Association Between Transferrin Receptor–Ferritin Index and Conventional Measures of Iron Responsiveness in Hemodialysis Patients

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• ***Background:*** **The diagnostic power of the transferrin receptor–ferritin (TfR-F) index for identification of iron responsiveness in long-term hemodialysis (HD) patients compared with the routine markers recommended by the current US and European guidelines was appraised.** ***Methods:*** **Initially, 121 long-term HD patients with a serum ferritin level less than 800 μg/L and on recombinant erythropoietin (rHuEPO) therapy for longer than 6 months were enrolled for intravenous iron (IVFE) supplementation (100 mg of iron polymaltose 3 times/wk for 4 weeks, then 100 mg every 2 weeks for 5 months). Routine iron tests (ie, serum ferritin and transferrin saturation [TSAT]), TfR-F index calculated by the ratio of soluble TfR to log ferritin level, hematocrit, hemoglobin, red blood cell count, and serum high-sensitive C-reactive protein were examined at baseline. Hematocrit and hemoglobin were followed up every 2 weeks during the study period.** ***Results:*** **One hundred patients (52 men, 48 women; mean age, 59 years) completed this study. Fifty-two patients were IVFE responders, defined as an increase in hematocrit greater than 3% and/or a decrease in rHuEPO dose greater than 30% of baseline values at the end of the study, and 48 nonresponders did not fulfill these criteria. Of 52 responders, only 14 patients (27%) could be recognized for iron deficiency by means of routine iron tests (ferritin < 100 μg/L and/or TSAT < 20%). Thirty-three responders (63%) could be further identified for iron deficiency by using TfR-F index (>0.6), but 5 (10%) still could not by either method. Analyses by using receiver operating characteristic (ROC) curves showed that a cutoff value greater than 0.6 for TfR-F index had greater sensitivity (90%) for the detection of iron deficiency than ferritin level less than 100 μg/L (29%) and TSAT less than 20% (6%). TfR-F index showed a greater area under the ROC curve than ferritin level (*P* < 0.05) and TSAT (*P* < 0.001).** ***Conclusion:*** **TfR-F index is superior to routine tests for predicting response to IVFE supplementation in long-term HD patients. Our study indicates that TfR-F index is a new and surrogate marker to estimate body iron stores and guide IVFE therapy for long-term HD patients.** ***Am J Kidney Dis*** **47:1036-1044.**
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INDEX WORDS: Transferrin receptor–ferritin index; recombinant human erythropoietin (rHuEPO); iron deficiency; hemodialysis (HD).

ANEMIA IS ENCOUNTERED frequently in patients with end-stage renal disease (ESRD). The advent of recombinant human erythropoietin (rHuEPO) can effectively alleviate or correct ESRD-related anemia and reduce the need for blood transfusion.[1] Because of accelerated erythropoiesis by rHuEPO, provision of insufficient available iron to erythroblasts will facilitate the development of iron-deficient erythropoiesis.[2,3] Early detection of iron deficiency is mandatory because it can be combated with intravenous iron (IVFE) supplementation and thereby decrease rHuEPO doses. However, aggressive IVFE therapy must be weighed in the context of such iron-associated risks as hypersensitivity; hemosiderosis; hepatic, cardiovascular, and infectious morbidities; and increased oxidative stress.[4-6]

To maximize the efficacy of rHuEPO therapy and avoid iron toxicity, it is of supreme importance to find a marker for early prediction of who will improve in erythropoiesis after IVFE supplementation. The conventional markers, serum ferritin level and transferrin saturation (TSAT), are widely used to indicate iron status in long-term hemodialysis (HD) patients.[7,8] However, serum ferritin and transferrin levels are affected by inflammation and malnutrition status, respectively. Moreover, TSAT fluctuates because of

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diurnal variation in serum iron levels. Cutoff ferritin and TSAT levels for predicting iron-deficient erythropoiesis during rHuEPO therapy still remain debatable.[9,10]

Iron delivery to erythroblasts is mediated by the interaction of transferrin with cell-surface transferrin receptor (TfR), and TfR expression is induced by a decrease in intracellular free iron level. Soluble TfR (sTfR) in plasma is a truncated form of the tissue receptor.[6,11] We and others[12-14] showed that an elevated sTfR level is a surrogate marker of iron status in long-term HD patients and not affected by acute-phase response, as in serum ferritin, TSAT, and percentage of hypochromic red blood cells.[15,16] Conversely, the total mass of erythropoiesis has a positive effect on sTfR concentrations in plasma. Elevated sTfR levels may reflect hyperplastic erythropoiesis induced by rHuEPO. Therefore, some studies failed to show sTfR as an iron-deficient index partly because of the confounding effect of rHuEPO-induced erythropoiesis in HD patients.[17,18]

