ANNALS OF SURGERY
Vol. 217, No. 3, 293–299

A Serial Study of the Erythropoietic Response to Thermal Injury

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Objective

Since controversy exists over whether erythropoietin levels are increased or decreased after thermal injury, a prospective study was performed to answer this question as well as to characterize the erythropoietic response to thermal injury.

Summary Background Data

The concept of using erythropoietin to reduce the need for blood transfusions after thermal injury is attractive. However, since the etiology of burn anemia is both unclear and multifocal, prior to initiating a trial of erythropoietin therapy, it will be necessary to better define the erythropoietic response to thermal injury.

Methods

Twenty-four burn patients with a mean burn size of 31 ± 18% had serial measurements of serum iron, total iron binding capacity (TIBC), ferritin, erythropoietin, transferrin saturation, hemoglobin, and reticulocyte counts performed on burn days 1, 3, 5, 7, 10, 14, and then weekly.

Results

The erythropoietic response was characterized by a decrease in hemoglobin levels as well as serum iron, TIBC, and transferrin saturation ($p < 0.05$). Ferritin and erythropoietin levels increased as did the reticulocyte count. The erythropoietin response to anemia appeared to be at least grossly intact, since there was an appropriate inverse relationship between the degree of anemia and the magnitude of the erythropoietin response ($r^2 = .61$, $p < 0.00001$).

Conclusions

Since the erythropoietin levels of these anemic burn victims reached supranormal levels and they manifested a moderate reticulocytosis, the role of replacement erythropoietin therapy after thermal injury requires further study.

Burn patients rapidly become anemic due to the increased destruction and impaired production of circulating red blood cells in combination with external blood loss associated with diagnostic testing, daily burn wound debridement, and operative procedures.[1-3] Consequently, multiple blood transfusions to maintain the circulating red blood cell mass and oxygen delivery has become an established component of burn care. Yet, based on the increasingly identified potential hazards of blood transfusions, it has become clear that, although fre-

Presented in part at the 24th annual meeting of the American Burn Association, April 3, 1992.
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Accepted for publication May 14, 1992.

Table 1. PATIENT DEMOGRAPHICS

Group	n	Age	%TBSA	%TBSA Grafted
13–19% TBSA	7	41 ± 4	16 ± 2%	7 ± 3%
20–39% TBSA	12	38 ± 4	27 ± 7%	10 ± 11%
≥40% TBSA	5	42 ± 3	60 ± 23%	36 ± 16%
All patients	24	40 ± 4	31 ± 18%	15 ± 15%

Age expressed as mean ± SEM in years. Other data expressed as mean ± SD.

quently necessary, blood transfusions are not without risk.[4] Therefore, attempts to reduce blood loss or bolster red cell production and thereby reduce transfusion requirements assume significant clinical importance in patients with major thermal injuries. One such potential therapeutic strategy to reduce transfusion requirements is the use of recombinant human erythropoietin to stimulate erythropoiesis.[5] However, since controversy exists over whether erythropoietin levels are increased[6,7] or decreased[8] after thermal injury we carried out a prospective study to answer this question as well as to characterize the erythropoietic response to thermal injury.

MATERIALS AND METHODS

Patients admitted to the LSU Shreveport Burn Center between May and September 1991 form the basis of this prospective study of the erythropoietic response to thermal injury. Entry criteria consisted of admission to the LSU Burn Center within 12 hours of injury, the absence of pre-existent hematologic disease, and a burn size between 15% and 80% of the total body surface area (TBSA) and/or a burn requiring excision and grafting of at least 10% TBSA. Twenty-four of 26 patients who met these entry criteria were enrolled in this study. The two patients were excluded because they had sustained severe CNS injuries. Serial measurements of serum iron, total iron binding capacity (TIBC), ferritin, and erythropoietin as well as a complete blood count and reticulocyte levels were obtained on burn days 1, 3, 5, 7, 10, 14, and then weekly until discharge. The erythropoietin levels were measured by radioimmunoassay.[9] The number and timing of all transfusions were recorded. Indications for transfusion were hemodynamic instability or a hemoglobin level less than 6–6.5 g/dL.

