Prospective Study of the Immune Effects of Normalizing the Hemoglobin Concentration in Hemodialysis Patients Who Receive Recombinant Human Erythropoietin

RENATO M.B. ROMAN,* PETER I. LOBO,* RONALD P. TAYLOR,* DAVID A. GOODKIN,† JOHN LABRECQUE,† KATHY L. POWERS,* and W. KLINE BOLTON*

**University of Virginia Health Sciences Center, Charlottesville, Virginia; and †Amgen, Inc., Thousand Oaks, California*

Abstract. Partial correction of anemia by erythropoietin improves hemodialysis (HD)-associated immunosuppression. It is not known whether hemoglobin normalization improves immune status further. The authors prospectively compared the immune function of HD patients with congestive heart failure or ischemic heart disease on erythropoietin therapy randomized to normal *versus* anemic blood hemoglobin concentration. HD patients were randomized into a normal hemoglobin group ($n = 17$, target hemoglobin of 14 ± 1 g/dl) or an anemic hemoglobin group ($n = 18$, target hemoglobin 10 ± 1 g/dl). Delayed-type hypersensitivity, CD4 and CD8 counts, anti–tetanus toxoid antibody levels, erythrocyte complement receptor 1 expression, and lymphocyte proliferative responsiveness were measured. The observation period was 1 yr, and the trial was open label. Target hemoglobin was achieved and maintained in both groups. Significantly improved cutaneous reactivity was seen in the normal hemoglobin group ($P = 0.003$). The prevalence of anergy decreased in the normal hemoglobin group (from 60 to 20%) but increased in the anemic hemoglobin group (from 57 to 86%). The anemic hemoglobin group had higher CD8 counts compared with baseline ($P = 0.0001$) and compared with the normal hemoglobin group ($P = 0.038$). Both groups had significant increases in tetanus toxoid antibody levels after vaccination but without significant differences between groups. The anemic hemoglobin group had a progressive increase in erythrocyte complement receptor 1 levels compared with baseline ($P = 0.002$) and relative to the normal hemoglobin group ($P = 0.023$). There was no consistent pattern of altered proliferative responsiveness of lymphocytes. The data suggest that certain aspects of immune function, particularly delayed-type hypersensitivity, may be improved in HD patients by normalization of hemoglobin through the administration of increased doses of erythropoietin.

Infection constitutes a leading cause of morbidity and mortality among dialysis patients. According to the U.S. Renal Data System, infections are second only to cardiovascular diseases in causing mortality (1). Also, malignancy is much more common in these patients (2). These observations may be related to the immunocompromise associated with uremia, similar to acquired immunodeficiency and immunosuppressive therapy. The exact mechanism of this immunocompromised state is not known, but abnormalities of cellular, humoral, and phagocytic immunity have been demonstrated both *in vivo* and *in vitro* (3–8). In addition, defects in clearance of bacterial and other foreign materials and abnormalities of natural clearance mechanisms *via* the red blood cell (RBC) complement receptor 1 (CR1) system have been described (9,10).

Numerous studies have investigated the immune effects of recombinant human erythropoietin (rHuEPO) used in the treatment of anemia of ESRD to hematocrits of 28 to 31%, showing improvement in cell-mediated and humoral immunity (4,5,10–15). In addition, CR1 levels per RBC rise in patients who are treated with rHuEPO (9). Antibody response to hepatitis B and tetanus toxoid vaccines are better in rHuEPO-treated ESRD patients than nontreated patients (5,10). Some investigators have shown an improvement in CD4/CD8 ratio (8,13), whereas others have shown an increase in both CD4 and CD8 counts with rHuEPO without significant change in the ratio (16). The last study also reported a decrease in natural killer cells and improvement in phagocytic activity by measuring respiratory burst of whole blood and phagocytic uptake of yeast cells.

Thus, it seems that both cellular and antibody-mediated immunity of dialysis patients are favorably affected by rHuEPO therapy. It is not clear whether this improvement is due to partial correction of anemia or is a direct effect of rHuEPO on the immune system. *In vitro* cytokine production of interleukin-2, γ-IFN, colony-stimulating factor, and TNF were found by Gafter *et al.* (17) to increase progressively and

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R.M.B.R. is currently at Danville Urologic Clinic, Danville, VA. J.L. is currently at Amgen, Inc., Thousand Oaks, CA. D.A.G. is currently at ICOS Corporation, Bothell, WA.

This work was performed at the University of Virginia Health Sciences Center, Charlottesville, VA.

