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The anemia of chronic renal failure: Pathophysiology and treatment with recombinant human erythropoietin

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Anemia is an almost invariable consequence of progressive renal failure. The anemia is hypoproliferative in nature as determined by a low reticulocyte count when corrected for the anemia, reduced ratio of erythroid to granulocytic elements in the marrow, and low values for quantitative iron kinetics [1]. Most investigators believe that inadequate erythropoietin (Epo) production is the primary cause of the anemia. However, several other factors may contribute to the anemia of uncomplicated chronic renal failure (CRF): (1) a mild to moderate shortening of red cell survival [2]; (2) gastrointestinal and other blood loss associated with platelet dysfunction [3]; and (3) the possible effect on erythropoiesis of uremic inhibitors which are retained in CRF [4]. Other factors which may contribute to the anemia are associated with specific complications and/or treatment of the dialysis patient. These factors include residual blood loss in the dialyzed, erythroid suppression from aluminium toxicity (brought about by the chronic ingestion of aluminum-containing phosphate binders), osteitis fibrosa from severe secondary hyperparathyroidism, and, rarely, acute or chronic hemolysis [5].

While all of these mechanisms have at one time or another been raised as significant contributors to the anemia, Epo deficiency remains foremost. Animal studies in both rodents [6] and sheep [7] suggested that Epo therapy should be effective, although it was acknowledged that the methods by which animals were made uremic and, to a variable degree, anemic, might not properly reflect the pathophysiology of renal disease in man. Nevertheless, these models did result in established anemia and, in the sheep, renal failure which required dialysis. In addition, the experience with the sheep model suggested that Epo worked equally well in the uremic and normal condition, predicting that Epo would be effective in uremic humans [7].

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The effectiveness of Epo as the recombinant hormone (rHuEpo) for therapeutic, as well as for investigative, purposes, now highlights the primacy of Epo deficiency as the cause of this anemia. However, many continue to think the anemia is on the basis of uremia, and hence the terms «uremic anemia» or «the anemia of uremia», which now must be discarded.

With the advent of rHuEpo as a therapeutic, the anemia will eventually cease to contribute to the debility so many patients with CRF previously exhibited. However, there are a number of issues related to how best to use rHuEpo. In addition, correction of the anemia with rHuEpo has made us more aware of the significance of the tissue hypoxia and its associated symptoms in patients with CRF. But elimination of the anemia now presents clinicians with other issues that must be addressed in order to optimize the care of the patients with CRF.

Erythropoietin therapy in CRF

Correction of the Anemia

Since Epo concentrations in serum are insufficient to be a source to treat patients with the anemia of CRF, this problem has been resolved by the application of recombinant DNA technology. The first published reports of the successful isolation, cloning and expression of the human Epo gene appeared in 1985 [8, 9]. This was rapidly confirmed and extended [10] and large amounts of recombinant human Epo (rHuEpo) became available for clinical trials. Such clinical trials were initiated in December, 1985 in Seattle [11] and in March, 1986 in London [12]. The results of these trials involving anemic patients on hemodialysis [11, 12], and the hemodialysis patients which form the basis of multicenter trials in the United States [13], Western Europe [14], and Japan [15], coupled with the results in anemic patients with CRF not yet on dialysis [16-18] support the concept that Epo defi-

ciency is the major mechanism responsible for the anemia.

In the United States multicenter trial [13], the rate of rise of hematocrit was shown to be dose-dependent, as had the phase I-II trial [11]. In almost all patients, target hemoglobin and hematocrit levels were achieved within eight to twelve weeks after starting therapy. In this multicenter trial, only eight of 309 patients failed to respond to rHuEpo and, of those, several had complicating medical conditions which might have predicted a lack of response to the hormone. These included unrecognized iron deficiency, osteitis fibrosa, and infection. In Seattle, some patients have now received rHuEpo replacement therapy for more than three years. Encouragingly, those patients who have entered maintenance therapy have continued to respond to rHuEpo without evidence of refractoriness or resistance and, no patients have developed antibodies to rHuEpo [13]. Thus, rHuEpo is remarkably effective and well tolerated.

We have also treated seventeen patients with the anemia (hematocrit 27 ± 3) of progressive renal failure not yet requiring dialysis [18]. These patients have responded to rHuEpo in a manner similar to hemodialysis patients, having received rHuEpo by intravenous or subcutaneous routes. While the experience with subcutaneous administration of the drug is limited, the results indicate that subcutaneous dosing with rHuEpo may be more effective [18-20], although the precise correlation with intravenous dosing and details of pharmacokinetics await the results of larger patient trials.

