Use of Recombinant Human Erythropoietin Outside the Setting of Uremia

By Mario Cazzola, Francesco Mercuriali, and Carlo Brugnara

RECOMBINANT human erythropoietin (rHuEpo) became available for clinical trials in 1985 and was introduced into clinical practice for correction of anemia of renal failure in 1989. More than 300,000 renal patients throughout the world are now receiving rHuEpo. For several reasons this use can be presently regarded as the gold standard of Epo therapy. First, renal anemia is the prototype of the Epo-deficient state. Second, although coexisting conditions may decrease rHuEpo effectiveness, more than 95% of renal patients treated with rHuEpo have a positive response if adequate doses are administered and become transfusion-independent. Third, the commonly used weekly maintenance dose of less than 100 IU/kg body weight is cost-effective compared with a regular transfusion requirement of 2 to 3 U of blood per month. Finally, quality of life improves in dialysis patients whose hemoglobin (Hb) concentration increases from 6 to 7 g/dL to 9 to 10 g/dL.

Several clinical studies in the last few years have shown that rHuEpo can be remarkably effective also outside nephrology. Because only a portion of nonrenal patients benefit from treatment, there is a need for reliable criteria to predict potential responders and ensure appropriate uses of rHuEpo. The aim of this article is to define a rational approach to rHuEpo treatment outside the setting of uremia.

PATHOPHYSIOLOGY OF Epo PRODUCTION AND Epo-DEFICIENT STATES

Epo Production

Epo is primarily made by a single organ, the kidney, outside the bone marrow and participates in a classic negative feedback control system. Hypoxia is the fundamental physiologic stimulus that causes a rapid increase in renal production of Epo through an exponential increase in the number of Epo-producing cells.

Factors other than tissue hypoxia might be involved in the regulation of Epo production or may influence serum concentration. Abnormally high Epo levels have been reported in patients with aplastic anemia, and dramatic changes in serum levels have been described after chemotherapy and during vitamin B12 or iron replacement therapy. These findings point to an inverse relationship between red blood cell (RBC) precursor mass and serum Epo level: the higher the number of RBC precursors, the faster the Epo clearance.

Inflammatory cytokines may interfere with Epo gene expression. Interleukin-1 (IL-1), tumor necrosis factor α (TNFα), and transforming growth factor β (TGFβ) have been found to inhibit hypoxia-induced erythropoietin production in vitro. These cytokines also inhibit erythroid progenitor cell proliferation, thus playing a major role in the pathogenesis of the anemia of chronic disease. At variance, IL-6 was shown to mimic hypoxia in vitro, and elevated levels in humans are associated with adequate endogenous Epo production.

Increased plasma viscosity inhibits Epo formation, thus contributing to anemia both in inflammation and monoclonal gammapathies.

Chemotherapeutic agents blunt Epo response. Cisplatin appears to be particularly toxic, causing a prolonged anemia.

Cyclosporin A also attenuates the production of Epo, and this may contribute to the anemia of patients undergoing organ transplantation. Theophylline is another drug attenuating the production of Epo. Finally, a direct suppression of Epo formation by human immunodeficiency virus (HIV) has been observed in vitro, suggesting that this may have a role in the pathogenesis of HIV-related anemia.

Physiologic Role of Epo in Erythropoiesis: Implications for the Clinical Use of rHuEpo

Epo is the primary regulator of erythropoiesis and exerts its effects by binding to a surface receptor present on erythroid progenitors and precursors. Although only a few receptors (<100/cell) are found on early burst-forming unit-erythroid (BFU-Es), their number increases with differentiation and a peak of about 1,100 receptors/cell is reached at the stages of colony-forming unit-erythroid (CFU-E) and proerythroblast. Receptor expression then decreases with erythroid maturation and almost undetectable levels are observed on peripheral reticulocytes.

Evidence has been provided that Epo may act both as a survival factor and a mitogen. However, enhancement of cell replication is only observed on mutated cell lines when the erythropoietic hormone is combined with stem cell factor. For normal human erythroid progenitors with high receptor number, ie, CFU-Es and proerythroblasts, Epo is mainly a survival factor. These cells vary widely in their Epo sensitivity, likely due to variations in internal signal transduction.

Recent studies on knockout mice have shown that Epo is crucial in vivo for the proliferation and survival of CFU-Es and their irreversible terminal differentiation, whereas it is
not required for generation of BFU-Es and their differentiation to CFU-Es. Epo can promote erythroid progenitor survival by repressing apoptosis through bcl-XL and bcl-2.

A model of erythropoiesis based on Epo prevention of programmed cell death in a population of erythroid progenitor cells with a wide heterogeneity of Epo-dependence has been proposed by Koury and Bondurant (Fig 1). In this model, which is consistent with the observations in knockout mice, erythropoiesis can be substantially and steadily expanded only through preamplification of Epo-dependent progenitors. Administration of rHuEpo to normal individuals triggers premature expulsion of immature reticulocytes from the bone marrow into the circulation, followed by a slow increase in Hb level, suggesting indeed an erythroid progenitor amplification followed by a gradual expansion of erythroblasts.

This model of erythropoiesis is extremely relevant to the clinical use of rHuEpo (Fig 1). When endogenous Epo levels are inappropriately low for the degree of anemia, administration of rHuEpo can be effective in increasing the amount of hormone reaching the erythroid marrow, thus allowing survival of more CFU-Es and output of more RBCs. Pharmacologic doses of the erythroid hormone can expand erythropoiesis also in normal individuals, such as candidates to autologous blood donation, by preventing programmed death of a few additional CFU-Es. When the endogenous plasma level of Epo is adequate for the degree of anemia, the amount of hormone circulating within the bone marrow may be increased 1 to 2 log and nearly all available marrow CFU-Es already survive; it is very unlikely that pharmacologic doses of rHuEpo can further increase the marrow Epo supply and expand erythropoiesis on these conditions.

Evaluation of Endogenous Epo Production and Epo-Deficient States

Assessment of endogenous Epo production has become a routine diagnostic procedure with the availability of com-

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**Fig 1.** Model proposed by Koury and Bondurant for expansion of erythropoiesis by prevention of apoptosis in erythroid progenitors (see also Wu et al and Koury and Bondurant). Late erythroid progenitors (CFU-Es and proerythroblasts) are dependent on the continuous presence of Epo to suppress apoptosis and are heterogeneous with respect to their Epo sensitivity. Under normal conditions (A), only a portion of late erythroid progenitors (those with lower Epo requirement) survive, generating erythroid precursors that produce normal amounts of mature RBCs. In conditions characterized by blunted Epo production (B), eg, renal failure, the large majority of erythroid progenitors undergo apoptosis due to the low Epo level within the bone marrow. Only a subpopulation of progenitors with very high Epo sensitivity and very low requirement survive; RBC production is inadequate and anemia develops. Administration of rHuEpo may allow a substantial expansion of erythropoiesis by preventing apoptosis of large numbers of late erythroid progenitors with intermediate Epo sensitivity. In anemia due to peripheral hemolysis or acute blood loss (C), renal Epo production is increased several fold and high levels of erythroid hormone are present in the bone marrow. Nearly all erythroid progenitors, even those with high Epo requirements, survive, with maximum preamplification of erythropoiesis. Administration of rHuEpo is unlikely to further enhance RBC production, because levels capable of preventing apoptosis of least sensitive cells cannot be reasonably achieved.
mercial immunoassays for serum Epo. Serum Epo levels in normal individuals are in the range of 5 to 30 mU/mL. Studies on different immunoassays have shown a wide range of estimates among normal individuals and among methods. Two-site (sandwich-type) enzyme-linked immunoassays appear to be more specific or at least to recognize only a proportion of Epo isoforms. From a practical point of view, every laboratory should use only one immunoassay and become familiar with it.