Correspondence to Dr. W. Kline Bolton, Division of Nephrology, University of Virginia, Post Office Box 800-133, Charlottesville, VA 22908-0133. Phone: 434-924-5125; Fax: 434-924-5848; E-mail: wkb5s@virginia.edu

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in parallel to the rise in hemoglobin levels achieved by rHuEPO or RBC transfusions in ESRD patients or after autologous transfusions in normal subjects. *In vitro* T-lymphocyte proliferation to monoclonal antibody to CD3 antigen (OKT3) and alloantigen (HLA-D) was enhanced by high-dose rHuEPO incorporated into media (11). Addition of rHuEPO, alone, to the media did not stimulate lymphocyte proliferation.

Previous studies have been performed with partial correction of anemia with rHuEPO, rather than full normalization of hemoglobin. We hypothesized that normalizing the serum hemoglobin concentration among hemodialysis patients might improve immune function. This could in turn decrease the incidence of infection and cancer. In the present study, we compared prospectively the immune system parameters of hemodialysis (HD) patients who received rHuEPO and were randomized to a normal hemoglobin *versus* an anemic hemoglobin.

Materials and Methods

Study Protocol

The study protocol was approved by the Institutional Review Board, and patients provided written informed consent. Each patient was followed for 12 mo with an additional serum sample obtained at 13.5 mo.

Patient Selection

Thirty-five dialysis patients in a single center were enrolled prospectively into the study. They were a subset of participants in a multicenter study investigating the cardiovascular effects of normalizing the hematocrit of hemodialysis patients with clinically evident congestive heart failure or ischemic heart disease (18). Seventeen patients were randomized in open-label manner into the normal hemoglobin group (target hemoglobin of 14 ± 1 g/dl); 18 patients were randomized into the anemic group (target hemoglobin to remain at the entry level of 10 ± 1 g/dl). The randomization method and inclusion and exclusion criteria are detailed in the cardiac study (18). Briefly, the patients were on maintenance hemodialysis and rHuEPO therapy for at least 3 mo at the University of Virginia Kidney Center. All patients were iron replete, defined as a serum transferrin saturation of $\geq$20%. They were excluded when they had uncontrolled hypertension, hematologic diseases, NYHA class IV cardiac disability, or significant coronary artery or valvular heart disease or when life expectancy was $<$6 mo.

Dose of rHuEPO

The normal hemoglobin group underwent an increase of rHuEPO dose (Epogen; Amgen, Thousand Oaks, CA) by a factor of 1.5 upon entry into the study. Subsequently, the dose was increased by 25% (based on prestudy dose) if the hemoglobin had not increased at least 0.67 g/dl during the previous 2 wk. When the hemoglobin increased $>$1.3 g/dl over 2 wk, the dose was reduced by 25 U/kg. In the anemia group, dose was adjusted every 2 wk by 10 to 25 U/kg as needed to maintain hemoglobin within the 10 ± 1-g/dl range.

Studies of Immune Function

In vivo tests. Cutaneous delayed-type hypersensitivity (DTH) to standard intradermal injections of tuberculin (PPD), tetanus toxoid, candida, and trichophyton antigens was determined at entry and at 12 mo. Absolute CD4 and CD8 counts were performed monthly. CR1 levels per erythrocyte were determined monthly. Lymphocyte proliferation studies were performed every 2 mo using Raji cells, IL-2 (at 2 and 20 units), OKT3 (at 0.001 and 0.1 μg), and concanavalin A as mitogens. Pre- and postvaccination anti–tetanus toxoid antibody levels were determined by ELISA (Bindazyme Antigen Specific Ig G Enzyme Immunoassay Kit; The Binding Site, San Diego, CA). Patients were immunized at the end of 1 yr. Postvaccination antibody levels were determined 6 wk after immunization with standard tetanus toxoid vaccine.

Infection rates per patient, infections per patient-year, and severity of infection in each group were determined. Infections and other events were classified arbitrarily into mild, moderate, or severe according to the judgment of the nephrology providers. As this was an intent-to-treat trial, patients who died before the end of the 12 mo of observation are included.

In vitro studies. *In vitro* were performed as described in detail previously (19).