The use of rHuEpo in anemic patients with CRF has raised three major management issues. These include the effect of rHuEpo on internal iron metabolism, the effect of the hematocrit on other organ systems such as blood pressure, and the role of inflammation in limiting the effectiveness of rHuEpo.

The effect of rHuEpo on internal iron metabolism

With the response to rHuEpo, erythropoiesis may be stimulated as much as three to four times normal [11, 21] depending upon hormone dose. This imposes a demand to mobilize iron from reticuloendothelial storage sites and to make it available to transferrin for transport to the marrow for incorporation into hemoglobin. Thus, during the initial period of response to rHuEpo, there is a one-way shunt of iron from stores, through the circulation, into the marrow and then into the circulating red cell mass. The amount of iron required for an effective response to rHuEpo can be calculated easily. If a 70 kilogram patient raises his/her hematocrit from 18 to 40, the increase in red cell mass will be approximately 1,000 ml, equivalent to 1 gram of elemental iron. In addition, with rHuEpo treatment, iron accumulation from red cell transfusions ceases while iron loss due to residual dialyzer blood loss continues. Severely anemic individuals who begin therapy with rHuEpo, and who have iron stores less than 1 gram, or, depending on the severity of the anemia, serum ferritin levels below 1,000 ng/ml, are at risk of becoming iron deficient during the course of therapy [22]. Currently, recommendations for managing patients during the acute or induction phase of therapy with rHuEpo include supplementing the diet with oral iron, or else supplementing reticuloendothelial stores more directly by the administration of iron dextran. It is our practice to administer intravenous iron dextran, one-half gram or more as required, prior to starting rHuEpo therapy in those individuals whose initial serum ferritin levels are less than 100 ng/ml. This will help to guarantee adequate iron availability for the anticipated increase in erythropoiesis.

Even when care is taken to maintain an adequate iron supply to the marrow, there will be individuals whose response to rHuEpo is so brisk that mobilization of iron from storage sites cannot keep pace with the demand. In this setting, rHuEpo may become less effective despite the fact that serum ferritin values clearly indicate that adequate iron stores are present. This condition represents a «relative» or «functional» iron deficiency. Relative iron deficiency, defined as a transferrin saturation of less than 20 % with a normal serum ferritin level, was seen in over 40 % of the patients treated with rHuEpo in the multicenter trial conducted in the United States [13]. While there are no obvious adverse effects of relative iron deficiency, it is a physiological state which reduces the effectiveness of rHuEpo therapy.

There are several approaches to relative iron deficiency. The dose of rHuEpo may be reduced in order to allow the rate of release of iron from storage sites to catch up with the demands for hemoglobin synthesis, or supplemental iron may be given orally or in the form of intravenous iron dextran. Because some patients are unable to tolerate oral iron and there is an 11 % incidence of anaphylaxis from intravenous iron dextran [23], there is concern that iron deficiency could be a limiting factor in the occasional patient because of the blood loss related to hemodialysis and occasional surgery.

The effect of correction of the anemia in CRF patients

Correction of the anemia in CRF patients results in better tissue oxygenation. The clinical benefits of this improved oxygenation have been reviewed recently [24], and include improved exercise tolerance, skin

circulation, central nervous system function [25], and increased peripheral vascular resistance. It is the last effect, and its effect on blood pressure, which warrants review at this time.

In the initial group of patients treated with rHuEpo, increases in blood pressure, including episodes of hypertensive encephalopathy, were observed with unexpected frequency, both in Seattle [11] and in the United Kingdom [12]. In the United States multicenter trial, 35 % of patients experienced an increase in diastolic blood pressure of $\geq$ 10 mmHg [13]. In some patients, this increase in blood pressure did not achieve hypertensive proportions. In others, however, the increase in blood pressure exacerbated already existing hypertension or required the initiation of antihypertensive medication. Overall, approximately 25 % of patients required new or increased blood pressure medications as they acutely responded to rHuEpo therapy [13]. Blood pressure also increased in pre-dialysis patients whose anemia was corrected with rHuEpo [16, 18, 26].

