml) are clear indicators of iron deficiency and predict a higher likelihood of response to i.v. iron.[1] When TSAT and ferritin are both elevated, that is, TSAT $>20\%$ and ferritin >200 ng/ml, adequate iron stores are likely present and the likelihood of response to iron is low. However, ferritin and TSAT values are frequently discordant, as they are, respectively, positive and negative acute phase reactants.[4] Consequently, in the setting of inflammation or malnutrition, simultaneously high ferritin and low TSAT are frequently encountered and difficult to evaluate.[1,2]

Ideally, other tests could predict responsiveness to i.v. iron. Studies in hemodialysis patients have repeatedly found TSAT and ferritin as poor predictors of hemoglobin responsiveness to i.v. iron.[5–9] However, these studies have several limitations, including enrolling limited numbers of patients with ferritin values >500 ng/ml and lack of adequate control groups.[4] The 2006 KDOQI Anemia guidelines noted a lack of sufficient evidence of responsiveness to iron when ferritin is >500 ng/ml, and stated 'routine administration' could not be recommended.[1] Additionally, the guidelines recommended use of reticulocyte hemoglobin content (CHr) <29 pg/cell as an indicator of iron deficiency.[1] When evaluating iron needs in patients with ferritin >500 ng/ml, factors such as erythropoiesis-stimulating agents dose,

clinical status, TSAT values, and hemoglobin trends should be taken into account.[1]

Since release of the 2006 KDOQI anemia guidelines, the Dialysis Patients' Response to i.v. iron with Elevated ferritin (DRIVE) study has demonstrated that ferric gluconate was superior to no iron in improving hemoglobin levels in anemic hemodialysis patients with ferritin of 500–1200 ng/ml and TSAT $\leqslant$25%.[10] By week 6, patients receiving 1 g of ferric gluconate in addition to a 25% increase in epoetin dose experienced a mean hemoglobin change of 1.6 g/dl compared with only 1.1 g/dl in patients receiving a 25% increase in epoetin dose alone. In addition, the ferric gluconate patients mounted a clinically significant hemoglobin response more frequently and more quickly than the no iron patients. The amount of i.v. iron received by either patient group in the 4 weeks before enrollment had no impact on hemoglobin change.[10] Further, in the observational extension study of DRIVE, also known as DRIVE-II, hemoglobin changes were sustained until at least week 12 from the start of therapy despite significantly lower epoetin doses in the patients randomized to ferric gluconate (Kapoian *et al. J Am Soc Nephrol* 2006; **17**: 479A).

In this report we explore the value of ferritin, TSAT, CHr, C-reactive protein (CRP), and soluble transferrin receptor (sTfR) as predictors of iron responsiveness based on the DRIVE study data, which were pre-specified objectives of that trial. We also investigated the effect of increasing epoetin doses on responsiveness, an important treatment component that has not been studied previously.

RESULTS

Of the 134 randomized patients, 129 were included in the intent-to-treat (ITT) population (no iron $n=65$, i.v. iron $n=64$).[10] Of those 129 patients, 93 were included in the per-protocol (PP) population (no iron $n=50$, i.v. iron $n=43$). Baseline demographic and laboratory characteristics were similar in the two groups in both the ITT and PP populations (Table 1). Of note, >80% of the patients had a baseline CHr >29 pg/cell, the target CHr level recommended by the 2006 KDOQI clinical practice recommendations.[1] Changes in homocysteine levels were similar in the two groups (median change; i.v. iron 0.5 μmol/L vs no iron −1.7 μmol/L, $P=0.598$).

We attempted to explore the underlying reason why patients had a baseline ferritin at or above vs below the

Table 1 | Baseline characteristics by treatment group and analysis population

	ITT population		PP population[a]	
Parameter	No iron (*N*=65)	i.v. iron (*N*=64)	No iron (*N*=50)	i.v. iron (*N*=43)
Age (years)	58.7±15.2	61.2±13.0	59.1±14.9	60.3±12.6
Females (*n* (%))	37 (56.9)	27 (42.2)	29 (58.0)	21 (48.8)
Weight (kg)	75.0±22.3	76.4±21.0	77.6±23.0	71.2±13.8
Height (cm)	168.1±9.8	171.9±36.1	168.9±9.9	165.1±9.6
Race, n (%)				
White	20 (30.8)	20 (31.3)	17 (34.0)	13 (30.2)
African American	33 (50.8)	30 (46.9)	26 (52.0)	20 (46.5)
Hispanic	9 (13.8)	9 (14.1)	6 (12.0)	6 (14.0)
Asian/Pacific Islander	2 (3.1)	5 (7.8)	1 (2.0)	4 (9.3)
Other	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hemodialysis access, n (%)				
AV fistula	30 (46.2)	33 (51.6)	26 (52.0)	20 (46.5)
AV graft	21 (32.3)	20 (31.3)	14 (28.0)	15 (34.9)
Temporary catheter	3 (4.6)	2 (3.1)	2 (4.0)	1 (2.3)
Permanent catheter	11 (16.9)	9 (14.1)	8 (16.0)	7 (16.3)
i.v. iron in previous 4 weeks, *n* (%)	24 (36.9)	22 (34.4)	21 (42.0)	13 (30.2)
i.v. iron given in previous 4 weeks (mg)	70±108	61±103	79.5±113.4	41.9±69.2
Homocysteine (μmol/l)	27.3±9.8	25.4±8.2	27.8±9.1	25.0±6.9
Most recent Kt/*V*	1.7±0.3	1.6±0.4	1.7±0.3	1.7±0.4
Hemoglobin (g/dl)	10.2±0.7	10.4±0.8	10.2±0.7	10.4±0.8
TSAT (%)	19.0±4.1	18.2±4.2	19.3±3.9	18.0±4.4
Serum ferritin (ng/ml)	765±193	759±190	768±182	772±200
CHr (pg/cell)	31.0±2.8	31.4±2.7	31.2±2.8	31.9±2.7
CHr>29 pg/cell, *n* (%)	54 (83.1)	51 (79.7)	43 (86.0)	36 (83.7)
sTfr (mg/l)	6.1±2.2	6.2±2.5	5.9±2.3	6.3±2.6
C-reactive protein (mg/l)[b]	25.5±29.3	29.3±39.2	22.0±23.1	25.5±34.5
Epoetin dose (IU/kg/week)	495±272	448±229	444±234	452±227

CHr, reticulocyte hemoglobin content; ITT, intent-to-treat; PP, per-protocol; TSAT, transferrin saturation; sTfr, soluble transferrin receptor.
Continuous variables are summarized using mean±s.d.
[a]More i.v. iron patients than no iron patients were excluded from the PP population because they had to satisfy one more criterion to be in the PP population (receiving the entire 1 g of i.v. ferric gluconate).
[b]C-reactive protein values were obtained using the high-sensitivity assay.