Editorials

Recombinant Erythropoietin Therapy in Renal and Nonrenal Anemia

In 1836 Richard Bright commented on the progressive fading of the "healthy colors of the countenance" of his patients,[1] and ever since anemia has been considered a hallmark of his disease. The pathogenesis of this anemia is complex and involves a shortened red cell life span due to hemolysis and blood loss without an adequate compensatory increase in the rate of red cell production. This lack of compensation was thought to be due primarily to erythroid suppression by uremic toxins. In 1957, however, studies by Jacobson and coworkers suggested strongly that the newly described erythropoietic hormone, erythropoietin,[2] was produced by the kidneys and that a relative erythropoietin deficiency in patients with kidney failure would explain the lack of bone marrow compensation.[3] It was not until it was found that isolated perfused kidneys can synthesize erythropoietin[4] and that messenger RNA for erythropoietin is present in anemic kidney homogenates[5] that the Jacobson hypothesis was fully accepted.

The recent observation that treatment with recombinant erythropoietin can restore the hemoglobin concentration to normal has shown that erythropoietin deficiency must be the most important pathogenic mechanism for anemia.[6] Of course, this finding does not rule out the presence of other mechanisms since a large dose of erythropoietin could have stimulated the rate of red cell production sufficiently to conceal an increase in red cell destruction or a uremic bone marrow suppression. In well-dialyzed and carefully managed patients, however, red cell survival is usually normal and the existence of a uremic bone marrow toxin has been exceedingly difficult to establish.[7] Furthermore, there appears to be an almost identical effect of erythropoietin in normal and uremic sheep,[8] strongly suggesting that uremia per se does not suppress red cell production. Nevertheless, we still do not understand why the level of circulating erythropoietin in anemic and uremic patients is often increased to levels capable of maintaining a much higher hemoglobin concentration in anemic patients with normal kidney function.

The spectacular success of recombinant erythropoietin therapy in ameliorating anemia both in dialysis patients and, as described by Pinevich and Petersen in this issue of the journal, in predialysis patients[9] has made a search for the exact pathogenic mechanism of anemia a little less urgent. Erythropoietin therapy works, it has relatively few side effects when used sparingly, it improves quality of life, and, despite its price, it is cost-effective by eliminating transfusion requirements. Furthermore, as emphasized by Pinevich and Petersen, an increase in hematocrit with a corresponding decrease in renal plasma flow does not, as could have been expected, affect renal function or the progression of kidney failure.[9]

The effectiveness of erythropoietin as a replacement agent in the anemia of kidney failure raises the question if exogenous erythropoietin can be of use in the treatment of anemic patients with intact renal function. This seems logical if the anemia is associated with subnormal levels of plasma erythropoietin such as occurs in patients with anemia of chronic disease.

Chronic disease is a somewhat motley designation for a sustained but not life-threatening illness. Anemia is a common denominator, and a number of studies suggest that one cause is an inadequate production of erythropoietin in response to anemia. Such a blunted response has been noted in patients with rheumatoid arthritis,[10,11] carcinoma,[11,12] lymphoproliferative disorders,[13] sickle cell anemia,[14] and human immunodeficiency virus infection.[15] It is tempting to invoke the action of inflammatory cytokines such as interleukin 1 and tumor necrosis factor on the renal biosynthetic mechanism responsible for the production of erythropoietin. Studies of erythropoietin production in hepatoma cells and isolated rat kidneys suggest indeed that these cytokines can suppress erythropoietin synthesis in response to hypoxia.[16] Unfortunately, the kidney is still a black box as far as an understanding of the relationship between the anemia and erythropoietin synthesis goes, and we need more basic information about the biosynthesis of erythropoietin before we can explain the blunted response in chronic disease.

For whatever reason the renal synthesis of erythropoietin is blunted, recombinant human erythropoietin should be of value as a replacement agent. This has been shown to be the case in therapeutic trials of patients with rheumatoid arthritis[17] and several other chronic illnesses.[13,18-20]

Because the use of erythropoietin is still expensive and demands parenteral administration, it is necessary to judge if a mild to moderate anemia in patients with chronic illnesses is a problem worth treating. Undoubtedly the anemia in some is a burden that needs to be corrected, but in many it is merely an asymptomatic nuisance.

In anemia not associated with a subnormal production of erythropoietin, the administration of recombinant erythropoietin may also be of value by boosting red cell production and partly replacing the need for endogenous erythropoietin. In chronic hemolytic anemia, the rate of red cell production is increased to balance a shortened red cell life span. This balance is first achieved when the red cell mass is decreased. Such a decrease reduces the volume of blood hemolyzed and replaced every day and provides the hypoxic drive necessary for the production of erythropoietin and in turn for the production of red cells. The administration of exogenous erythropoietin should relieve the pressure to produce endogenous erythropoietin and result in setting a new balance at a higher hemoglobin concentration.

In patients with chronic bone marrow failure, the hemoglobin concentration is also reduced until anemic hypoxia generates enough erythropoietin to stimulate a sluggish marrow to offset the daily destruction of a fortunately reduced red cell mass. The administration of exogenous erythropoietin replaces some of the endogenous erythropoietin and decreases the need to maintain a low hemoglobin level.

A number of clinical trials are under way to test these suppositions, and the results are still being evaluated. Unfortunately, the most desirable forms of anemia to treat are those in which a balance between production and destruction cannot be achieved without the use of blood transfusions. Because the rate of red cell production of a normal bone marrow, regardless of the amount of erythropoietin available, cannot exceed six to ten times baseline production, it cannot compensate for severe hemolysis. Similarly, aplastic bone

marrow or bone marrow with severe or ineffective red cell production cannot be stimulated any further regardless of the amount of erythropoietin available. Consequently, the administration of exogenous erythropoietin in patients with chronic bone marrow failure will probably be of little value. This has been found to be the case in myelodysplastic syndromes in which only a few patients receive any benefits from exogenous erythropoietin administration.[21-25]

As is evident from these remarks, it is difficult to predict if the administration of recombinant erythropoietin will be of therapeutic value in patients with nonrenal anemia. In patients with moderate anemia and an erythropoietin concentration of less than 100 U per liter, it is reasonable to assume that erythropoietin production is subnormal and that, if clinically indicated, a therapeutic trial of recombinant erythropoietin is justified. In patients with more severe anemia and especially if the erythropoietin level is higher than 500 U per liter, administering recombinant erythropoietin may be of little help. There are many exceptions, however, and because even a slight increase in red cell production may render some patients transfusion-independent, it seems reasonable to conduct a therapeutic trial. Such a trial should consist of giving 10,000 units three times a week subcutaneously. If no appreciable increase in hemoglobin concentration or decrease in transfusion requirements occurs, augmentation of the dose is probably of little benefit. This questionable benefit of recombinant erythropoietin therapy in patients with nonrenal anemia stands in stark contrast to its predictable benefit for patients with anemia due to kidney failure, and that in itself may be enough of an accomplishment.

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