The mechanism underlying the increase in blood pressure may be related to an increase in total peripheral vascular resistance [27, 28]. Blood viscosity, which increases as the hematocrit increases, is similar in normotensive and hypertensive patients responding to rHuEpo [29], and therefore is not the sole cause. In studies from several centers, the increase in peripheral vascular resistance was associated with a decline in cardiac output [28, 30], although these findings are not uniformly agreed upon [31]. Nevertheless, these observations are similar to data published by Neff and co-workers [32] which demonstrated that acutely raising the hematocrit in normotensive dialysis patients with red cell transfusions resulted in a progressive increase in diastolic and mean arterial blood pressure. These changes, similar to those found in dialysis patients receiving rHuEpo, were mediated by an increase in peripheral vascular resistance which was associated with a decrease in cardiac output. It is believed that the increased vascular resistance results from the correction of the peripheral vasodilatation which accompanies profound, sustained anemia [27]. The blood pressure changes are not due to a direct pressor effect of rHuEpo since hypertension has not been observed in normal volunteers or in other patient groups receiving rHuEpo [33].

We have analyzed which factors impose an increased risk for the development or aggravation of hypertension in anemic patients with CRF. In an analysis of sixty-three patients in Seattle, the appearance of hypertension was more prevalent if the hematocrit was $\leq$ 20 at the outset of therapy regardless of whether there was a prior history of hypertension [28]. Of non-hypertensive patients in the Seattle study, 66 % developed an increase in blood pressure while 79 % of previously hypertensive patients required an increase in antihypertensive medication after the hematocrit increased to over 30 [28].

Eighty-nine percent of patients whose hematocrits were $\leq$ 20 at baseline developed an increase in diastolic blood pressure or frank hypertension as opposed to 57 % of those whose hematocrits were > 20. In the Seattle patients, factors such as age, sex, number of years on dialysis, presence or absence of kidneys, or the disease which led to renal failure, had no relationship with the appearance of hypertension [28].

Thus, the analysis of the Seattle patients indicated that the major risk factor for developing hypertension or an exacerbation in hypertension was severe anemia and not the rate of rise of hematocrit. An analysis of the multicenter trial results in the United States also failed to show that the rate of rise of hematocrit was a risk factor with doses of 300 and 150 U/kg, IV, three times a week [13]. Further studies in Seattle failed to show any increased incidence of hypertension with 150 U/kg, compared to 50 U/kg. Peripheral arterial resistance increased significantly in both groups as the hematocrit approached 30, but a slower rise in hematocrit at the lower dose provided more time to intervene with appropriate anti-hypertension therapy in order to prevent hypertensive encephalopathy [34], a complication of a sudden rise in blood pressure that could lead to a seizure [11-13].

Since there is no way, at this time, to predict who will develop hypertension or become more hypertensive when rHuEpo therapy is initiated, our recommendation for the anemic, hemodialysis patient is to use a relatively low dose, i.e., 50-150 U/kg, thrice weekly, intravenously. As the hematocrit approaches 30, the dose should be reduced to more gradually reach the target hemoglobin/hematocrit. Reducing the dose allows more time to observe the blood pressure response and to initiate appropriate antihypertensive therapy. If, at any time, serious hypertension develops during the acute phase of therapy, rHuEpo should be withheld until the blood pressure is controlled. Experience to date indicates that a rising blood pressure during the acute phase of treatment (i.e., when the hematocrit is increasing toward target levels) is more likely to precipitate seizures and/or hypertensive encephalopathy, than similar changes in blood pressure during the maintenance phase of therapy at a time that the hematocrit is relatively stable.

The effect of inflammation on the effectiveness of rHuEpo

Considerable interest exists in using rHuEpo in patients with anemia associated with chronic inflammatory or infectious diseases or malignancies. While fragmentary early results appear promising [33], there is an added feature of inflammation which predictably

would blunt the response to rHuEpo. Specifically, chronic inflammatory diseases of many kinds are associated with a reduced release of iron from storage sites and a reduced percent transferrin saturation. This characteristic alteration in internal iron metabolism is referred to as reticuloendothelial iron blockade and is one of the major criteria for the diagnosis of the anemia of chronic disease [35]. Because this relative iron deficiency has been so refractory to simple manipulations such as oral or parenteral iron supplementation, it may be anticipated that rHuEpo will be less effective in this setting than in otherwise normal individuals. The effect of elective hip replacement in a patient with end-stage renal disease who was receiving rHuEpo, is such an example. The patient's hematocrit had been maintained by thrice weekly rHuEpo doses of 62.5 U/kg. Prior to surgery, the rHuEpo dose was increased to enable the patient to donate blood for self-use during surgery. The effect of surgery on the response to rHuEpo was dramatic in that the hematocrit fell to below 20 and only after four to six weeks had passed was the response to rHuEpo re-established. Two other patients had similar periods of refractoriness to rHuEpo after hip replacement surgery. Another patient developed tuberculosis of the sacro-iliac joint. While the patient was febrile, the reticulocyte count and hematocrit decreased despite the maintenance of a previously effective rHuEpo dose of 125 U/kg, three times/week. After appropriate antibiotics were begun, the hematocrit rose at an even faster rate than prior to the development of symptoms. As more data accumulate in patients with active inflammatory disease, a pattern of relative rHuEpo resistance may emerge, and it is likely that the doses required to maintain target hematocrit in these patients will be higher than the doses required in stable CRF patients.