Lymphocyte proliferation. Lymphocytes were isolated from freshly obtained peripheral blood cells by standard density gradient centrifugation (Ficoll-Hypaque), washed twice in Hank's balanced salt solution, and resuspended at 1×10^6 cells/ml in RPMI containing 10% heat-inactivated FCS, 80 μg/ml glutamine, 50 μg/ml streptomycin, and 50 μg/ml penicillin. A total of 2×10^5 cells in 0.2 ml of medium were cultured in quadruplicate in the presence of OKT3 (0.001 to 0.1 μg), IL-2 (2.0 and 20 units), and concanavalin A. For evaluating allogeneic proliferative response, 2×10^5 cells in 0.2 ml of medium were co-cultured with 2×10^5 cells from a B cell line (Raji, obtained from American Type Culture Collection, National Institutes of Health, Bethesda, MD). Cells were harvested on day 5 when OKT3, IL-2, or concanavalin A was used and on day 6 when Raji cells were used. $[H]^3$ thymidine was added 12 h before harvesting to quantify the proliferative response. The incorporated radiolabel was quantified using a Multiple Automated Harvesting Unit, dried, then counted with a Beckman Liquid Scintillation Counter using Omnifluor in toluene as the scintillation fluid (19).

T cell subsets. Mononuclear cells were isolated from peripheral blood using the procedure described above. The cells were then stained with FITC monoclonal antibodies specific for CD4 and CD8 antigens (Becton Dickinson, La Jolla, CA). The percentage of positive cells was determined by flow cytometry. The absolute CD4 or CD8 count was determined by multiplying the percentage determined with flow cytometry by the absolute lymphocyte count.

CR1 level per RBC. CR1 levels were determined in a RIA with ^{125}I-labeled anti-CR1 monoclonal antibody 7G9 (20,21). Saturating levels of the monoclonal antibody were mixed with human erythrocytes, and after a 15 to 30 min of incubation, the amount of bound antibody was determined by centrifuging the cells through oil. Controls included sheep erythrocytes, which lack CR1 (20,21).

Statistical Analyses

Statistical analysis was done using SAS software version 8.2. $P \leq 0.05$ was considered significant. The unpaired *t* test was used to test the difference in mean hemoglobin, CD4 and CD8 counts, and CR1 levels per erythrocyte between the two groups. The ratios of the 12-mo anti–tetanus toxoid antibody level to the baseline value was compared between the two groups using the nonparametric Wilcoxon two-sample test. For the repeated measurements of lymphocyte proliferation, CD4, CD8, and CR1, a linear mixed models approach was used. χ^2 analysis or the Fisher exact test was performed to test differences between the groups with regard to cutaneous reactivity and other nominal data. Data are presented as mean $\pm$ SD.

Results

Patients

None of the patients was receiving corticosteroids or other forms of immunosuppressive therapy. Table 1 shows the baseline characteristics of the groups. There were no differences in age, race, hemoglobin, cause of ESRD, or prevalence of comorbid states between groups. There were more women and nonsmokers in the anemic group compared with the normal hemoglobin group.

For analysis of repeated measurements, each patient is considered to have his or her own regression equation. Three patients in the normal hemoglobin group and two in the anemic group had insufficient data points to construct regression lines. However, as noted above, all patients were considered in assessment of infection rate and mortality.

Of the 17 patients in the normal hemoglobin group, three were not included in the repeated measures mixed model analyses because they discontinued the study or died. Two requested discontinuation from the study for personal reasons, and the other died from a myocardial infarction. There were two other deaths in the normal hemoglobin group, one of unknown cause and one from sepsis. In the anemic group, two patients had insufficient data for regression analysis. Two patients died from sepsis, and an additional patient died from cirrhosis of the liver. Twelve normal and 15 anemic hemoglobin patients survived for 1 yr to the end of the study.

Hemoglobin

At entry, the hemoglobin values of the normal hemoglobin group (10.8 ± 1.1 g/dl) and the anemic group (10.7 ± 1.0 g/dl) were comparable. Figure 1 shows the hemoglobin results over time. By the third month, a statistically higher hemoglobin was achieved in the normal hemoglobin group when compared with the anemic group (12.2 ± 1.3 g/dl *versus* 11.0 ± 0.8 g/dl; $P < 0.005$). The hemoglobin increased in the normal hemoglobin group to 12.7 ± 1.3 g/dl by the fourth month and to target by 6 mo. The target hemoglobin in the anemic group was maintained throughout the study. Individual hemoglobins demonstrated fluctuation out of range during the study, but group mean values were well separated. At baseline, the mean rHuEPO dose for the anemic group was 9,662 ± 4,400 units/wk; 6 mo later, the dose was 10,671 ± 7,236 units/wk. For the normal hemoglobin group, the rHuEPO increased from 14,143 ± 7,319 units at baseline to 37,600 ± 16,074 units/wk at 6 mo. Serum ferritin concentration and transferrin saturation did not decline during the study (data not shown).

