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ORIGINAL ARTICLE

Anemia

Predictors of iron versus erythropoietin responsiveness in anemic hemodialysis patients

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Abstract

Anemia protocols for hemodialysis patients usually titrate erythropoietin (ESA) according to hemoglobin and iron according to a threshold of ferritin, with variable response seen. A universally optimum threshold for ferritin may be incorrect, and another view is that ESA and iron are alternative anemia treatments, which should be selected based on the likely response to each. Hemodialysis patients developing moderate anemia were randomised to treatment with either an increase in ESA or a course of intravenous iron. Over 2423 patient-months in 197 patients, there were 133 anemia episodes with randomized treatment. Treatment failure was seen in 20/66 patients treated with ESA and 20/67 patients treated with iron (30.3 vs. 29.9%, $p = 1.0$). Successful ESA treatment was associated with lower C-reactive protein (13.5 vs. 28.6 mg/L, $p = 0.038$) and lower previous ESA dose (6621 vs. 9273 μg/week, $p = 0.097$). Successful iron treatment was associated with lower reticulocyte hemoglobin (33.8 vs. 35.5 pg, $p = 0.047$), lower hepcidin (91.4 vs. 131.0 μg/ml, $p = 0.021$), and higher C-reactive protein (29.5 vs. 12.6 mg/L, $p = 0.085$). A four-variable iron preference score was developed to indicate the more favorable treatment, which in a retrospective analysis reduced treatment failure to 17%. Increased ESA and iron are equally effective, though treatment failure occurs in almost 30%. Baseline variables including hepcidin can predict treatment response, and a four-variable score shows promise in allowing directed treatment with improved response rates.

KEYWORDS
anemia, hemodialysis, hepcidin, iron

INTRODUCTION

The pathogenesis of anemia in chronic kidney disease involves both deficiency of, and resistance to erythropoietin, though the relative contribution of these mechanisms can be difficult to determine. The concept of erythropoietin deficiency has the longer history, and following the introduction of recombinant erythropoietin, a

paradigm of dose titration according to hemoglobin level rapidly became the standard clinical approach,[1] with optimum hemoglobin targets examined by interventional study.[2]

With the introduction of erythropoietin, iron overload became rare and iron deficiency more frequent,[3] but the correct amount of therapeutic iron has been harder to define.[4] Recognition of the clinical significance of erythropoietin resistance,[5] combined with advances in the understanding of hepcidin and iron regulation,[6,7] has led to a concept of functional rather than absolute iron deficiency.[8] Functional iron deficiency is defined by the response to iron treatment, but is not easy to predict before treatment is given, and intravenous iron is therefore often given according to a threshold of ferritin well above the normal range, with the aim of eliminating any functional deficiency of iron and maximizing erythropoietin response. The PIVOTAL study recently compared two thresholds for iron treatment in incident hemodialysis patients, demonstrating improved clinical outcomes with more liberal iron use, using a ferritin threshold of 700 ng/ml.[9]

However, some patients with low ferritin have nothing to gain from further iron,[10] while others with high ferritin may still be iron responsive,[11] and ferritin levels differ widely between geographic regions, so the concept of a universally optimum ferritin threshold may be flawed.[12]

A different view is that erythropoietin and iron are alternative treatments for anemia, and that the preferred treatment could be selected according to the likely responses if these were predictable. This aim of this study was to compare increased erythropoietin versus iron treatment, as alternative strategies for anemia in prevalent hemodialysis patients, with the randomized design permitting an unbiased analysis of hepcidin and other potential markers, as diagnostic markers of optimum treatment.

METHODS

Study population and setting

This was a single center, open-label randomized trial, involving a mixed ethnicity hemodialysis population in London, UK. Stable adult patients, on hemodialysis for at least 3 months, were recruited from their satellite hemodialysis units. Those with an established hematological diagnosis, an active malignancy or disorder leading to chronic blood loss were excluded. The study was registered with ClinicalTrials.gov (NCT02707757) and performed in accordance with the Declaration of Helsinki, with written informed consent from participants.