Of the 24 patients studied, 17 (71%) were male and 13 (54%) were black. As outlined in Table 1, the patients were stratified into three groups based on their burn size. This stratification was done to better assess the potential effects of the magnitude of the injury on the erythropoietic response.

All the patients were treated with a standard therapeutic regimen, which was modified according to the clinical response of each patient.[10] This regimen consisted of fluid resuscitation based on the Parkland formula, topical antimicrobial agent administration (sulfadiazine silver, initially), and aggressive nutritional support based on each patients estimated caloric and protein requirements. Nutritional support was primarily enteral, although supplementation by peripheral alimentation was used when enteral nutrition alone was not sufficient. Prophylactic antibiotics were not routinely used. All deep partial and full-thickness burns were excised and grafted as soon as the patients were hemodynamically stable, with the first operation usually occurring between the 3rd and 5th postburn day. All of the patients studied survived. This study was approved by the Human Rights Committee of LSUMC-Shreveport.

Comparisons between or within groups (continuous data) were analyzed by multiple analysis of variance (MANOVA) with the post hoc Neuman-Keuls test for parametric data or the Kruskal Wallis H test for nonparametric data. Chi-square analysis, with the Yates correction when indicated, was used for comparisons between groups when the data was discontinuous. Multiple regression analysis was used to test for associations between different variables. Statistical significance was considered to be achieved at $p \leq 0.05$.

RESULTS

The hemoglobin levels of all three groups of patients progressively decreased during the first 14 to 21 days postburn (Fig. 1a). In contrast, after an early decrease, which was maximal on the 3rd postburn day, the total white blood cell and platelet levels returned to normal or supranormal levels by postburn days 5 to 7 (Fig. 1b, c). Despite the progressive decrease in hemoglobin levels, all three groups of patients had normal or elevated serum erythropoietin levels (Fig. 2) and manifested a moderate reticulocytosis (Fig. 3). The erythropoietin levels were significantly higher in the patients with burns ≥40% TBSA than the other groups on postburn days 3 and 10 ($p \leq 0.01$) and just missed statistical significance on postburn day 7 ($p = 0.068$) (Fig. 2). In addition, the incidence of supranormal erythropoietin levels was significantly higher in the group of patients with the largest burns (Table 2). Likewise, the reticulocyte count was higher in the patients with burns over 40% TBSA than the other two groups and this difference reached statistical significance on postburn day 7 ($p = 0.002$) (Fig. 3).

To assess whether there was an association between the degree of anemia (measured as hemoglobin) and the erythropoietin response, multiple linear regression analysis was performed. For the entire burn patient popula-