Levels found in anemic patients cannot be simply compared with normal values. In fact, as far as the Epo-generating apparatus in the kidney is efficient, serum levels increase exponentially as the hematocrit (Hct) decreases. Serum Epo must therefore be evaluated in relation to the degree of anemia and every single laboratory should determine the exponential regression of serum Epo versus Hct (or Hb) in a home-made reference population of anemic subjects and define the 95% confidence limits as reported in Fig 2. The patients gathered to calculate a reference regression equation should have no evidence of renal failure and inflammation. Patients with iron deficiency anemia, hemolytic anemia, or thalassemia intermedia may be studied as reference subjects.

The definition of defective Epo production relies on a low serum Epo in comparison with reference patients with similar Hct (or Hb). Analysis of covariance is the most appropriate statistical method for comparing a population of patients with reference subjects. This has led us to define a number of states characterized by blunted Epo production; the most common clinical conditions are listed in Table 1. With the exception of prematurity and renal failure, serum Epo levels should be obtained in all anemic patients before initiating rHuEpo therapy.

In an individual patient, the adequacy of endogenous Epo production can be easily assessed by graphic evaluation, as shown in Fig 2, or through the observed/predicted log (serum Epo) ratio (O/P ratio); the predicted value is derived from the regression equation. The O/P ratio is less than 1 if the observed value is lower than the predicted one; in reference subjects, the 95% confidence interval ranged from 0.80 to 1.20. The O/P ratio provides a measure of the magnitude of inadequacy of Epo production. For practicing physicians to gainfully use the O/P ratio for evaluation of endogenous Epo production, every laboratory should routinely provide this ratio together with the serum Epo concentration.

**Table 1. Most Common Clinical Conditions Outside Uremia Associated With Defective Endogenous Epo Production**

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Anemia of prematurity</td>
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<tr>
<td>Anemia of inflammation</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Chronic infection</td>
</tr>
<tr>
<td>AIDS</td>
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<tr>
<td>Anemia of malignancy (with or without concomitant chemotherapy)</td>
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<tr>
<td>Solid tumors</td>
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<tr>
<td>Multiple myeloma</td>
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<td>Malignant lymphomas</td>
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The pharmacokinetics of rHuEpo and the route of administration differ substantially between intravenous (IV) and subcutaneous (SC) administration. SC administration of rHuEpo induces lower peak plasma Epo concentrations, with an elimination half-life of about 19 to 22 hours versus the 4 to 5 hours of IV rHuEpo. SC administration of smaller doses of rHuEpo more closely resembles the physiology of Epo production and leads to greater efficacy than IV administration of larger doses. Therefore, rHuEpo should routinely be administered SC.

**Dosing and Monitoring rHuEpo**

A variety of dosages and administration schedules have been used for rHuEpo outside the uremia setting. Reported doses (from 150 to >1,000 IU/kg/wk) are clearly higher than those effective in renal anemia, indicating that rHuEpo is not just a replacement therapy in the nonrenal applications. Certain uses, in particular short-term treatments concerning prevention of anemia, involve fixed schedules (see below).
USES OF RECOMBINANT ERYTHROPOIETIN 4251

B. Regular need for transfusion, platelet count
A. No regular need for transfusion, platelet count <100 x 10^9/L, inflammatory condition, or concomitant chemotherapy (one of these)

Table 2. Criteria to Establish the Initial Dose of rHuEpo in an Individual Anemic Patient Outside the Setting of Uremia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Dose</th>
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<tbody>
<tr>
<td>A. No regular need for transfusion, platelet count ≥100 x 10^9/L, no evidence of inflammation, and no concomitant chemotherapy (all of these)</td>
<td>Start with 200 to 250 IU/kg/wk SC (divided in 3 administrations)</td>
</tr>
<tr>
<td>B. Regular need for transfusion, platelet count &lt;100 x 10^9/L, inflammatory condition, or concomitant chemotherapy (one of these)</td>
<td>Start with 400 to 500 IU/kg/wk SC (divided in 3 administrations)</td>
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However, when facing an individual anemic patient, practicing physicians must decide the initial dosage.

Erslev recommended a dosage of 80 IU/kg twice weekly for anemic patients with serum Epo levels greater than 100 mU/mL, and dosages at least 10 times higher for anemic patients with levels greater than 500 mU/mL. Besides endogenous Epo levels, additional factors determine the amount of rHuEpo required to expand erythropoiesis. A major factor is residual marrow function, which can be estimated from platelet count and transfusion requirement. Concomitant chemotherapy is also a crucial variable. The optimal interval between rHuEpo doses has not been established. A recent report suggests that, in normal subjects treated with IV iron, an interval of 72 hours between two doses of rHuEpo induces a higher reticulocyte response than a 24-hour interval.

Practical criteria for deciding the initial dosage of rHuEpo in an anemic patient are listed in Table 2. In view of the high cost of the therapy, it is mandatory to choose a dose that allows the optimal use of each vial and avoids wastage.

Indicators of response should be used to monitor patients treated with rHuEpo. Increments in Hb after 2 to 4 weeks have been shown to be a powerful predictor of responsiveness to rHuEpo treatment. However, this parameter may be useless in patients receiving transfusions and/or concomitant chemotherapy. Whereas changes in reticulocyte count after 2 weeks may simply reflect output of shift reticulocytes and not true expansion of erythropoiesis, an increase in reticulocyte count of ≥40 x 10^9/L after 4 weeks was found to be a significant predictor of response in cancer anemia. Thus, treatment efficacy should be assessed by measuring Hb and reticulocyte count after 4 weeks: patients showing a 4-week change in Hb level ≥1.0 g/dL and/or a change in reticulocyte count ≥40 x 10^9/L are those most likely to respond to rHuEpo.

A 2-week increment in circulating transferrin receptor ≥25% has been found to predict response to rHuEpo in both renal and nonrenal anemia. Because this parameter may show nonspecific increases (eg, variations not related to the RBC precursor mass) and its assay is not widely available, it cannot be recommended for use at this time.

Response to rHuEpo should be monitored for the possible appearance of signs of iron-deficient erythropoiesis (see below).

Only a portion of anemic patients respond to the initial dosage of rHuEpo, and some of the unresponsive ones can benefit from higher doses. Thus, after 4 weeks of treatment, if the Hb increase is less than 1 g/dL in untransfused individuals or there is no reduction in transfusion requirement in transfusion-dependent patients, the dosage should be increased (eg, it may be doubled). It is very unlikely that patients unresponsive to a rHuEpo dose of up to 900 IU/kg/wk will benefit from a further escalation; we therefore recommend not to exceed this dose, unless this is justified by very specific reasons.

When response is achieved, dose adjustments should be performed to maintain Hb within the optimal range; for each individual patient, this decision represents a compromise between subjective and objective benefits and treatment costs.

Epo and Iron: Functional Iron Deficiency

The bone marrow can be compared with a car engine, in which an adequate response to pushing on the accelerator (Epo) can be achieved only by a properly matched injection of fuel (iron). Administration of rHuEpo in excess of functionally available iron will lead to iron-deficient erythropoiesis, diminished erythroid marrow response, and a waste of this costly drug.

Two different patterns of iron-deficient erythropoiesis may develop with rHuEpo administration. True iron deficiency may develop during chronic rHuEpo administration due to a progressive shift of iron from body stores to the erythrocyte. The term functional or relative iron deficiency is used to define a situation in which the body iron stores are normal (or even increased) but iron supply to the erythroid marrow is inadequate for RBC precursor demand. Functional iron deficiency, or iron-restricted erythropoiesis, appears in the initial phase of RBC regeneration after the administration of rHuEpo to subjects with normal iron stores. Serum iron and transferrin saturation are low, serum ferritin is normal to low (presumably because the amount of readily exchangeable iron in the reticuloendothelial cells is insufficient), and iron procurement by transferrin is inadequate.