Intervention

Once enrolled, patients continued with standard care including maintenance erythropoietin and monthly monitoring, but without intravenous iron. Stable outpatients developing moderate anemia (90 < hemoglobin<105 g/L) with non-extreme ferritin (100 < ferritin<800 ng/ml) were randomized 1:1 to treatment with either an increase in erythropoietin dose (according to a pre-defined scale, Table S1) or with a course of intravenous iron (iron sucrose 200 mg ×5 doses at consecutive dialysis sessions) without change in erythropoietin dose. No control group (receiving no treatment) was included, since the aim was to compare responses in order to identify markers of the more favourable agent, in those who had reached a threshold for treatment. An online randomization tool was used to generate treatment allocation. Patients already receiving maximal erythropoietin (over 30,000 units per week) were excluded. Treatment response was assessed at 1 and 2 months from randomization with no further treatment change during this interval. Participants were excluded from further study randomization for 6 months. Anticipating the analysis of up to ten variables predictive of treatment response, this study aimed to recruit sufficient patients to achieve 200 randomization episodes.

Outcome measures

The primary outcome was treatment response, defined as positive if an increase in hemoglobin of at least 5 g/L was observed within 2 months from randomization. Those remaining moderately anaemic and consenting to continue with the study were given the alternative treatment after month 2, with response assessed by month 4. Baseline variables were assessed for their ability to predict treatment response. Additional blood samples were taken at randomization for measurement of red cell parameters including reticulocyte hemoglobin using the XN-9000 analyzer (Sysmex, UK) and hepcidin by enzyme-linked immunosorbent assay (DRG International, New Jersey).

Statistical analysis

The proportion of patients responding and the hemoglobin level achieved were compared between groups with the Fisher exact test and students' *t* test, respectively. The

t test was also used to compare potential diagnostic parameters between responders and non-responders in either group, with analysis of variance (ANOVA) used to detect treatment interactions, suggesting a parameter's ability to detect the preferred treatment. Odds ratios were calculated for erythropoietin versus iron response at different levels of predictive markers, with those over 2 or below 0.5 used to develop a clinical score, which was then assessed by retrospective performance in the same patients. Analyses were performed using SPSS v 23.0 (IBM, New York).

RESULTS

From three satellite hemodialysis units, between June 2015 and December 2016, 197 stable hemodialysis patients (aged 25–91, 69.9% male) were recruited. During the observation of 2423 patient-months there were 150 episodes of moderate anemia (90 < hemoglobin<104 g/L) with non-extreme ferritin (100 < ferritin<800 ng/mL) leading to randomization and treatment, either with an increase in erythropoietin dose (according to a predefined scale, Table S1) or with a course of intravenous iron (iron sucrose 200 mg x5 doses at consecutive dialysis sessions) without change in erythropoietin dose, with complete follow-up in 133 cases. Randomization episodes took place between July 2015 and November 2016, with baseline characteristics given in Table 1, and full details of patient flow and numbers available for analysis given in Figure 1.

Treatment failure (hemoglobin failing to increase by at least 5 g/L within 2 months of randomization) was seen in 20/66 patients treated with erythropoietin and 20/67 patients treated with iron (30.3 vs. 29.9%, $p = 1.0$, Table 2). In those with persistent moderate anemia at month 2, there were 34 continuing in the study who were given crossover treatment (12 receiving iron and 22 receiving increased erythropoietin). Amongst those suitable for analysis 2 months later, continuing treatment failure was observed in 2/18 subsequently given erythropoietin, and 2/9 patients subsequently given iron (11.1 vs. 22.2%, $p = 0.58$, Table 2). Mean hemoglobin at month 2 [and month 4 in those with continuing anemia] did not differ between those randomised initially to receive erythropoietin or iron (106.8[109.6] vs. 105.6[109.0]g/l, respectively, $p = 0.55$[0.89], Figure 2).