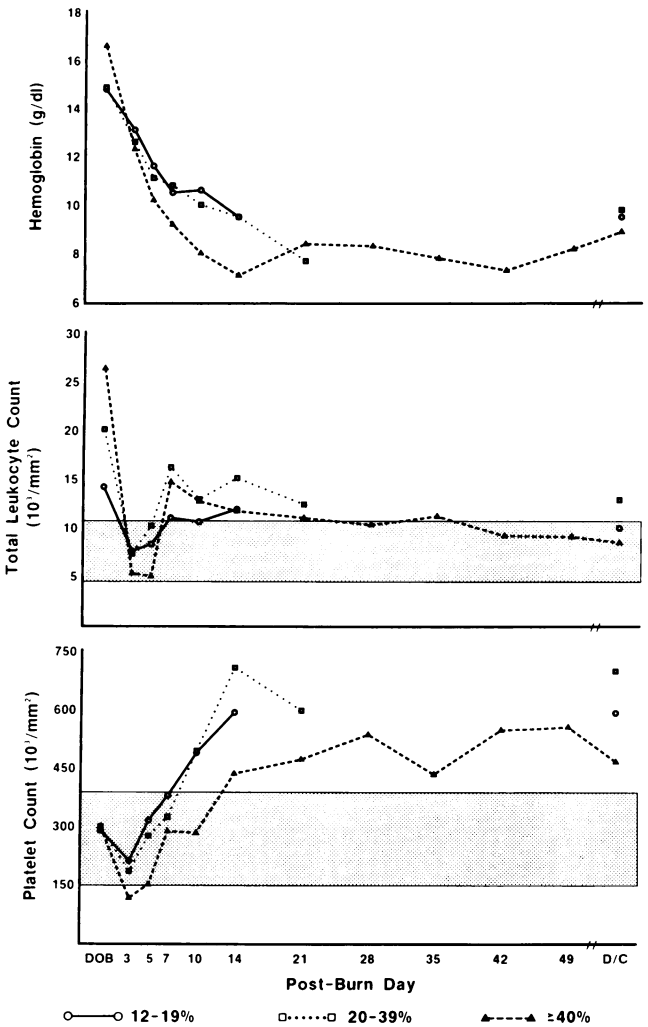

Figure 1. Serial measurements of serum hemoglobin, total leukocyte and platelet counts in patients stratified according to burn size. For clarity, the data is expressed as mean values. Shaded boxes represent control ranges. D/C represents mean value at time of hospital discharge.

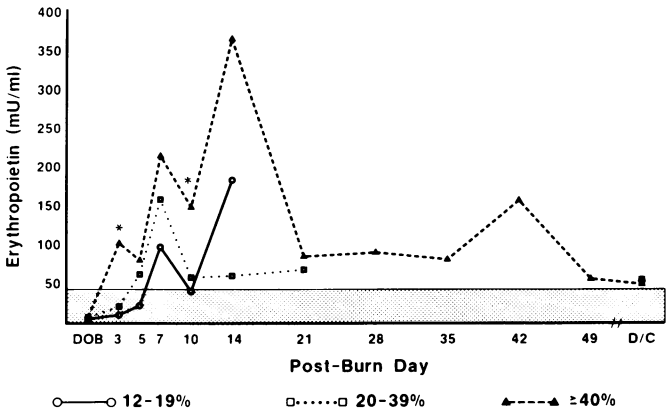

Figure 2. Serial measurements of serum erythropoietin levels in patients stratified according to burn size. For clarity, the data is expressed as mean values. Shaded box represents control values. *indicates $p < 0.01$ between patients with burns greater than 40% TBSA and other groups.

tion there was an inverse correlation between the hemoglobin and $\log_{10}$ erythropoietin levels ($r^2 = .61$, $p < 0.00001$) with the greatest correlation being observed in patients with burns of 20–39% TBSA ($r^2 = .71$). These results indicate that as hemoglobin levels decrease serum erythropoietin levels rise.

Since adequate amounts of iron must be available for erythropoietin to induce a maximal reticulocyte response, we also measured serum iron, total iron binding capacity (TIBC), and ferritin levels in these patients. Although serum iron levels were within the normal range on admission, they rapidly fell to extremely low levels and remained depressed throughout the patients' hospital courses (Fig. 4a). This decrease in serum iron levels was associated with a decrease in TIBC levels (Fig. 4b). In contrast to the serum iron and TIBC levels, serum ferritin levels did not decrease but instead rapidly reached supranormal levels where they remained throughout the patients' hospitalizations (Fig. 4c). The decrease in TIBC levels appeared to be related to the magnitude of the injury, since there was an inverse correlation between the size of the burn and the serum TIBC level ($r^2 = .51$; $p < 0.0002$). No such correlation was found between burn size and serum iron levels (data not shown).