Cumulative data show that TfR-ferritin (TfR-F) index is a noteworthy tool to differentiate iron-deficient anemia from anemia of hyperplastic erythropoiesis, ie, thalassemia, hemolytic anemia, and myelodysplasia.[6,19-21] TfR-F index is superior to sTfR level alone for the identification of latent iron deficiency in patients with anemia of chronic disease[6,19] and high C-reactive protein (CRP) levels.[19,21-23] To the best of our knowledge, there is no study stating whether TfR-F index is feasible to identify functional iron deficiency in rHuEPO-treated long-term HD patients. Bone marrow biopsy traditionally is the gold standard measure of iron stores. Nevertheless, it is invasive and not practical to perform serial follow-up biopsies to monitor iron status in long-term HD patients. Accordingly, the aim of this study is to investigate whether TfR-F index can detect iron deficiency early and predict responsiveness to IVFE therapy compared with conventional iron parameters in long-term HD patients.

METHODS

Patients and Study Design

A prospective study was conducted at the dialysis center of the affiliated hospital of National Yang-Ming University, Taipei, Taiwan. First, 121 patients agreed to participate in this study. Inclusion criteria were as follows: on HD treatment for 6 months, on rHuEPO therapy for 6 months, serum ferritin level less than 800 μg/L, no hematologic disorder other than renal anemia, no blood transfusions or iron supplementation in the preceding 3 months, and no inflammatory diseases or infections that might affect erythropoietic response to rHuEPO therapy. Twenty-one patients were excluded during the study because of clinically significant bleeding (n = 6), infections (n = 8), treatment modality shift to peritoneal dialysis (n = 2) or renal transplantation (n = 3), and poor compliance with IVFE therapy (n = 2). Finally, 100 patients (52 men, 48 women; mean age, 59 years) completed the study. All patients were dialyzed for 4.0 to 4.5 hours 3 times a week using a single-use dialyzer with a 1.5-m^2 effective surface area of cellulose diacetate membrane, blood flow of 300 to 350 mL/min, and dialysate flow of 500 mL/min. The study was approved by the local medical ethics committee, and informed consent was obtained from each patient.

All patients were supplied with 100 mg of iron polymaltose (Ferrum Hausmann; Hausmann Lab Inc, St Gallen, Switzerland) 3 times a week for 4 weeks (total dose, 1,200 mg of elemental iron) and then 100 mg of iron polymaltose every 2 weeks for 5 months (total dose, 1,000 mg of elemental iron). Iron supply was administered intravenously at the end of each HD session. Before the first dose was administered, a test dose of 25 mg of iron polymaltose was administered for 30 minutes to observe any adverse reaction development. If no adverse reactions occurred, the IVFE supplementation protocol was started. Response to IVFE therapy is defined as an increase in hematocrit of 3% or greater (ie, increase from 30% to 34%) and/or decrease in rHuEPO dose of 30% more than baseline values at the end of the study. Those who did not fulfill these criteria are defined as nonresponders. Routine iron tests (ie, TSAT, serum iron, and ferritin), TfR-F index, hematocrit, hemoglobin, red blood cell count, reticulocyte count, serum albumin, and high-sensitive CRP (hs-CRP) were examined at baseline. Hematocrit and hemoglobin were followed up every 2 weeks during the study period. Epoetin β (Roche Diagnostics GmbH, Mannheim, Germany) was administered subcutaneously 2 or 3 times a week, and the dose was titrated biweekly to maintain a target hematocrit of 32% to 33%. During the study period, epoetin β dose could be adjusted by 20% every 2 weeks. For example, a 20% decrease in dose for hematocrit greater than 33% was recorded or a 20% increase in dose if hematocrit decreased greater than 3% from baseline levels.

Laboratory Measurements

Blood was drawn predialysis after an overnight fast. Hematocrit, hemoglobin, and red blood cell count were determined by using a Coulter counter, and reticulocytes were measured by means of an automated flow cytometer. Serum iron was measured by using a calorimetric method (Hitachi 736-60 autoanalyzer; Hitachi, Naka, Japan); total iron-binding capacity, by using the TIBC Microtest (Daiichi, Tokyo, Japan); and ferritin, by using radioimmunoassay (Incstar, Stillwater, MN). TSAT was calculated by dividing serum iron by total iron-binding capacity $\times$ 100. Serum hs-CRP was quantitatively determined by means of rate

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