Functional iron deficiency has been described when rHuEpo is used to increase autologous blood donation, based on the appearance of RBCs with abnormally low Hb concentration and/or increased RBC protoporphyrin, and, in the absence of blood donation, on the appearance of reticulocytes with reduced Hb content. As shown in Fig 3, in individuals with normal iron stores, reticulocytes demonstrate earlier changes than RBCs. Interestingly, subjects with increased body iron stores and elevated transferrin saturation, in particular those with hereditary hemochromatosis, show nonspecific increases (eg, variations not related to the RBC precursor mass) and its assay is not widely available, it cannot be recommended for use at this time.

Iron supplementation (200 mg of oral elemental iron daily, ie, 900 mg of iron sulfate) should be administered routinely during the first 4 to 6 weeks of rHuEpo treatment to all patients but those with increased serum iron and transferrin saturation. Although iron absorption can increase several fold when rHuEpo is used, oral iron supplementation may
Fig 3. Functional iron deficiency in subjects receiving rHuEpo. (Top) Production of RBC with abnormally low Hb concentration in 3 normal subjects receiving rHuEpo to promote autologous blood donation. The percentage of RBCs with cell Hb concentration lower than 28 g/dL is plotted on the y-axis versus time (x-axis). The dose used in this trial was 200 IU/kg/d SC for 3 weeks. rHuEPO was started 1 week ahead of blood donations.58 (Bottom) Production of reticulocytes with abnormally low Hb content (CHr) in 24 normal males receiving 1,200 IU/kg of rHuEpo over 10 days. The dose was divided into either 4, 3, or 2 administrations (groups A, B, and C, respectively). Group C has higher baseline ferritin values compared with group A.60,103

still be insufficient in matching iron demands by the rHuEpo-expanded erythroid marrow.60

IV iron dextran (available in the United States) has about 0.1% incidence of anaphylaxis and, due to this potentially life-threatening complication, many hematologists are reluctant to use it routinely. Iron saccharate (available in Europe) is much safer: no anaphylactic reaction or any other life-threatening complication has been observed by us with over 1,000 IV administrations. Iron saccharate is effective in preventing the functional iron deficiency associated with rHuEpo treatment.56,61 The optimal treatment schedule is 100 mg of iron saccharate administered by intravenous infusion (250 mL of saline) 2 to 3 times weekly for 3 to 4 weeks.

For the patient’s convenience, 200 mg by slow IV infusion once weekly for 3 to 4 weeks may represent a satisfactory compromise. Autologous blood donors need a more aggressive iron supplementation, ie, 200 mg by slow IV infusion at each donation visit (see below). Iron saccharate may be administered routinely to all patients with normal to low values for serum iron, transferrin saturation, and serum ferritin.

Monitoring iron status in patients receiving rHuEpo may allow prompt detection of iron-deficient erythropoiesis. However, this is feasible only if the physician may rely on simple tests. An impaired iron supply to the erythroid marrow is indicated by low transferrin saturation (<20%).56,57.
however, this measurement shows marked variation and is relatively time consuming. Serum ferritin levels less than 100 μg/L are generally associated with insufficient amounts of ready exchangeable iron in the reticuloendothelial cells and may be regarded as predictive of functional iron deficiency under rHuEpo treatment.\textsuperscript{54,60} Macdougall et al\textsuperscript{62} have proposed a simpler approach to the detection of functional iron deficiency during rHuEpo treatment. Using an automated cell counter, it is possible to obtain the percentage of hypochromic RBCs (defined as an individual cell Hb concentration <28 g/dL). These are normally lower than 2.5% of all RBCs. An increase to greater than 10% during rHuEpo would indicate the development of functional iron deficiency and the need for more intensive iron supplementation.\textsuperscript{62} Early detection of iron-restricted erythropoiesis can be achieved with the monitoring of reticulocyte Hb content (CHr).\textsuperscript{60} As shown in Fig 3, the appearance of reticulocytes with abnormally low CHr precedes by several days the detection of hypochromic RBCs. Any patient fulfilling at least one of the above criteria (transferrin saturation <20%, serum ferritin <100 μg/L, >10% hypochromic RBCs, or reticulocytes with low CHr) should be promptly considered for more aggressive iron supplementation therapy.

\textit{Side Effects of rHuEpo Treatment}

rHuEpo is remarkably well tolerated. Adverse reactions have been described mostly in chronic renal failure, with development of hypertension and seizures. Outside of the renal setting, there are no reports of significant side effects. Aggravation of splenomegaly has been occasionally observed in patients with myeloproliferative disorders.\textsuperscript{50} Although rHuEpo may slightly increase platelet count in occasional patients, no significant changes in any hemostatic variable can be shown in the vast majority of treated individuals.\textsuperscript{53} Very seldom (4 case reports in the literature)\textsuperscript{64} antibodies against Epo have been shown in patients treated with rHuEpo.

\textbf{CLINICAL USES OF rHuEpo IN NONUREMIC PATIENTS}

In the United States, rHuEpo is approved for treatment of anemia induced by zidovudine (AZT) therapy in HIV-infected patients with endogenous Epo levels less than 500 mU/mL, of anemia induced by chemotherapy of nonmyeloid malignancies, and for the reduction of allogeneic blood transfusion in elective surgery patients (with the exception of cardiac and vascular surgery). In some European countries, rHuEpo is now approved also for potentiation of preoperative autologous blood donation and for treatment of anemia of prematurity.

The clinical uses of rHuEpo in nonuremic patients can be schematically divided into prevention and treatment of anemia.

\textbf{PREVENTION OF ANEMIA}

Patients facing surgery or chemotherapy are obviously at risk of developing anemia. Some of them may benefit from the prophylactic use of rHuEpo, as summarized in Table 3 and detailed below.

\textbf{Potentiation of Preoperative Autologous Blood Donation and Perisurgical Use of rHuEpo}

Different uses have been proposed for rHuEpo in transfusion medicine.\textsuperscript{65} rHuEpo may be used to enhance the collection of autologous blood in patients facing elective surgery, to correct anemia before surgery, and to accelerate postoperative erythropoietic response. The primary aim is to avoid the risks of blood transfusion from donors.\textsuperscript{66} In addition, patients who refuse transfusion on religious or ideological grounds or patients for whom it can be difficult to find compatible blood can undergo invasive surgical operations with a greater margin of safety.

\textit{Autologous blood transfusion.} For surgical patients, particularly candidates for elective surgery, the safest alternative to transfusion with allogeneic blood is the use of the patient’s own blood, obtained using various autotransfusion techniques.\textsuperscript{67-69} Autologous donation is poorly effective if the patient, during the relatively short time for which the collected units can be stored, is unable to predeposit sufficient blood to meet his/her transfusion needs.\textsuperscript{70}

The amount of blood that may be predeposited depends on the subject’s RBC mass and ability to rapidly reconstitute the volume of RBCs withdrawn. Subjects of small size and/or with low baseline Hct do not generally succeed in predepositing the amount of blood required to cover their transfusion requirements. In a retrospective study on 2,500 cases, only two thirds of patients were found to be able to predeposit the optimal amount of autologous blood: the major cause for failure was a decrease in the Hct to less than the threshold of 33%, which often occurred after the first or second donation.\textsuperscript{71}

The ability to promptly reconstitute the RBC mass might be limited by endogenous Epo production.\textsuperscript{72} As shown in Fig 2, serum Epo levels increase significantly above normal only for Hct values of less than 30% (or Hb <10 g/dL).\textsuperscript{73} This Hct value is below the acceptable level for donation of autologous blood. According to American Association of Blood Banks (AABB) standards,\textsuperscript{74} donation should not take place when Hct is less than 33% and Hb is less than 11 g/dL. Therefore, the degree of anemia induced by autologous blood donations is never sufficient to increase endogenous Epo levels significantly.