Since transferrin saturation measurements are a relative index or iron availability, this value can be used to monitor iron availability. (Transferrin saturation is calculated by dividing the serum iron levels by TIBC and multiplying by 100 to give the transferrin saturation in percent). Although both serum iron and TIBC levels were depressed in these patients, based on the transferrin saturation values (Table 3), the serum iron levels ap-

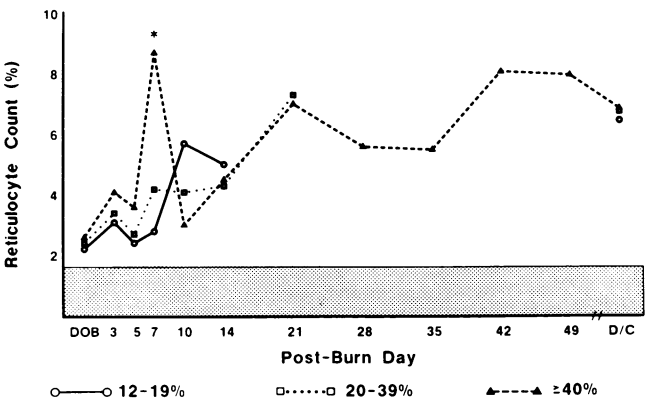

Figure 3. Serial measurements of reticulocyte counts in patients stratified according to burn size. For clarity, the data is expressed as mean values. Shaded box represents control values. *indicates $p < 0.01$ between patients with burns greater than 40% TBSA and other groups.

Table 2. COMPARISON OF ERYTHROPOIETIN LEVELS BETWEEN THREE PATIENT GROUPS

Group	n*	Erythropoietin Levels (mU/mL) Decreased (<2)	Normal (2–19)	Increased (>19)
13–19%TBSA	47	5 (11%)	25 (53%)	17 (36%)
20–39%TBSA	68	4 (6%)	30 (44%)	34 (50%)
≥40%TBSA	49	1 (2%)	8 (16%)	40 (82%)

* n = number of assays performed in each group. Number in parenthesis is % of assays Chi-square = 21.95; p = 0.0004.

peared to be depressed to a greater extent than the TIBC. In fact, transferrin saturation had fallen below the normal range (20–55%) by the third to fifth postburn day and essentially remained depressed throughout the hospitalization period.

At discharge, there was no difference between the hemoglobin levels or reticulocyte counts between any of the groups, although the patients with burns over 40% TBSA required the largest number of transfusions and had the longest hospital stays (Table 4). In fact, only three patients received more than 4 units of blood and they were all in the group with burns over 40% TBSA. These patients required 11, 14, and 33 units of blood respectively. One of these three patients did not manifest a sustained reticulocytosis and, since this patient (76% TBSA and 61% TBSA grafted) had the highest erythropoietin levels of any patient in the study, it appears that some patients may not be able to respond to elevated erythropoietin levels. The exact reasons why this patient did not develop a sustained reticulocytosis in the presence of greatly elevated erythropoietin levels is not known but it may be related to the fact that he required 10 operations to excise and graft his burn wounds and had sustained multiple infectious episodes.

Postdischarge hemoglobin levels were obtained on eight of the ten patients who were discharged with hemoglobin levels less than 9.0 g/dL. The hemoglobin levels of these patients had risen from a mean ± SD of 8 ± .8 g/dL to 11.5 ± 1.6 g/dL by an average of 6 weeks postdischarge.

DISCUSSION

Blood transfusions are an essential component of modern burn care and are necessary to replace blood drawn for diagnostic tests, blood lost at surgery or during dressing changes, as well as to treat burn-induced anemia. Yet, blood transfusions have risks as well as benefits. The risks of blood transfusions include the development of mild to life-threatening transfusion reactions as well as the transmission of potentially lethal infectious agents, including hepatitis or AIDS. In addition, blood transfusions appear to be immunosuppressive[11] and a direct association between the number of units of blood transfused and the development of infectious complications has been documented recently in a study of burn patients.[12] Until recently, therapeutic options directed at limiting blood transfusions consisted primarily of attempts to limit blood loss and the provision of agents that support normal erythropoiesis, such as iron, folate, and vitamin B_{12}. However, the recent availability of hu-