DTH

All patients initially consented to baseline and end-of-study skin testing. Two patients withdrew from the study, six died, and three refused end-of-study skin tests. Ten patients from the normal hemoglobin group and 14 from the anemic group had cutaneous skin testing both at baseline and at 12 mo. Data on

Table 1. Baseline characteristics of patients[a]

Clinical Parameter	Normal Hemoglobin Group ($n = 17$)	Anemic Group ($n = 18$)	*P* value
Age, yr (mean ± SD)	62 ± 9	66 ± 8	NS
Gender, Male/Female	8/9	3/15	<0.001
Race, Black/White	13/4	13/5	NS
Cause of ESRD			
DM	6	9	
HTN	6	5	
SLE	1	0	NS
nonspecific nephropathy	1	1	
obstructive uropathy	1	2	
PKD			
other	2	1	
Comorbid states			
PVD	12	14	NS
NYHA class I/II/III	9/7/1	8/8/2	NS
CAD	8	5	NS
HTN	7	10	NS
DM	1	2	NS
other	1	1	NS
Tobacco use			
never	8	12	<0.001
active	5	0	
quit > 9 yr ago	4	6	

[a] CAD, coronary artery disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; NYHA, New York Heart Association; PKD, polycystic kidney disease; PVD, peripheral vascular disease; SLE, systemic lupus erythematosus.

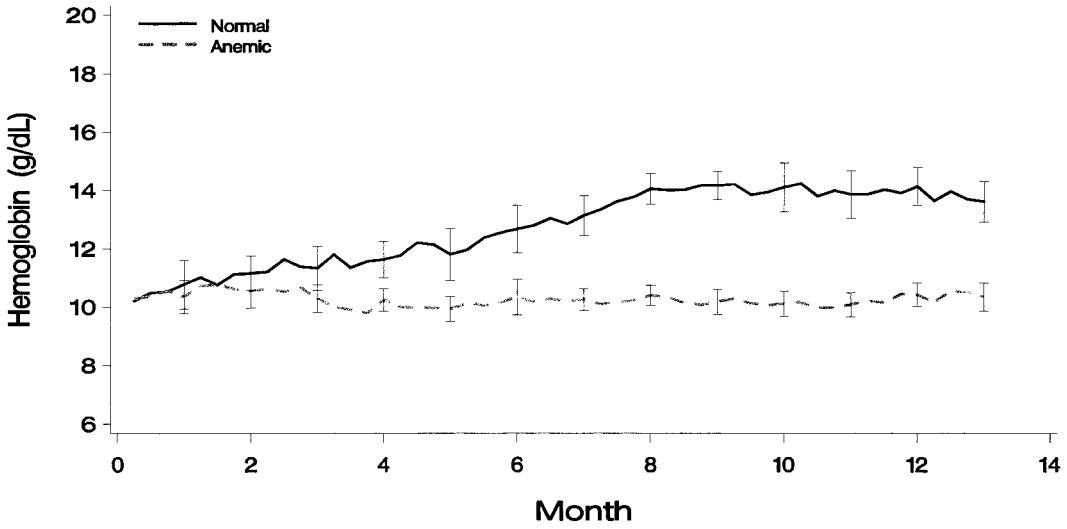

Figure 1. Trend of hemoglobin over time. Statistical differences in hemoglobin between the normal hemoglobin and anemic groups occurred by the third month. Target hemoglobin was achieved in the normal hemoglobin group by 4 to 6 mo. Hemoglobin was kept constant in the anemic group.

DTH are presented in Figure 2. At baseline, there was no difference in cutaneous response to recall antigens between the two groups. Sixty percent of the normal hemoglobin group and 57% of the anemic group were anergic. After 1 yr, 20% of patients from the normal hemoglobin group were anergic *versus* 86% in the anemic group ($P = 0.003$, Fisher exact test, two-tailed). Five (83%) of six of the normal hemoglobin anergic group converted to a nonanergic state. In the anergic anemic group, 50% remained anergic, whereas five (83%) of six nonanergic patients became anergic. Only one patient in the normal hemoglobin group lost reactivity and became anergic. None of the patients was PPD positive either at baseline or after 1 yr. Thus, normal hemoglobin patients who were anergic tended to become nonanergic, and those who were nonanergic tended to remain so. This is opposite to the anemic group" nonanergic patients tended to become anergic, and anergic patients tended to remain so.