Considering both study stages together, erythropoietin and iron were equally effective treatments with treatment failure seen in 22/84 and 20/74 patients, respectively (26.2 vs. 28.9%, $p = 0.91$). The initial characteristics of responders and non-responders were compared to determine markers associated with response to either treatment. Compared to non-responders, those with increased hemoglobin following erythropoietin treatment had lower C-reactive protein (CRP, 13.5 vs. 28.6 mg/L, $p = 0.038$), lower previous erythropoietin dose (6621 vs. 9273 μg/week, $p = 0.097$), and higher serum hydroxycobalamin (B12, 531 vs. 389 ng/ml, $p = 0.059$) despite only four patients being biochemically deficient (2 of whom still responded). Following treatment with iron, compared to non-responders, those with increased hemoglobin had lower mean cell volume (MCV, 90.6 vs. 94.5 fl, $p = 0.034$), lower reticulocyte hemoglobin (Ret-He, 33.8 vs. 35.5 pg, $p = 0.047$), lower hepcidin (91.4 vs. 131.0 μg/ml, $p = 0.021$), lower transferrin saturation (Tsat, 24.4 vs. 31.2%, $p = 0.017$), and higher CRP (29.5 vs. 12.6 mg/L, $p = 0.085$).

Ferritin was not predictive of treatment response in either group (Figure 3). Other non-predictive parameters included reticulocyte count, albumin, parathyroid

TABLE 1 Characteristics of participants and baseline parameters at randomization episodes

	Erythropoietin increase	Iron sucrose 200 mg x5
Patients	61	59
Age	65 (55–75)	63 (53–73)
Gender (male)	45 (73.8%)	43 (72.9%)
Ethnicity		
White	30 (49.2%)	25 (42.4%)
Black	10 (16.4%)	8 (13.6%)
Asian/other	21 (34.4%)	26 (44.0%)
Comorbidity		
Diabetes	28 (45.9%)	24 (40.7%)
Vascular disease	23 (37.9%)	21 (35.6%)
Randomization episodes	66	67
Treatment parameters		
Ferritin (ng/ml)	267 (159–394)	235 (172–314)
Hemoglobin (g/L)	97 (95–101)	99 (97–102)
Albumin (g/L)	34 (32–37)	34 (31–37)
Hepcidin (ng/ml)	60 (45–106)	81 (60–133)
CRP (mg/L)	12.4 (5.0–19.3)	9.4 (5.0–20.5)
Tsat (%)	25 (20–31)	24 (17–33)
EPO dose (units/week)	6000 (3000–9000)	6000 (3000–15,000)

Note: Results given as median (IQR) or number(%).
Abbreviations: CRP, C-reactive protein; EPO, erythropoietin; Tsat, transferrin saturation.