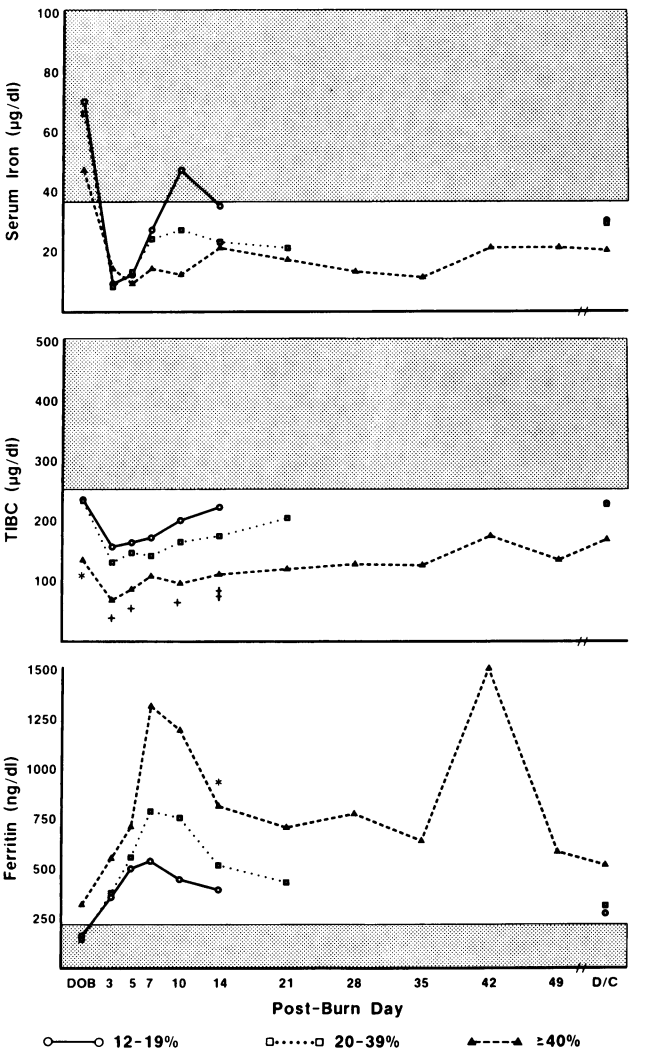

Figure 4. Serial measurements of serum iron, total iron binding capacity, and ferritin. For clarity, the data is expressed as mean values. Shaded boxes represent control ranges. *indicates $p < 0.05$ between patients with burns greater than 40% TBSA and other groups. †indicates $p < 0.01$ between patients with burns greater than 40% TBSA and other groups. ‡indicates $p < 0.02$ between patients with burns greater than 40% TBSA and patients with burns of 12–19% TBSA.

Table 3. TRANSFERRIN SATURATION (%)

Day	10–19% TBSA	20–39% TBSA	≥40% TBSA
Day 1	30 ± 16	27 ± 19	29 ± 38
Day 3	6 ± 4	5 ± 5	27 ± 23*
Day 5	8 ± 5	9 ± 6	12 ± 12
Day 7	16 ± 7	13 ± 8	12 ± 16
Day 10	23 ± 9	16 ± 10	14 ± 15
Day 14	15 ± 8	13 ± 7	24 ± 27
At discharge	14 ± 10	12 ± 6	12 ± 3

* $p < 0.01$ vs. other groups.
All values expressed as mean ± SD.
% transferrin saturation = (serum iron/TIBC) × 100.

man recombinant erythropoietin adds a potential new approach to the care of these patients.[5,13]