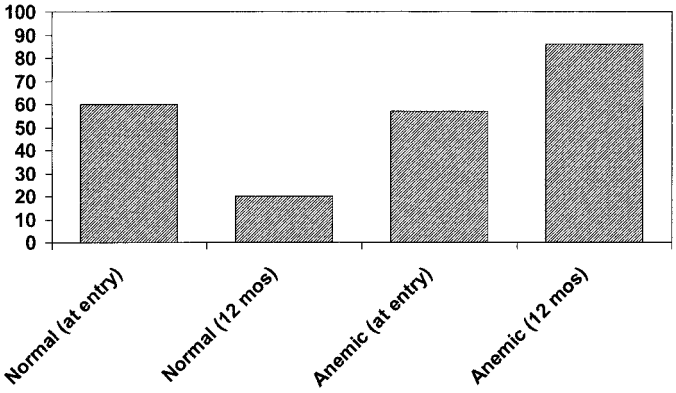

Figure 2. Cutaneous response to delayed-type hypersensitivity testing. The first two bars present cutaneous reactivity in the normal hemoglobin group at entry and after 12 mo in the study. The second two bars present cutaneous reactivity in the anemic group at entry and after 12 mo. Anergy decreased in the normal hemoglobin group but increased in the anemic group ($P = 0.003$).

CD4 and CD8 Levels

There were no significant differences in mean CD4 counts from baseline or between the two groups at any time during the study (data not shown). However, there were significant differences in CD8 counts (Figure 3). During the course of the study, the slope of CD8 cells increased significantly from baseline in the anemic group ($P < 0.0001$), whereas there was no change in the normal hemoglobin group. The mixed model, repeated measures analysis to test whether the slopes of the two groups differed was significant ($P = 0.038$). Thus, the CD8 counts increased over the observation period for the anemic patients but not for the normal hemoglobin group.

The slope of the CD4/CD8 counts for the anemic group ($P = 0.02$) and for the normal hemoglobin group ($P < 0.0001$) both were different from zero (data not shown). However, there were no differences between the groups using the mixed model, repeated measures analysis for a change over the 12 mo of observations ($P = 0.08$). Thus, the ratios of CD4/CD8 decreased over the observation period for both groups, but the decreases were not significantly different between the two groups.

Antibody Response to Tetanus Toxoid

Anti–tetanus toxoid antibody levels for each group were obtained at baseline and 6 wk after vaccination. At baseline, the mean ($\pm$ SD) serum antibody level for the normal hemoglobin group (46.3 $\pm$ 62.8 mg/L) and anemic group (13.5 $\pm$ 18.6 mg/L) did not differ significantly. When mean postvaccination and baseline antibody levels were compared, both the normal hemoglobin group (200.9 $\pm$ 293.0 mg/L postvaccination; $P = 0.009$) and the anemic group (65.2 $\pm$ 94.7 mg/L; $P = 0.001$) responded to the vaccine. The increment in each group was fivefold. The absolute rise was 155 mg/L for the normal hemoglobin group *versus* 52 mg/L for the anemic group. However, the differences between the groups for change in anti–tetanus antibody level for the 12-mo observation were not statistically significant.