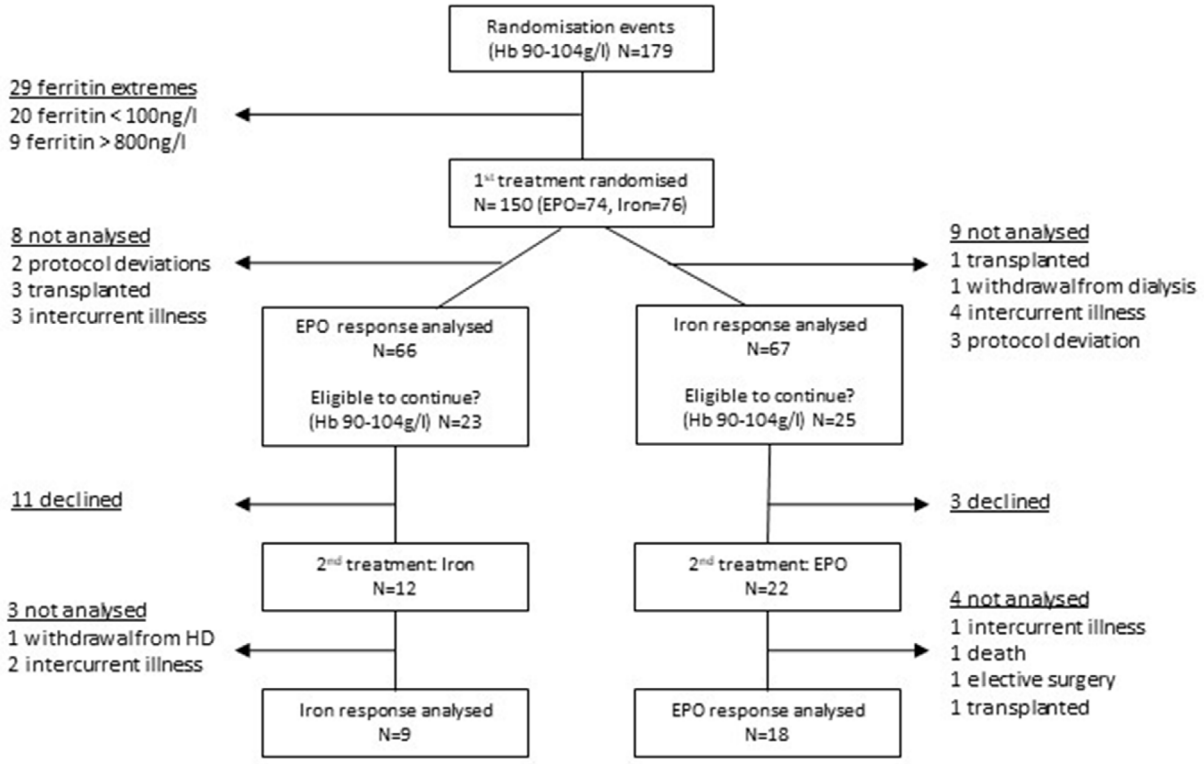

FIGURE 1 Patient flow through the study. The number of participants is provided at each stage and reasons for exclusion from analysis

TABLE 2 Hemoglobin outcome within two months of treatment

		1st treatment (randomised)		2nd treatment (crossover)	
		EPO	Iron	EPO	Iron
Number analyzed		66	67	18	9
Responders	Hb ≥ 105 g/L	37 (56.1)	37 (55.2)	13 (72.2)	6 (66.7)
	Hb < 105 g/L	9 (13.6)	10 (14.9)	3 (16.7)	1 (11.1)
Non-responders	Hb ≥ 90 g/L	14 (21.2)	15 (22.4)	1 (5.6)	2 (22.2)
	Hb < 90 g/L	6 (9.1)	5 (8.3)	1 (5.6)	0 (0.0)

Note: Results given as number(percentage).
Abbreviations: EPO, erythropoietin; Hb, hemoglobin.

hormone, comorbidity, and number of therapeutic anti-platelet agents taken.

The ability of parameters to distinguish between erythropoietin and iron as the preferred treatment was assessed by ANOVA with significant treatment interaction effects seen for CRP and previous erythropoietin dose, and weaker interactions seen for Ret-He and hepcidin (Figure 3). Effect sizes were explored by calculating odds ratios for erythropoietin versus iron response at three levels for each parameter (Figure 4). Odds ratios over 2 or below 0.5 were seen for high and low levels of CRP and erythropoietin dose, as well as for low hepcidin and high Ret-He. While high Tsat predicted a poor iron response, it also predicted a poor erythropoietin response, with neither ferritin nor Tsat determining the preferred treatment.

Odds ratios over 2 or below 0.5 were used to construct an iron preference score for selecting preferred treatment (higher score indicating more likely response to iron rather than erythropoietin), based on baseline levels of four parameters: CRP, erythropoietin dose, hepcidin and Ret-He (Table S2). The percentage treated with erythropoietin or iron, and treatment failure rates for different thresholds of the iron score were then estimated using

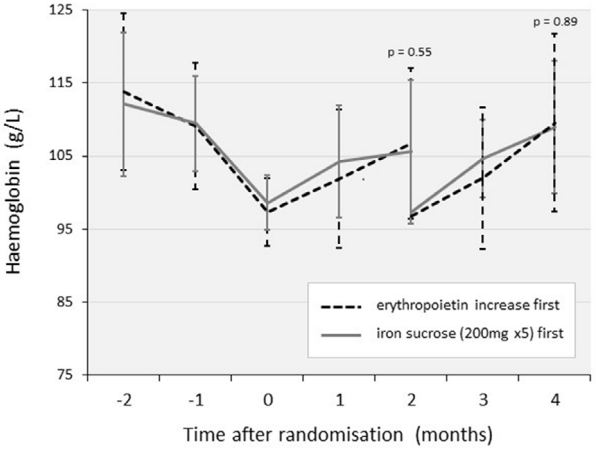

FIGURE 2 Hemoglobin response by randomization group. Participants continuing in the study, with inadequate response at 2 months, received crossover treatment, and are represented in months 2–4

actual responses within the study, in a manner analogous to a receiver operating characteristic curve (Figure S1). At the optimum threshold, this score selected erythropoietin as the treatment in 44% of cases and iron in 56%, and suggested that overall treatment failure would be reduced to 17%.