\textit{Efficacy of rHuEpo in increasing the volume of predeposited blood.} Several studies have shown that rHuEpo can increase autologous blood donation.\textsuperscript{61,75-80} In all of the clinical studies considered, rHuEpo was found to be effective in stimulating erythropoiesis and increasing new RBC production (although this was found to vary considerably [250 to 900 mL]) and the number of units predeposited. It was also effective in correcting anemia induced by blood collection.\textsuperscript{51,82}

The increase in the amount of blood deposited correlated fairly well with the dose of rHuEpo administered. The most common treatment protocol used involved IV administration twice weekly for 3 weeks together with oral iron supplements. Total doses of less than 600 IU/kg were ineffective in promoting sufficient erythropoiesis to significantly in-
crease the volume of predeposited blood. Higher doses yield a dose-dependent production of new RBCs ranging from 250 mL for total doses of 600 IU/kg to more than 900 mL for doses of 3,600 IU/kg. It should be noted that, despite oral iron supplementation, the effect of rHuEpo therapy in autologous donors is very often restricted by iron depletion. IV iron administration allows a more adequate iron supply for erythropoiesis, with either an increased Hb response to the same dose of rHuEpo or a reduction in the dose of rHuEpo required. With the use of IV iron saccharate, RBC regeneration and volume of predeposited blood were identical when total rHuEpo doses of 1,800 and 3,600 IU/kg were compared.

The effectiveness of the SC route for rHuEpo has been shown in several studies. In our experience (Fig 4), SC administration of rHuEpo combined with intravenous iron is highly effective in autologous blood donation and, compared with intravenous administration, allows a marked reduction (approximately 50%) in the total rHuEpo dose. In a recent study, SC administration of rHuEpo combined with intravenous iron saccharate infusion has been shown to have facilitated the donation of autologous blood and reduced perioperative homologous blood transfusion in anemic patients with cancer.

At least two studies have clearly shown that rHuEpo is safe and effective in stimulating erythropoiesis and allowing preoperative donation of blood for autologous use in patients who are unable to deposit blood preoperatively because of anemia. This appears to be one of the major indications to the use of rHuEpo in transfusion medicine.

**Efficacy of rHuEpo in reducing the exposure to allogeneic blood transfusion within autotransfusion programs**. The patient’s basal Hct determines both the amount of blood that can be predeposited (direct relationship) and the transfusion requirement during and after surgery (inverse relationship). Patients with high Hcts (>40%) usually succeed in predepositing 4 U or more of blood before surgery without any rHuEpo treatment (provided that adequate iron supplements are administered). This amount of autologous blood is suf-

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**Table 3. Clinical Uses of rHuEpo for Prevention of Anemia**

<table>
<thead>
<tr>
<th>Use</th>
<th>Subjects Most Likely to Benefit From Treatment</th>
<th>Optimal Treatment Schedule</th>
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<tbody>
<tr>
<td>1. Autologous blood donation before surgery</td>
<td>Anemic patients (Hb &lt;13.5 g/dL or Hct &lt;40%), subjects with a calculated blood volume &lt;5 L and expected blood loss ≤ 4 U, and alloimmunized patients. Treatment may also be justified in patients who reject transfusions because of religious conviction and in bone marrow donors.</td>
<td>250-300 IU/kg rHuEpo SC twice weekly over the 3-week period before surgery. IV iron supplementation (iron saccharate at 200 mg) is administered at each donation visit. Alternatively, at least 200 mg of oral elemental iron should be administered daily (see also Fig 5).</td>
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<tr>
<td>2. Perioperative adjunctive therapy</td>
<td>Surgical patients who are excluded from autologous blood programs because of a time to surgery &lt;3 weeks or for logistical reasons.</td>
<td>See Fig 5. Normovolemic hemodilution should be considered in combination.</td>
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<tr>
<td>3. Prevention of anemia and transfusion requirement in patients undergoing platinum-based combination chemotherapy</td>
<td>Patients undergoing platinum-based combination chemotherapy (with doses prone to induce anemia: cisplatin at 75 mg/m²/cycle or more; carboplatin at 350 mg/m²/cycle or more) and showing borderline or low Hb levels.</td>
<td>150 IU/kg rHuEpo SC three times weekly during the whole chemotherapy treatment.</td>
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**Fig 4.** Production of new RBCs in patients treated with IV rHuEpo at a total dose of 1,800 IU/kg and in patients treated with SC rHuEpo at a dose of 800 IU/kg. Both groups received IV iron supplements. Data are from the Department of Immunohematology and Blood Transfusion, Istituto Ortopedico Gaetano Pini (Milan, Italy). The study was performed on 22 patients suffering from rheumatoid arthritis and about to undergo total hip replacement or total knee replacement who were unsuitable for inclusion in the predeposit program due to anemia (Hct <34%). Patients enrolled in the study received 100 IU/kg rHuEpo SC twice a week for 3 weeks + one 200 IU/kg bolus of IV rHuEpo at the time of the first administration (total dose, 800 IU/kg; 11 patients) or 300 IU/kg IV rHuEpo twice a week for 3 weeks (total dose, 1,800 IU/kg; 11 patients). Apart from 1 patient in the group treated with IV rHuEpo, all the remaining were able to predeposit autologous blood units. SC administration of a rHuEpo dose 55% less than the IV dose was found to be equally effective in terms of average number of units predeposited (2.6 ± 0.9 v 2.6 ± 0.6), the number of allogeneic units transfused per patient (0.3 ± 0.8 and 0.8 ± 0.8, respectively), and the total number of units transfused per patient (3.1 ± 0.9 and 3.1 ± 0.6, respectively). A significant reduction in the number of allogeneic units transfused per patient was noted compared with an untreated historical group (0.5 ± 0.8 v 2.6 ± 1.6; P = .002).
sufficient to cover transfusion requirements of most surgical operations. Therefore, for studies enrolling patients with high Hcts, it is difficult to show any efficacy of rHuEpo in reducing the risk of homologous transfusion, because patients in the placebo group also succeed in predepositing sufficient autologous units to cover their transfusion requirements. On the other hand, patients with a baseline Hct less than 37% generally predeposit insufficient autologous blood (0 to 1 U) to cover their transfusion requirements. For Hct values between 37% and 40%, requirements are covered by autologous blood in some 56% of cases.

Clinical trials enrolling selected patients at high risk for transfusion (anemic patients or individuals with low RBC mass and facing operations with high transfusion requirement) have shown that treatment with rHuEpo significantly lowers homologous blood requirement in autologous blood donors. This observation indicates that rHuEpo use in autologous blood donation programs should be restricted to individuals who can benefit from it in terms of lower risk of exposure to allogeneic blood.

**The issue of cost-effectiveness and indications to the use of rHuEpo in autologous donors.** Routine use of rHuEpo for autologous donors is unlikely to be cost-effective. Cost-effectiveness of simple autologous donation has been questioned, given the improved safety of allogeneic transfusions and owing to the high cost of collecting and discarding units that are not used. In a recent study, 54% of the patients who received rHuEpo did not use the blood they had deposited. Despite the apparent financial disadvantage, reduction of allogeneic blood use via autologous blood donation should be recommended. All elective transfusion of blood via autologous blood donation should be recommended. Allogeneic transfusion is still to be regarded as an outcome to be avoided because, despite all technical and scientific achievements, a “zero risk” cannot exist in this setting.

In autologous blood donation programs, rHuEpo should be used in a carefully targeted approach for conditions likely to yield significant reductions in the transfusion of allogeneic blood, such as in anemic patients, individuals with a calculated blood volume less than 5 L, or with alloimmunization. At the present time, there is no consensus on the optimal schedule of rHuEpo administration. In orthopedic patients who donated 2 U of blood before surgery and received SC rHuEpo twice a week for 3 weeks, doses of 250 and 500 IU/kg yielded similar Hb levels that were higher than those of untreated controls or patients receiving 125 IU/kg. However, a recent study showed effective responses with dosages of 100 IU/kg administered to nonanemic patients twice a week in the 2 weeks before surgery.