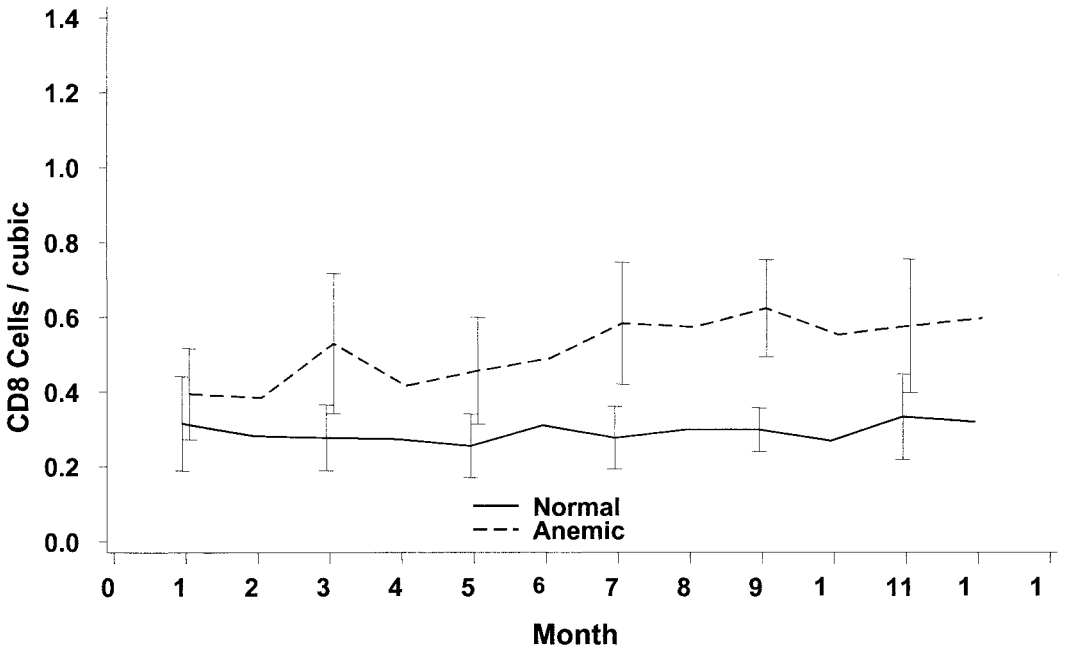

Figure 3. Absolute CD8 counts over time. Statistically higher CD8 counts were seen in the anemic group compared with baseline ($P = 0.0001$) and with the normal hemoglobin group ($P = 0.038$).

Lymphocyte Proliferation

Lymphocyte proliferation did not differ between groups (data not shown). Lymphocyte responses to Raji cells, IL-2 at 2 units and at 20 units, OKT3 at 0.001 μg and 0.1 μg, and concanavalin A were similar between groups.

CR1 Levels per Erythrocyte

At entry into the trial and for the first 3 to 4 mo, CR1 levels were comparable and stable between groups. CR1 remained essentially constant in the normal hemoglobin group but increased in the anemic group with time (Figure 4). The mixed model, repeated measures analysis to test for change over time for the two groups showed no change for normal hemoglobin patients from baseline, whereas the anemic group rate of change from baseline was significant ($P = 0.0023$), as was the difference between the slopes of the two groups ($P = 0.023$).

Analysis of Infection

A total of 65 infection episodes were recorded during the year of observation, 38 among the anemic group *versus* 27 among the normal hemoglobin group. During the 12-mo observation period, there were 1.6 episodes of infections per patient in the normal hemoglobin group and 2.1 episodes of infections per patient in the anemic group. Considering only the patients who survived 12 mo, there were 1.8 infections events per patient-year in the normal hemoglobin group and 2.1 infections per patient-year in the anemic group. More infections that were classified as mild were observed in the normal hemoglobin group (85 *versus* 74%). There was one infectious death in the normal hemoglobin group and two in the anemic group. None of these differences reached statistical significance.

Discussion

rHuEPO represents a major breakthrough in the care of patients with chronic renal failure. The currently recommended hemoglobin in the treatment of anemia in dialysis patients is 11 to 12 g/dl (22), although the target range was generally lower at the time the study was initiated. The advantages of rHuEPO therapy—improvement in quality of life, exercise tolerance, left ventricular hypertrophy, and decrease in transfusion requirements—were appreciated at partially corrected anemia (hematocrit 28 to 31%) (23–28). Studies by several investigators (5,10,13) demonstrated an enhancement of T cell function, particularly cutaneous reactivity to recall antigens, and antibody response to T cell–dependent antigens, after partial correction of anemia (from hematocrits in the 20s to the 30s). Our study sought to determine whether the immune system of HD patients with normalized hemoglobin differed from that of HD patients with partially corrected anemia.

Infection is a major cause of morbidity and mortality in ESRD patients and results from multiple causes, including the immunosuppressed state of uremia (1). The risk of cancer is also increased in patients with ESRD, with a distribution pattern similar to the increased malignancy after organ transplantation (2). The increased risk seems to be secondary to the uremic state with its associated immunosuppression. One of the most important defense mechanisms against infection and malignancy is the cell-mediated immune response that augments the action of leukocytes, including lymphocytes and macrophages (29). DTH is an *in vivo* sign of cell-mediated immunity and represents true patient cell-mediated functionality, rather than an *in vitro* test tube phenomenon that may or may not extrapolate to the *in vivo* situation. We found that cutaneous reactivity was better at a normal hemoglobin than with a partially corrected anemia. During the course of the