Following randomization, unrelated intercurrent illnesses leading to exclusion from analysis occurred in three patients treated with erythropoietin and four treated with iron, some of whom received transfusion during their inpatient episode. There were also five protocol deviations leading to exclusion from analysis: in one of these, following randomization to iron, a patient received a blood transfusion after a non-scheduled blood test, without developing symptoms. Other than this, there were no other transfusions in randomized patients.

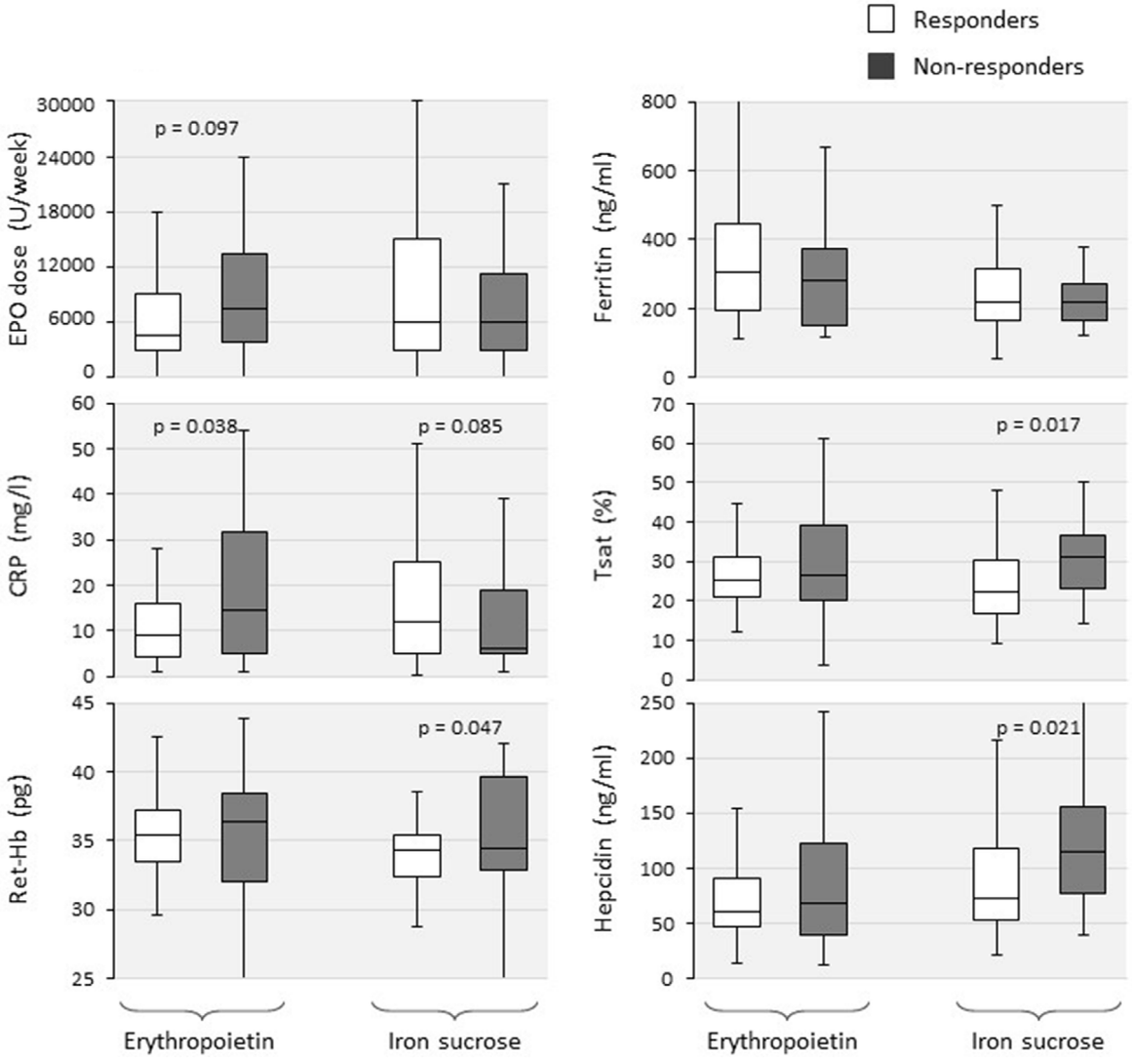

FIGURE 3 Baseline predictors in responders and non-responders. Erythropoietin responders had lower baseline CRP and EPO dose, whereas iron responders had lower hepcidin, Tsat and Ret-Hb, and higher CRP

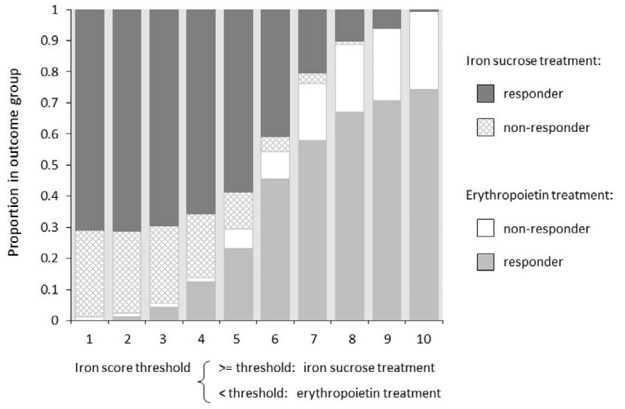

FIGURE 4 Response observed by threshold of iron score. Higher iron score predicts a more favorable response to iron than erythropoietin. In this model, iron is given to those with iron score > = threshold, erythropoietin is given otherwise, with outcomes estimated by retrospective analysis of the group. At a low threshold (left of the chart) almost all receive iron with around 30% non-response. Moving to the right as threshold increases, iron is given to smaller proportion of patients but the non-response rate is reduced. The same is true for erythropoietin moving from right to left of the chart. Using a threshold of 6, overall non-response (middle two categories) was seen in 12.4%

DISCUSSION

For a stable hemodialysis patient developing moderate anemia with non-extreme ferritin, increased erythropoietin and intravenous iron are equally effective at improving hemoglobin. With no parameter to choose between them, neither strategy has a clear advantage, but failure to respond occurs in almost 30% with either. Several baseline parameters including hepcidin, but not ferritin, were predictive of treatment response to either erythropoietin or iron, and parameters best able to determine preferred treatment were CRP and current erythropoietin dose. A four-variable iron preference score was developed to predict optimum strategy, which in a retrospective analysis reduced treatment failure to 17%.