We recommend a dosage of 250 to 300 IU/kg SC twice weekly for 3 weeks plus an optional initial IV administration of 150 to 200 IU/kg at the time of enrollment. Alternatively, the dose can be individualized using predictive algorithms. We recommend combination of rHuEpo with IV iron saccharate (200 mg by IV infusion at each donation visit). If this or any other safe preparation of IV iron is not available, oral supplementation should be provided by administering at least 200 mg of elemental iron daily.

**Perioperative use of rHuEpo.** Although preoperative donation is now considered a viable and safe way to obtain autologous blood, there are subgroups of elective surgery patients for whom preoperative autologous blood donation is not feasible. These include patients with anemia or other disorders precluding donation, patients with limited time to surgery, and individuals who are unwilling to participate in an autologous blood donation program because of logistical problems or religious beliefs. For example, postponing the operation in cancer patients or candidates to heart surgery might be more detrimental than receiving allogeneic blood transfusion.

In these cases, rHuEpo can be used to turn the patient into his/her own blood bank by increasing RBC production before and immediately after surgery, without concomitant autologous blood donation. To test the hypothesis that the preoperative and postoperative administration of rHuEpo to patients undergoing elective hip replacement would increase the Hb level and decrease the rate of transfusion, the Canadian Orthopedic Perioperative Erythropoietin Study Group conducted a double-blind, placebo-controlled, randomized trial. Overall, this perioperative use of rHuEpo decreased the need for transfusion. Most of the benefit of rHuEpo occurred in the 40% of patients whose Hb was less than 13.5 g/dL, in whom treatment reduced from 74% to 33% the portion of subjects requiring transfusion. The optimal treatment schedule in the Canadian study proved to be subcutaneous administration of 300 IU/kg daily for 14 days, starting 10 days before surgery and continuing until 3 days after surgery. This use was not cost-effective because the cost of perisurgical rHuEpo per patient ($2,880) balanced that of 17 U of allogeneic blood ($168 per unit). However, it should be noted that the Canadian study might considerably underestimate the transfusion costs. In fact, a more recent work has calculated a mean cost of $1,696 per transfusion episode for patients with the most common cancer types.

The American Erythropoietin Study Group has recently reported a randomized, double-blind, placebo-controlled study in 200 patients scheduled for elective orthopedic surgery who declined or were unable to donate autologous blood preoperatively. Patients were randomly assigned to one of three treatment groups: rHuEpo at 300 IU/kg/d (n = 60), rHuEpo at 100 IU/kg/d (n = 71), and placebo (n = 69). A total of 15 doses was administered SC, beginning 10 days before the operation and extending through postoperative day 4. All patients were maintained on iron supplementation orally. Fewer patients treated with rHuEpo (22%) received allogeneic transfusions compared with placebo-treated patients (54%; P < .001). Patients with a baseline Hb level of ≥13 g/dL were at significantly higher risk for transfusion than those with Hb level greater than 13 g/dL and benefited most from rHuEpo. A similar study in 316 patients undergoing orthopedic surgery (112 and 101 patients treated SC with 300 and 100 IU/kg rHuEpo, respectively, and 103 with placebo) showed a comparable reduction in exposure to allogeneic blood transfusion for patients receiving 300 IU/kg of rHuEpo when baseline Hb levels were greater than 10 and less than 13 g/dL.

Because blood transfusions might be associated with
higher postoperative morbidity and tumor recurrence in colorectal cancer surgery, a trial was performed to investigate whether perisurgical Epo can reduce the need for transfusions in anemic patients who are not suitable for autologous blood donation. In a double-blind randomized study, 150 IU/kg body weight Epo was administered SC every 2 days beginning 10 days before the operation and continuing until postoperative day 2. There was no reduction in the need for transfusion in the rHuEpo-treated group, but selected patients with high iron availability (higher transferrin saturation) apparently benefited from treatment.

In a simulated perisurgical setting, administration of a total dose of 1,200 IU/kg of rHuEpo in conjunction with oral iron supplementation (300 mg elemental iron daily) over 10 days induced an increase of 6.2 Hct points in 24 normal males, corresponding to 2 U of RBCs. Thus, two doses of 600 IU/kg administered SC in the 10 days before surgery may be sufficient in patients with an expected blood loss of ≈2 U. A weekly SC dose of 600 IU/kg (total of 4 doses starting at surgery day −21) has been shown to provide a greater Hb increase than a daily SC regimen of 300 IU/kg (total of 15 doses, from surgery day −10 to +5) in patients undergoing major orthopedic surgery. This study and the study of Breyman et al in normal volunteers suggest that a proper interval between rHuEpo doses may have a significant influence on the erythropoietic response. As in other indications, the Hb response to perisurgical rHuEpo varies according to the iron stores and is higher in subjects with higher baseline serum ferritin or transferrin saturation.

A short-term perisurgical use of rHuEpo was studied at the Istituto Ortopedico Gaetano Pini in Milan. Sixteen patients for whom autologous blood donation was contraindicated for various clinical reasons and who were about to undergo major orthopedic surgery with a predicted blood loss of 2 to 3 U of blood were enrolled in a pilot study. Treatment protocol involved SC administration of rHuEpo at a daily dose of 100 IU/kg from the preoperative day 4 (day −4) to the second postoperative day (day +2). On the first day of treatment, one 200 IU/kg bolus was also administered IV. IV iron saccharate was administered concomitantly at a total dose of 600 to 1,000 mg, according to baseline iron stores. This treatment produced a 2% to 7% increase in Hct, with an average increase in circulatory RBC mass of some 100 mL (from 0 to 245 mL) before surgery. Twelve of 16 patients did not require allogeneic transfusions, whereas a total of 6 U of blood was transfused in the remaining 4 patients. Although preliminary, these findings suggest that rHuEpo administered together with IV iron during a preoperative period of 4 to 5 days is able to stimulate erythropoiesis and reduce transfusion requirements in patients with very limited time to surgery who cannot deposit autologous units.

The combination of perisurgical rHuEpo with acute normovolemic hemodilution and/or perioperative RBC salvage may further decrease the need for autologous transfusion. In patients undergoing open-heart surgery, the use of rHuEPO induced higher oxygen half saturation tension ($P_{50}$) and RBC 2.3 diphosphoglycerate (2.3-DPG) compared with placebo. This was shown to be associated with a significant increase in extractable O$_2$ and a decrease in the occurrence of lactic acidosis postsurgery.

Epo can also be used to improve postoperative erythropoietic recovery. In a study on 40 Jehovah’s Witness patients with severe postsurgical anemia (Hct < 25%) refusing transfusion, administration of rHuEpo accelerated Hct recovery.

Current uses of rHuEpo in the surgical setting. rHuEpo has been approved by the FDA for the reduction of allogeneic blood transfusion in surgery patients. The approved indication includes anemic patients (Hb >10 and <13 g/dL) undergoing elective, noncardiac, and nonvascular surgery and patients at high risk for significant perioperative blood loss. This indication excludes anemic patients who are willing and capable of donating autologous blood.

Several different administration protocols have been used in the surgical setting. We suggest four alternative schedules, which are summarized in Fig 5. Criteria for selection among these four schedules should be primarily based on time to surgery and availability of an autologous blood donation program.

Prevention of Anemia and Transfusion Requirement in Patients Undergoing Platinum-Based Combination Chemotherapy

A randomized trial has shown that cisplatin-induced anemia can be corrected by rHuEpo. The efficacy of rHuEpo in reducing transfusion requirements has been tested in women with ovarian carcinoma treated with platinum-containing chemotherapy regimens. Eight of 87 patients (9.2%) in the rHuEpo group received at least one transfusion, compared with 13 of 33 patients (39.4%; $P = .0002$) in the control group. A dose of 150 IU/kg three times weekly was effective, and a low serum Epo was a predictor of response, confirming the validity of the model reported in Fig 1. Decreased transfusion requirements were demonstrated in patients receiving rHuEpo during intensive chemotherapy for small-cell lung cancer or primary malignant bone tumors. In the latter study, rHuEpo was equally effective in patients receiving platinum-based chemotherapy and those receiving intensive chemotherapy without cisplatin or carboplatin.