With the development of recombinant DNA technology, it first became possible in 1985 to produce sufficiently large amounts of recombinant human erythropoietin (rHu-EPO) for clinical use.[14] Since then, rHu-EPO has been used successfully in numerous clinical trials to correct the anemia of chronic renal failure in both children and adults and is being used with increasing frequency to treat an ever expanding range of diseases associated with anemia.[5] Since the anemia of thermal injury is associated with a relatively modest level of reticulocytosis and decreased bone marrow erythroid cellularity[6,15] and erythropoietin is the primary regulator of human erythropoiesis, the exogenous administration of rHu-EPO to these patients would make sense if endogenous erythropoietin production is inadequate. A review of the literature does not clearly answer this question. For example, interpretation of the initial studies investigating the effects of thermal injury on erythropoietin production are confounded by conflicting results and the fact that these investigators used a bioassay to measure urinary erythropoietin activity.[6,8] Two subsequent studies, in which serum erythropoietin levels were directly measured by radioimmunoassay, indicate that erythropoietin levels do increase after thermal injury.[7,16] However, in one study only seven patients were studied,[16] while in the other no information on iron metabolism was presented.[7] Furthermore, in both these clinical series,[7,16] since routine blood transfusions were given to maintain the hemoglobin level at or above 10 g/dL, the frequent administration of blood transfusions may have partially suppressed the endogenous erythropoietic response. Consequently, we carried out a prospective study to characterize the erythropoietic response to thermal injury.

Our study on the natural history of the erythropoietic response to thermal injury is unique in that routine blood transfusions were not administered to maintain an arbitrary hemoglobin level. Instead, the indications for transfusion were a hemoglobin less than 6–6.5 g/dL or evidence of inadequate oxygen delivery or hemodynamic instability, which clinically appeared to require blood rather than asanguinous fluids. Since none of the patients in this study required transfusions for cardiovascular instability, the primary indication for transfusion was to maintain a hemoglobin level above 6 g/dL. Although a clinical consensus has not been reached on the threshold for prophylactic transfusion in the anemic patient, based on human[17,18] and animal[19,20] studies on the physiology of anemia some observations appear relevant in making this decision. First, human studies in healthy individuals indicate that weakness at rest does not occur until the hemoglobin level drops below 6 g/dL, while cardiac output does not change significantly until the hemoglobin levels fall below 7 g/dL.[17,18] Furthermore, these human[17,18] and similar studies in primates and other animals,[19,20] indicate that cardiovascular failure in normovolemic anemic healthy individuals does not occur until the hemoglobin level drops below 3–4 g/dL or the hematocrit drops below 10–12%. The lack of adverse effects of our policy of limited transfusions in these patients is consistent with the abovementioned physiologic studies. Our selective approach towards blood transfusion had two additional benefits. First, it decreased the amount of blood these patients received and secondly it

Table 4. ERYTHROPOIETIC RESPONSE AND TRANSFUSION REQUIREMENTS OF PATIENTS AT TIME OF DISCHARGE

Group	Hemoglobin (g/dL)		Reticulocyte Count at Discharge (%)	Units of Blood Transfused	Days of Hospitalization
	Admission	Discharge			
13–19% TBSA	14.8 ± 1.8	9.5 ± 1.7	6.5 ± 5.5	.6 ± .9	19 ± 3.5
20–39% TBSA	14.9 ± 1.1	9.8 ± 2.1	6.8 ± 3.8	1.4 ± 1.8	21 ± 8.7
≥40% TBSA	16.6 ± 1.5	8.9 ± 1.4	6.9 ± 4.9	13.2 ± 10.6*	60 ± 26

* One patient required 33 units of blood. If this patient is excluded, then transfusion requirements were 8.3 ± 4.4 units.
Values expressed as mean ± SD.

allowed us to better study the erythropoietic response to thermal injury and anemia by reducing the confounding influence of repeated transfusions.