Current protocols for anemia in most dialysis units titrate erythropoietin dose to hemoglobin level: the development of anemia therefore leads to an increase in erythropoietin, without consideration of iron treatment alone.[13] Separately, iron treatment is titrated according to ferritin, or a combination of ferritin and Tsat, but largely without reference to hemoglobin.[14,15] Using this kind of protocol, the PIVOTAL study compared two different iron dosing patterns in incident hemodialysis patients, according to ferritin and Tsat threshold.[9] Throughout the study (median 2.1 years), the liberal iron group received almost twice as much iron, but required around 25% less erythropoietin, and demonstrated fewer clinical events (HR 0.85, 95%CI 0.73–1.0).

However, ferritin is known to be a poor marker for functional iron deficiency[10]: it is a common observation that patients not requiring erythropoietin may have very low ferritin, while well-known studies have demonstrated that patients with high ferritin may still be iron responsive.[11] Apart perhaps from extreme values which may indicate clear iron deficiency or overload, ferritin thresholds are arbitrary, having no clear meaning for an individual: this is demonstrated in the relationship between ferritin and mortality, which in international studies is seen to reflect comorbidity rather than treatment.[12] A ferritin threshold therefore determines quantity of iron given to a group of patients, without determining which individuals require it. One might conclude from the PIVOTAL study, that in the absence of a test for functional iron deficiency, giving more iron to everyone is better. But while it is well known that increasing iron treatment in a group allows erythropoietin reduction,[16] testing individuals for functional iron deficiency would reduce unnecessary treatments and improve hemoglobin responses.[17] Diagnostic markers of functional iron deficiency would therefore be valuable, and this study goes some way to evaluating several potential markers.