Patients who are anemic before chemotherapy or become so after the first cycle are more likely to require blood transfusions. These individuals will benefit from prophylactic use of rHuEpo. In addition, because there is a significant dose-related impact of the platinum-based chemotherapy on the severity of anemia, it is appropriate to restrict the use of rHuEpo to patients treated with doses prone to induce anemia (cisplatin 75 mg/m$^2$/cycle or more; carboplatin 350 mg/m$^2$/cycle or more).

Adjuvant Treatment for Regular Phlebotomy

Most patients with hereditary hemochromatosis tolerate the removal of 1 to 2 U of blood per week with only a slight decrease in Hb level. Occasional patients become severely...
Fig 5. Uses of rHuEpo in surgical patients. (A) When the time to surgery is ≥3 weeks, the use of rHuEpo for facilitating autologous blood donation may be considered. Patients are treated with rHuEpo at 250 to 300 IU/kg twice weekly over the 3-week period before surgery. IV iron supplementation (iron saccharate at 200 mg) is administered at each of the six visits before surgery, when the patient donates 1 U of autologous blood (350 mL) if his/her Hct is ≥34%. If IV iron is not available, oral supplementation should involve the administration of at least 200 mg of elemental iron daily (900 mg iron sulphate) and rHuEpo doses should be doubled. (B) When the time to surgery is 2 to 3 weeks or when autologous donations are not possible, a preoperative use may be considered. We suggest SC administration of 6 doses of rHuEpo (250 to 300 IU/kg) and iron supplementation as detailed above in (A). These administrations may be distributed over a variable period, from 10 to 21 days. (C) Alternative protocol for perisurgical use of rHuEpo, based on 4 SC rHuEpo administrations of 600 IU/kg each, every 7 days, starting at surgery day –21. Daily oral iron supplementation is provided with 200 mg of elemental iron in the form of a polysaccharide-iron complex (Niferex; Central Pharmaceuticals Inc, Seymour, IN). (D) When time to surgery is 1 week or less, a short perisurgical use of rHuEpo may be considered. The schedule used at the Istituto Ortopedico Gaetano Pini (Milan, Italy) involves SC administration of rHuEpo at a daily dose of 100 IU/kg from preoperative day 4 (day –4) to postoperative day 2 (day +2). On the first day of treatment, one 200 IU/kg bolus is also administered IV. IV iron saccharate is administered concomitantly at a total dose of 600 to 1,000 mg, according to baseline iron stores.

anemic. These individuals may benefit from rHuEpo to continue phlebotomy therapy. rHuEpo and phlebotomy have also been used in patients with porphyria cutanea tarda.

TREATMENT OF ANEMIA

Anemia of Prematurity

Otherwise healthy infants who are born prematurely undergo an exaggerated decrease in Hb concentration compared with term infants. Multiple factors play a role in determining the anemia of prematurity, including a defective Epo response to decreasing Hb levels.

Data from various clinical trials indicate that the use of rHuEpo reduces transfusions in premature infants weighing more than 1,000 g. In infants weighing less than 1,000 g or requiring artificial ventilation, the reduction in transfusion needs is less impressive. This limited response may be due to poor Epo responsiveness or insufficient iron supplements. There is probably no benefit in using rHuEpo for infants weighing more than 1,300 g, because they rarely require transfusion. Premature infants who have received rHuEpo show a normal pattern of erythropoiesis after the drug has been discontinued, indicating that the anemia of prematurity is the result of a transient developmental abnormality in Epo production. The dosages of rHuEpo used have been in the range of 75 to 1,200 IU/kg/wk, with one recent study using 6,300 IU/kg/wk.

Adopting selective criteria, treatment can be cost-effective. However, in our opinion, the need of providing cost-effective care should not prevent the intuitive benefit of reducing use of allogeneic blood products in this particular setting. We recommend early rHuEpo treatment for the premature infants who have an intermediate weight of approximately 750 to 1,300 g. The optimal dosage is 250 IU/kg subcutaneously three times weekly, from week 1 to 6 of life. Iron supplementation (5 mg of oral elemental iron per kilogram daily) appears to be crucial.

Anemia of Rheumatoid Arthritis and Other Inflammatory Conditions

Anemic patients with rheumatoid arthritis generally have lower plasma Epo levels than patients with comparable anemia due to iron deficiency. However, only occasional patients have Hb levels lower than 8 to 9 g/dL and practically none of these patients is dependent on transfusion. Many severely anemic patients have coexistent iron deficiency and may benefit from IV iron administration. Thus, although patients with rheumatoid arthritis may show excellent hema-

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Epo. There is little rationale for widespread treatment. This does not exclude the use of rHuEpo in individual cases who are severely anemic and do not respond to iron therapy. On the other hand, the use of rHuEpo appears fully justified in the perisurgical setting.

It has been shown that rHuEpo treatment can increase Hb levels in patients with inflammatory bowel disease and anemia refractory to treatment with oral iron and vitamins. Many of these patients are likely to have iron deficiency associated with inflammation and, although resistant to oral iron, may respond to IV iron. A low mean corpuscular volume (MCV), a serum ferritin level below 70 μg/L or an increased serum transferrin receptor level can be used for defining iron depletion with concomitant inflammation. Bone marrow stainable iron is also a useful parameter, but this is an invasive test that cannot be used routinely in all patients. If any of these parameters suggests concomitant iron deficiency, a short treatment with IV iron should be performed before considering the use of rHuEpo in these individuals.

**HIV Infection**

Anemia is found in about two thirds of patients with acquired immunodeficiency syndrome (AIDS) and generally worsens during treatment with AZT. Dosages of rHuEpo of 100 to 200 IU/kg administered IV or SC three times a week induced increased Hct and reduction of transfusion requirements in patients with baseline serum Epo levels less than 500 mU/mL. A large study using weekly dosages of 24,000 to 48,000 U/wk in patients with baseline Epo less than 500 mU/mL and Hct less than 30% showed an increase in Hct of at least 6 Hct points and a decrease in transfusion requirement in 44% of the patients. Positive results have also been obtained with rHuEpo in the treatment of anemia induced by antiretroviral therapy in HIV+ children. Although widespread use of rHuEpo in HIV-related anemia is not justified, symptomatic AIDS patients with baseline Epo less than 500 mU/mL should be treated.

**Anemia of Cancer**

Anemia is a frequent finding in patients with cancer and may be due to different causes. In untreated subjects, the most common type is anemia of chronic disease, a condition characterized by excessive release of inflammatory cytokines and variable degrees of defective endogenous Epo production. Chemotherapy and radiotherapy frequently cause or exacerbate anemia in patients with cancer due to their suppressive effects on either erythropoiesis or renal production of Epo.

A very thorough review on the use of rHuEpo in cancer anemia has already been published in Blood. Following phase I-II clinical trials, two controlled studies have shown that rHuEpo at a dose of 100 to 150 IU/kg three times weekly corrects chemotherapy-induced anemia and reduces transfusion requirements. Epo has been found to be both safe and effective at increasing Hb levels in anemic patients receiving radiation therapy alone or combined with chemotherapy.

Improvement of anemia after rHuEpo treatment is seen in only a portion of cancer patients, and data on the relationship between response to rHuEPO and improvement of quality of life are preliminary and controversial. Therefore, we agree with Spivak that the most important issue is whom to treat. This is discussed below in the chapter on a patient-oriented approach to the use of rHuEpo outside nephrology. However, there is a need for prospective clinical trials aimed at evaluating the impact of rHuEpo treatment on the quality of life of anemic patients with malignant disease.