There are other issues that also must be addressed: who should be treated, what should be the initial dose, and what should be the target hematocrit?

1. *Who Should Be Treated?*

Patients who are symptomatic of anemia should be treated. But it may be difficult to define who is symptomatic. Patients requiring red cell transfusions should be treated. In the non-transfusion dependent patient with CRF, the following symptoms are associated with anemia and improve with partial correction of the anemia (hematocrit 32-38): physical fatigue, poor appetite, coldness, disordered sleep/awake pattern, depression, sexual disinterest [36], and mental slowness [25]. Since these symptoms are often present with a hematocrit < 30, all patients in this category should be candidates for therapy.

There is yet no evidence to suggest that patients with baseline hematocrit levels of 30-35 function better at a higher hematocrit level. CRF patients with chronic obstructive pulmonary disease might benefit from a higher hematocrit than 35, since a «normal» hematocrit with this lung disorder may be 50.

There is no experience, as yet, in treating the anemic patient with renal failure due to sickle cell disease. Aggravation of sickle cell crises by a rHuEpo-induced hematocrit increase might be counterproductive, although fetal hemoglobin, which is also increased by rHuEpo [37], is not susceptible to intravascular sickling and might allow for partial correction of the anemia, at least to levels to eliminate the need for transfusions.

CRF patients should have other causes of anemia excluded or corrected before beginning rHuEpo. Initial iron stores chould be adequate as indicated by a serum ferritin greater than 100 ng/ml. Any infection should be resolved before initiating rHuEpo therapy.

2. *What Should be the Initial Dose?*

The initial IV dose, given t.i.w., needed to acutely raise the hematocrit to a target level of 35 ± 3 varies from 40 U/kg and above. At 40 U/kg, only 8/29 (28 %) had a complete response, whereas at 80 and 120 U/kg, 21/28 (75 %) and 26/28 (93 %), respectively, responded by increasing their hematocrit to a target level [14]. When 150 U/kg is the initial dose regimen, > 97 % respond [13]. Patients failed to respond to 1.5 and 5.0 U/kg, and 1 of 4 patients treated with 25 U/kg had a partial response, but enough to eliminate transfusion requirements [11].

The dose required to maintain a stable hematocrit (35 ± 3) varies between 15 to over 300 U/kg, IV, t.i.w., with a mean of 100 U/kg [13]. This has been the experience of most investigative groups using two recombinant products [13, 14].

3. *What Should Be The Target Hematocrit/Hemoglobin?*

If the normal hematocrit is 36-44 for women and 39-51 for men, why shouldn't these criteria apply to patients with CRF? There are at least five reasons why many nephrologists do not feel such criteria is appropriate for their patients: hypertension may be more difficult to control at higher hematocrit levels; most patients feel much better when their hematocrit reaches 30-35 that they are satisfied to remain at that level; dialysis efficiency decreases as the plasma volume (and therefore plasma water) decreases; the incidence of vascular access clotting may increase; and because there is no data that quantitates a better quality of life or better exercise capacity at a «normal» hematocrit. In addition, the cost of rHuEpo might be greater if a higher hematocrit were maintained. Unfortunately, as yet there is no data to «prove» that a hematocrit of 30-33 (as recommended by the United

States Federal Drug Administration)[38], or 35-38 (as arbitrarily defined for most of the clinical trials) is as physiologic and safer for the patient with CRF as a «normal» hematocrit.

In summary, rHuEpo has proved to be an extremely effective and well-tolerated drug. It can be predicted that nearly all patients with uncomplicated anemia associated with CRF will respond to rHuEpo replacement therapy. Iron availability and blood pressure must be monitored and managed to minimize adverse effects of rHuEpo therapy. These management issues in patients with CRF make it prudent to begin with rHuEpo doses that are in the range of 50 to 150 U/kg and to bring the hematocrit gradually to target levels. We believe that the morbidity and impaired quality of life which characterize virtually all patients with CRF will be markedly improved as a result of rHuEpo treatment.

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