Since the discovery of its key role in iron metabolism, hepcidin measurement has shown some promise as a diagnostic marker: levels rise with iron treatment and fall with erythropoietin,[18] and observed dialytic removal of hepcidin also associates with erythropoietin sensitivity,[19] suggesting that mid-range levels could indicate balanced treatment effects. Some investigators have found hepcidin to be poorly predictive of iron response, but studies have generally been small, and have not included an erythropoietin group.[20] As anticipated, this study demonstrated improved iron response with low hepcidin and poorer iron response with high levels; however, high hepcidin levels had a weaker but similar effect on response to erythropoietin, so that high hepcidin appears to indicate "treatment resistant anemia" as much as poor response specifically to iron. A similar effect was seen with Tsat, and neither ferritin nor Tsat performed well in determining the prefered treatment, calling into question their widespread use in clinical protocols, and suggesting the need to look beyond iron-based parameters.

Other markers were better at distinguishing response: with both CRP and erythropoietin dose, treatment interaction effects were detected, observed across parameter levels as a diminishing response to erythropoietin but improving response to iron. A similar though weaker effect was seen for reticulocyte hemoglobin. One might speculate that patients with high CRP might have

reduced iron transport which can be overcome by iron treatment, or that iron may have been underdosed in previous months due to reliance on ferritin, artificially elevated by inflammation. A four-variable iron preference score was developed to predict optimum strategy, which in a retrospective analysis reduced treatment failure to 17%. This score was developed and tested in the same patient group rather than with a separate validation group, so the effect size may be over-estimated, but the analysis provided supports the concept of a score, based on currently available markers, providing an evidence-based approach with reduced treatment failure.

The relationship between treatment response and B12, across levels generally within the reference range, suggests a dynamic relationship between erythropoiesis and this vitamin, with optimum levels in hemodialysis patients which are above the normal range for healthy individuals.

By using baseline markers associated with response to guide treatment, this study moves beyond the concept of an optimum ferritin, to one in which functional iron deficiency is clinically defined, so that treatments are titrated to hemoglobin, and selected for efficacy. Protocols developed through artificial intelligence have used a similar approach, balancing the use of erythropoietin and iron primarily to achieve optimum hemoglobin, whilst minimizing the use of both agents.[21] An example is the Anemia Control Model, developed by Fresenius Medical Care, which is reported to achieve stable hemoglobin targets with reduced use of erythropoietin and iron, though details of the algorithm are not provided.[22] This study, which compares intravenous iron and increased erythropoietin as alternative treatments with random allocation, allows baseline parameters to be compared in unbiased interaction models, with selection of the most discriminating markers.

However, there are important limitations which may limit the conclusions. Firstly, the sample size is relatively small, reducing confidence in the certainty of some results. Secondly, the results may be dependent on previous anemia management, including the omission of maintenance iron, and therefore not generalizable. Numbers are insufficient for a logistic regression approach, or to allow separation into separate groups for development and validation of the clinical score. Retrospective assessment within the same group would tend to over-estimate the extent to which treatment failure might be reduced, and this result should therefore be seen as demonstration of the concept, rather than an estimate of effect size, and should not be understood as applicable to a other dialysis populations.

In conclusion, in this group of hemodialysis patients treated without maintenance iron, increased erythropoietin and intravenous iron were equally effective strategies in those developing moderate anemia. Significant treatment failure occurred, and was associated baseline parameters including hepcidin, CRP, and erythropoietin dose, which might therefore be useful in selecting the preferred treatment. This treatment approach moves beyond the concept of optimum ferritin, using evidence on effectiveness to target therapy more accurately, leading to improved clinical response.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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