**Anemia Associated With Multiple Myeloma and Non-Hodgkin Lymphoma**

Although almost every patient with multiple myeloma (MM) eventually becomes anemic, anemia is more frequent and severe in subjects with advanced disease. A quarter of MM patients have inadequate Epo response and this proportion increases to more than 50% in advanced clinical stages.

In a pilot study, rHuEpo induced complete correction of anemia in 11 of 13 patients with myeloma-associated anemia without severe renal failure. Recent randomized trials have provided response rates of 55% to 65%. In a multicenter study, approximately three quarters of MM patients presenting with Epo levels inappropriately low for the degree of anemia responded to rHuEpo, whereas only one quarter of those with adequate Epo levels did so. A dose of 200 IU/kg/wk was effective in patients showing residual marrow function (as indicated by a platelet count >150 × 10^9/L), whereas 500 IU/kg/wk was required to achieve response in subjects with hypoproliferative marrow. A recent study on transfusion-dependent anemic patients with MM has shown that rHuEpo can eliminate transfusion needs in individuals with defective endogenous Epo production and a baseline platelet count ≥100 × 10^9/L.

The results obtained by using rHuEpo in the treatment of anemia associated with non-Hodgkin lymphomas are comparable to those obtained in MM. Only a few studies have treated patients with Hodgkin’s disease, likely because anemia is less frequent in this condition than in non-Hodgkin lymphomas. However, rHuEpo appears equally effective in both conditions.

**Hematopoietic Stem Cell Disorders**

Anemia is a major clinical problem in conditions such as aplastic anemia, myelodysplastic syndromes (MDSs), and idiopathic myelofibrosis. Many patients are adversely affected by transfusion-dependency and secondary hemochromatosis. Unfortunately, the large majority of available studies on the use of rHuEpo in these conditions are uncontrolled.

There is no evidence of any effect in severe aplastic anemia, whereas occasional patients with pure RBC aplasia may respond despite elevated endogenous Epo levels.
Endogenous Epo production is frequently inadequate in recipients of allogeneic BMT and this may delay erythropoietic recovery. A pilot study showed that rHuEpo administration can accelerate erythroid reconstitution after allogeneic BMT with no stem cell competition effect. Three randomized clinical trials have confirmed that rHuEpo in high doses reduces transfusion requirements during the first 2 months after BMT, whereas low doses are poorly effective. In one of the previous studies, rHuEpo appeared to be very useful in overcoming graft-versus-host disease that occurred with allogeneic BMT. Treatment adds approximately $2,000 to the cost of managing these patients. After autologous BMT or peripheral blood progenitor cell transplantation, the use of rHuEpo is not recommended because it does not significantly enhance recovery of erythropoiesis.

Use of rHuEpo in the transplantation setting can be extended to the potentiation of autologous blood collection in the donor plus stimulation of erythroid recovery in the recipient; predeposited blood was to be later used by the donor or the recipient. Donors were phlebotomized a median of 6 U of blood over a 5-week period; 5 of 11 BMT recipients underwent transplantation, receiving only donor-derived RBC transfusions.

Induction of Fetal Hb Synthesis in Sickle Cell Anemia and Thalassemia

Inappropriately low levels of serum Epo for the degree of anemia have been described in sickle cell disease. Use of rHuEpo to simply increase Hct would lead to increased viscosity and worsen vaso-occlusion and sickling. A possible beneficial effect of rHuEpo could be to increase the cellular concentration of Hb F at the expenses of Hb S when used in combination with hydroxyurea or alone. Whereas one study reported no additional benefit from the addition of rHuEpo (maximum dosage of 1,500 IU/kg/wk, administered in 2 divided doses, 6 to 8 hours apart, IV) to a stable hydroxyurea regimen (9 to 23 mg/kg/d), a subsequent study using higher rHuEpo doses (maximum dosage 9,000 IU/kg/wk, administered in 3 daily IV doses of 3,000 U), lower hydroxyurea doses (20 to 25 mg/kg, 4 doses/wk) and oral iron sulfate supplements showed that rHuEpo enhanced Hb F production compared with hydroxyurea alone. Anemia may be particularly severe in individual patients with sickle cell disease and renal failure. Treatment with rHuEpo can increase Hb from extremely low to moderate levels, providing enhanced function without enhanced cell crises.

Because of the ineffective erythropoiesis and the large expansion of the erythroid tissue characteristic of β-thalassemia, use of rHuEpo in this setting has been attempted with the aim of increasing Hb F synthesis and/or reducing the unbalance between the α and β globin chain synthesis, which is responsible for the premature death of both immature and circulating RBCs. Thalassemic patients have adequate or

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**Table 4. Considerations for the Use of rHuEpo Outside the Setting of Uremia**

<table>
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<tr>
<th>Consideration</th>
<th>Notes</th>
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<tbody>
<tr>
<td>HIV-related anemia*</td>
<td>Approved in the United States for treatment of anemia induced by AZT therapy in HIV-infected patients with endogenous Epo levels less than 500 mU/mL.</td>
</tr>
<tr>
<td>Chemotherapy-induced anemia†</td>
<td>Approved in the United States for anemia induced by chemotherapy of nonmyeloid malignancies.</td>
</tr>
<tr>
<td>Perisurgical setting‡</td>
<td>Approved in the United States for reduction of allogeneic blood transfusion in surgery patients. Indication limited to anemic patients (Hb &gt; 10 and &lt;13 g/dL) undergoing elective surgery and patients at high risk for significant perioperative blood loss. Nonindicated for anemic patients willing to donate autologous blood or undergoing cardiac or vascular surgery.</td>
</tr>
<tr>
<td>Autologous blood collection§</td>
<td>Approved in some European countries.</td>
</tr>
<tr>
<td>Anemia of prematurity</td>
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<tr>
<td>Anemia of cancer</td>
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<tr>
<td>Anemia associated with MM</td>
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<tr>
<td>Anemia associated with non-Hodgkin lymphoma</td>
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<tr>
<td>Acceleration of erythroid repopulation after allogeneic BMT</td>
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<tr>
<td>Hypoprogenative anemia in patients undergoing organ transplantation and receiving cyclosporin A to avoid rejection</td>
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<tr>
<td>Adjuvant for phlebotomy</td>
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<td>Anemia of rheumatoid arthritis</td>
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<td>Anemia of inflammatory bowel disease</td>
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<td>MDS</td>
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<td>Pure RBC aplasia</td>
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<tr>
<td>Induction of Hb F synthesis in sickle cell anemia and thalassemia</td>
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<td>Orthostatic hypotension</td>
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Overall, 15% to 20% of patients with MDS respond to rHuEpo treatment, but the vast majority of responders are not transfusion-dependent and the doses required to achieve response are greater than 450 IU/kg/wk. Recognizing potential responders can be extremely important in individual cases. Refractory anemia (RA) is the class among the MDSs with reasonable response rates, and additional factors predicting response include serum Epo levels less than 100 mU/mL, female gender, and normal karyotype. Because the basic defect resides within the stem cell, the typical anemic MDS patient is expected to have a high serum Epo level, ie, appropriately increased endogenous Epo production. It is therefore unclear why some individuals show inappropriately low Epo levels.

The response rate to rHuEpo increases to approximately 40% when rHuEpo and granulocyte colony-stimulating factor (G-CSF) are used in combination in MDS patients. About one half of responding patients require both G-CSF and rHuEpo to maintain an effective response, suggesting that synergy between these hematopoietic factors exists in vivo for the production of RBCs in MDS.

Early reports suggest that rHuEpo is unlikely to be effective in myelofibrosis with myeloid metaplasia.
overexpressed serum Epo levels for their degree of anemia. Studies in small groups of patients indicate that rHuEpo increases Hb levels in thalassemia intermedia, with no or small changes in the percentage of Hb F. The use of rHuEpo in patients with severe thalassemia or sickle cell disease must be considered experimental. Practicing physicians might consider it in selected individuals who show defective endogenous Epo production.