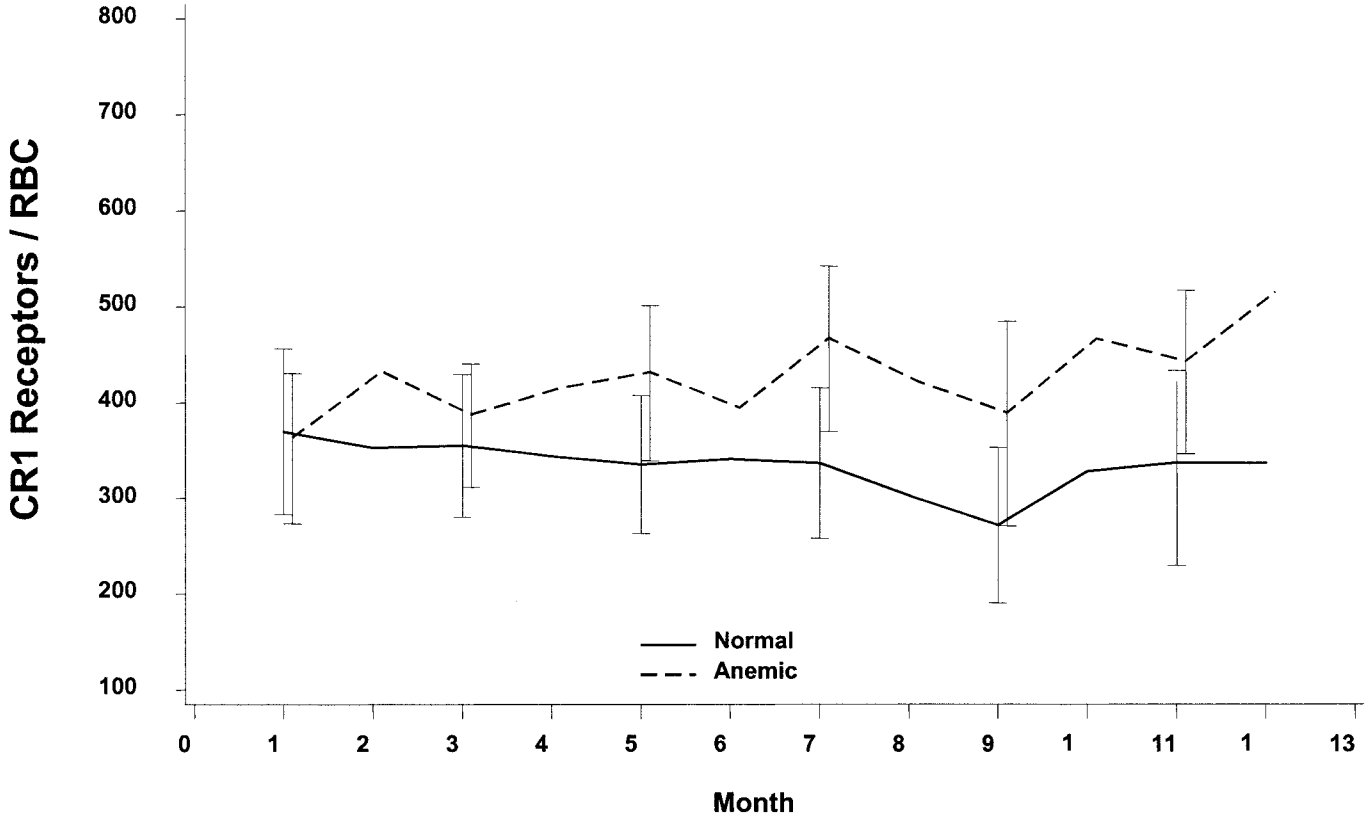

Figure 4. Complement receptor 1 (CR1) level per erythrocyte. The normal hemoglobin group maintained constant levels of CR1, whereas the anemic group demonstrated a progressive rise over time compared with baseline ($P = 0.002$) and with the normal hemoglobin group ($P = 0.023$).

study, the degree of DTH anergy decreased with normalization of hemoglobin, whereas the degree of anergy increased in the anemic group of patients by the year's end. This *in vivo* test of T cell immunity is important because it entails functioning antigen-presenting cells, Th_1 cells, and effector cells together with elaborated cytokines and their corresponding receptors to produce the DTH reaction (29). Of all of the parameters examined, improvement in DTH is probably of most clinically significance.