Our results that hemoglobin levels progressively decrease in the burn patients, while white blood cell and platelet counts reach supranormal levels after an early postburn decrease are consistent with the work of many investigators.[1,15,21] Our observations that erythropoietin levels were increased and that the magnitude of the erythropoietin response correlated well with the degree of anemia indicates that erythropoietin production is largely intact after thermal injury. However, in spite of the increased levels of erythropoietin and a modest reticulocytosis, these patients remained anemic. There are several possible explanations for this apparent paradox. First, the combination of external blood loss and decreased intravascular red cell survival time[3] may have exceeded the ability of the erythropoietic capacity of the patients' bone marrow. This possibility does not seem likely for two reasons. First, the reticulocyte count, although increased, was frequently lower than would be predicted if the bone marrow was fully responding to the level of the anemia.[22] Secondly, erythroid cellularity of the bone marrow is decreased after thermal injury.[6,15] These two observations suggest that the bone marrow does not respond normally to the anemia-induced elevations of erythropoietin after thermal injury. One explanation for this failure of bone marrow responsiveness could be the presence of an erythropoietic inhibitory factor.[23–25] Wallner and coworkers[23–25] had demonstrated the presence of such an inhibitory factor in the serum of burned patients and animals. Their studies indicate that this factor, which has not yet been fully characterized, acts directly on erythroid stem cells and not by inactivating or interfering with erythropoietin.[25] The exact role of this inhibitory factor in the etiology of the anemia of thermal injury must await further studies.

Other potential explanations for this decrease in bone marrow erythropoietic responsiveness to erythropoietin could be a lack of a necessary substrate for erythropoiesis, such as iron, or a decrease in the sensitivity to erythropoietin. Both our results and the work of others[6] document that circulating iron levels are depressed after thermal injury. The profound hypoferremia occurring after thermal injury appears to be a stereotyped response to inflammation which is largely mediated by interleukin 1.[26] Based on extensive experience with rHu-EPO therapy of patients with chronic renal failure, adequate iron availability is crucial to assuring a rapid and complete response to rHu-EPO.[5,27] Thus, failure to respond to erythropoietin or a decrease in responsiveness may reflect a functional iron deficiency state even in patients with normal iron stores. This functional iron deficiency state appears to be due to a failure of the reticuloendothelial system to release iron to transferrin fast enough to meet the increased demands for hemoglobin synthesis imposed by erythropoietin. Therefore, the lack of available iron for new hemoglobin synthesis is a potential explanation for why the erythropoietic response is not fully turned on after thermal injury. Although serum iron and transferrin saturation decreases after thermal injury and these patients thus demonstrate a plasma profile of iron deficiency anemia, their total body iron and bone marrow iron stores do not appear to be decreased and their red cell morphology does not show the hypochromic microcytic appearance characteristic of iron deficiency anemia.[6] Therefore, whether these patients are functionally iron deficient and whether the low levels of serum iron limit erythropoietin-induced bone marrow erythropoiesis is unclear. Although one might be tempted to administer iron to these burn patients on the chance that it might improve erythropoiesis, this policy may not be wise, since hypoferremia is a protective response of the host against infection.[28] In fact, the overriding of this hypoferremic response by the administration of excess iron has been documented to increase the incidence and severity of infection in both animal models and man.[28] Further work will be required to both sort out the potential role of decreased plasma iron levels in the anemia of thermal injury as well as to determine the risk–benefit ratio of iron administration.

The last potential explanation for why the erythropoietic response is impaired could be related to a decreased sensitivity of bone marrow erythroid progenitor cells to erythropoietin or to the fact that, although elevated, the erythropoietin response is suboptimal for the level of erythropoiesis required for the level of anemia. No information is available to support or refute the possibility that progenitor cell sensitivity to erythropoietin is decreased after thermal injury. However, there is evidence to suggest that cytokines, such as interleukin-1 and tumor necrosis factor can blunt the normal exponential relationship between hematocrit and plasma erythropoietin titers.[29] There is also evidence in anemic AIDS patients that exogenous erythropoietin therapy will accelerate erythropoiesis even when the baseline endogenous erythropoietin levels are as high as 500 mU/mL.[30] Since the erythropoietin levels in 22 of our 24 (92%) patients never exceeded 500 mU/mL, these patients may respond to administered rHu-EPO. However, until the mechanisms responsible for the anemia of thermal injury and the biology of erythropoiesis are more fully understood, the role of erythropoietin therapy in the burn patient must remain speculative.

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