**Miscellaneous Uses**

Patients undergoing organ transplantation are treated with cyclosporin A to avoid rejection. As previously discussed, this drug reduces Epo production and therefore may be responsible for the development of hyporegenerative anemia. rHuEpo was shown to correct anemia and abolish transfusion requirement in children undergoing cardiac transplantation. Patients with orthostatic hypotension caused by autonomic neuropathy frequently have a decreased RBC mass. Increasing the RBC volume with rHuEpo has been found to elevate blood pressure while standing, but this use has not proven to be beneficial.

**INDICATIONS FOR THE USE OF rHuEpo OUTSIDE THE SETTING OF UREMATIA AND THE ISSUE OF COST EFFECTIVENESS**

Indications for the use of rHuEpo in nonrenal patients are listed in Table 4. These indications span from the three currently approved by the FDA to uncontrolled studies in patients with extremely rare disorders. Variable portions of patients within each condition are likely to respond to rHuEpo, based on the extent of defective endogenous Epo production, iron stores, and bone marrow functional capacity. The response will also vary greatly depending on the rHuEpo route of administration, dosing intervals, and concomitant iron supplementation.

rHuEpo primarily offers an alternative to blood transfusion. Based on the current hospital costs of rHuEpo ($9 to $8 per 1,000 IU), only to the extent that a dose of 75 U rHuEpo per kilogram per week in a 70-kg patient is successful in eliminating 1 U of blood transfused per month, rHuEpo affects the cost of transfusions. This simple calculation does not account for any improvement in quality of life, income productivity, and/or survival. Based on the prevention of transfusion complications, a mean incremental effectiveness per unit of allogeneic blood saved equal to 0.0003 quality-adjusted year of life (QALY) can be assumed. A dose of 10 U of rHuEpo per kilogram per week in excess of the above-reported dose (75 U) would impose a cost of $77,000 per QALY.

As discussed before, the figure of $168 per RBC unit could be a gross underestimate of the cost of blood. Mohandas and Aledort have calculated an overall mean cost per transfusion episode equal to $1,696 in cancer patients. Assuming that 2 U of RBCs is transfused each time, rHuEpo would affect the cost of transfusions to the extent that a dose of 433 U rHuEpo per kilogram per week in a 70-kg patient is successful in eliminating 1 U of blood transfused per month. Clearly, this latter figure would make rHuEpo highly cost-effective. To solve this problem, we need reliable calculations of costs of both rHuEpo treatments and transfusions.

**A Patient-Oriented Approach to the Clinical Use of rHuEpo**

Based on the published clinical trials, an effect of rHuEpo therapy can be shown for selected indications outside the setting of uremia in a variable portion of patients. Cost-effectiveness cannot be demonstrated for the majority of these indications, at least using death and dollars as primary endpoints. Physicians can prescribe rHuEpo for nonapproved indications, but they should do so only for patients who are likely to benefit from its administration. Ideally, rHuEpo should be indicated for treatment of defective endogenous Epo production.

We favor a patient-oriented approach in which the physician carefully evaluates the individual patient’s symptoms,
USES OF RECOMBINANT ERYTHROPOIETIN

Fig 7. A patient-oriented approach to the clinical use of rHuEpo in anemic patients or individuals who are very likely to become anemic. The use of rHuEpo should be limited to patients with symptomatic anemia and those who are transfusion-dependent or candidates for blood transfusion. This approach does not apply to the anemia of prematurity (see the pertinent section). Treatment should be considered only after the nature of the anemia has been clearly established. Furthermore, before using rHuEpo, other concomitant, correctable causes of anemia such as iron deficiency or folate/vitamin B12 deficiency should be recognized and remedied. Treatment should be started only after an inadequate Epo production has been documented, with the exception of patients undergoing chemotherapy, who may still have adequate endogenous Epo production but are likely to develop a defective one. Several studies have shown that a cutoff for serum Epo of 100 mU/mL allows the best discrimination between responders and nonresponders.51,54,154,156 This threshold has a high predictive power for Hb values less than 10 g/dL. For higher Hb values, the use of a threshold of 0.9 for the O/P ratio should be preferred. For AIDS patients, the most useful serum Epo level for deciding treatment has been found to be 500 mU/mL. 132 Iron supplements should be routinely provided to prevent functional iron deficiency during the first 4 to 6 weeks, except in patients with iron overload and increased transferrin saturation. A safe preparation of IV iron is superior to oral iron. If iron saccharate is available, 100 mg should be administered by IV infusion three times weekly for 3 to 4 weeks. An impaired iron supply to the erythroid marrow will blunt the erythropoietic response to rHuEpo; “unresponsive” patients may become “responsive” after correction of the functional iron deficiency. Indicators of early response might allow clinicians to decide whether to continue or terminate rHuEpo therapy after 4 weeks. Changes in Hb concentration51,178 and reticulocyte count54 proved to be useful indicators for this purpose. These changes should be examined after 4 weeks of treatment in patients who do not receive concomitant chemotherapy and/or blood transfusion; for those who receive these concomitant treatments and are less likely to respond quickly, a second check after 8 weeks may be appropriate.

Fig 7. A patient-oriented approach to the clinical use of rHuEpo in anemic patients or individuals who are very likely to become anemic. The use of rHuEpo should be limited to patients with symptomatic anemia and those who are transfusion-dependent or candidates for blood transfusion. This approach does not apply to the anemia of prematurity (see the pertinent section). Treatment should be considered only after the nature of the anemia has been clearly established. Furthermore, before using rHuEpo, other concomitant, correctable causes of anemia such as iron deficiency or folate/vitamin B12 deficiency should be recognized and remedied. Treatment should be started only after an inadequate Epo production has been documented, with the exception of patients undergoing chemotherapy, who may still have adequate endogenous Epo production but are likely to develop a defective one. Several studies have shown that a cutoff for serum Epo of 100 mU/mL allows the best discrimination between responders and nonresponders.51,54,154,156 This threshold has a high predictive power for Hb values less than 10 g/dL. For higher Hb values, the use of a threshold of 0.9 for the O/P ratio should be preferred. For AIDS patients, the most useful serum Epo level for deciding treatment has been found to be 500 mU/mL. 132 Iron supplements should be routinely provided to prevent functional iron deficiency during the first 4 to 6 weeks, except in patients with iron overload and increased transferrin saturation. A safe preparation of IV iron is superior to oral iron. If iron saccharate is available, 100 mg should be administered by IV infusion three times weekly for 3 to 4 weeks. An impaired iron supply to the erythroid marrow will blunt the erythropoietic response to rHuEpo; “unresponsive” patients may become “responsive” after correction of the functional iron deficiency. Indicators of early response might allow clinicians to decide whether to continue or terminate rHuEpo therapy after 4 weeks. Changes in Hb concentration51,178 and reticulocyte count54 proved to be useful indicators for this purpose. These changes should be examined after 4 weeks of treatment in patients who do not receive concomitant chemotherapy and/or blood transfusion; for those who receive these concomitant treatments and are less likely to respond quickly, a second check after 8 weeks may be appropriate.

life style, and potential for response178 and follows the decision trees shown in Figs 6 and 7. Premature infants should not be included in the above-mentioned algorithms. In fact, the criteria for deciding the use of rHuEpo in this setting do not include the serum Epo level, which can be assumed as inadequate in all cases.
the patient is undergoing a platinum-based combination chemotherapy). Similar algorithms have already been shown to be useful in predicting response to rHuEpo. A patient-oriented approach to the use of rHuEpo entails administration only to patients who are very likely to respond and benefit from this treatment, thus reducing rHuEpo wastage. Although this approach also maximizes the potential cost-effectiveness of rHuEpo therapy, it needs to be refined and validated in further studies. Additional studies are also needed to identify reliable and early indicators/predictors of the erythropoietic response to rHuEpo therapy.

ACKNOWLEDGMENT

We thank Dr Giovanni Barosi (Policlinico S. Matteo, Pavia, Italy) for comments and suggestions.

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