We did not examine the mechanism of improved cutaneous reactivity in the normal hemoglobin group at the end of the study. We do not know whether antigen presentation, CD28 stimulation, or effector cell function was altered. We did not find any difference in *in vitro* response of lymphocytes to IL-2 and OKT3. This suggests that better cutaneous reactivity is not related to the upregulation of IL-2 or OKT3 receptors or increase in cytokine levels. A previous study (12) showed better lymphocyte mitogenic response to OKT3 in dialysis patients with partially corrected anemia using rHuEPO. In our study, CD8 counts were significantly higher in the anemic group over time. It is possible that the higher suppressor cell levels maintained until the end of the study are associated with the persistence and even worsening of anergy rates observed in the anemic group.

Uremia is associated with activated B cells with elevated levels of soluble CD23, which decrease with rHuEPO therapy (30). We did not measure soluble CD23 or other markers of B cell activation in this study. We did examine the antibody response to tetanus toxoid vaccine, and no difference in antibody response to tetanus toxoid vaccine between the groups was evident. Each group had a significant rise in antibody levels after vaccination, approximately five times higher than the baseline. Conversion rates between the groups were similar with 11 of 13 in the normal hemoglobin group and 13 of 14 seroconverting in the anemic group. This suggests that a maximal antibody augmenting effect was already present at the routine rHuEPO dose and hemoglobin used in dialysis.

We did not study phagocyte function. RHuEPO improves phagocytic function in uremic patients with normal iron stores (16,31), and one study (32) demonstrated that use of rHuEPO was associated with improved phagocytic function even in iron-overloaded patients, possibility by utilization of iron during erythropoiesis.

CR1 on erythrocytes aids in the clearance of C3/C4 opsonized immune complexes from the circulation (9,10,33). CR1 is a complement receptor specific for C3b/C4b, and its expression per RBC is reportedly increased by erythropoietin (9,34). Although young erythrocytes express more CR1 than older erythrocytes, we did not find any significant increase in CR1 levels in patients with normal hemoglobins. There was, however, a statistically significant increase of CR1 over time in the anemic group. Our observations may indicate an increasing

proportion of younger erythrocytes with time in the anemic group relative to the normal hemoglobin group, possibly related to longer RBC survival in the latter group (35–37).

During the period of observation, infections tended to be fewer and milder in the normal hemoglobin group. However, the total number of infections was small, the evaluator was not blinded to group assignments, and clinical judgment was used to gauge the severity of a particular event. Furthermore, the type of infection, whether viral, bacterial, or fungal, could not always be determined in this study. One patient in the normal hemoglobin group and two in the anemic group died of sepsis. These observations contrast with the results from the parent study, which showed more deaths from infection or sepsis in the normal hematocrit group than in the low hematocrit group (18), and support findings from a study by Collins *et al.* (38). Studies focused on the issue of the type and severity of infection using larger numbers of patients with documentation of causative agent will be needed to clarify the impact of normalization of hemoglobin on infection risk and outcomes.

Several caveats need to be considered. This study demonstrated improved immune function when serum hemoglobin concentration was increased to within the normal range. It did not test intermediate levels of hemoglobin and therefore did not establish the lowest threshold value for hemoglobin concentration associated with improved immune function. The study included only patients with clinically evident ischemic heart disease or congestive heart failure, and the mean age was higher than that of the general dialysis population; therefore, the findings may not apply to all HD patients (18). How cytokines and other cells are affected by full correction of anemia (or higher doses of erythropoietin) is not known. For better addressing these issues, randomized, prospective, blinded studies on large numbers of patients more representative of the general population of dialysis patients would have to be undertaken. The present study, although showing a significant benefit for certain immunologic parameters, was underpowered to show benefits for infection and malignancy. Measures such as infection rates, types of infectious agents, hospitalization rates, antibiotic use, and assays of effector cells and other lymphokines involved in mounting an immune response assessment of additional required intravenous iron supplementation all would be needed to clarify more thoroughly the links between anemia correction and infection. Even longer periods of follow-up and larger numbers of patients would be needed to assess the potential impact of our observations on malignancy in HD patients.

In summary, our study shows that normalization of the hemoglobin in HD patients, compared with partial correction of hemoglobin to 10 $\pm$ 1 g/dl, affected a number of immunologic parameters. These include improved DTH, lower CD8 counts, and lower CR1/RBC. These findings could represent generally improved cellular immune function as postulated by others. If confirmed, then the impact of normalization of hemoglobin in dialysis patients could have substantial importance in view of the significant role of infection and malignancy in the morbidity and mortality of these patients.

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