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Review Article

A review on pharmacological use of recombinant human erythropoietin in renal and nonrenal anemia and other potential applications in clinical practice

G.K. Thilaka, S. Vijaya Kumar *

PG and Research Department of Botany and Microbiology, A.V.V.M. Sri Pushpam College (Autonomous), Poondi, Thanjavur 613503, Tamil Nadu, India

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ABSTRACT

The introduction of recombinant human erythropoietin (rHuEPO) has revolutionized the treatment of patients with anemia of chronic renal disease. Clinical studies have demonstrated that rHuEPO is also useful in various nonuremic conditions, including hematological and oncological disorders, prematurity, HIV infection, and perioperative therapies. Since the cloning and first clinical introduction of recombinant erythropoietin (epoetin) in the late 1980s, indications and usage of epoetin have expanded significantly. It is estimated that as many as one-third of patients with substantial anemia (hemoglobin less than 10.0 g/dl) resulting from chemotherapy for cancer are treated with epoetin. Research suggests there is considerable variation in epoetin usage in practice. This review highlights the applications of rHuEPO in clinical practice and also addresses the usage of recombinant erythropoietin in situations where benefit is substantiated by high-quality studies.

1. Introduction

Erythropoietin is an endogenous hormone produced in the kidney that regulates red blood cell production within the body. The human gene for erythropoietin was closed in the early 1980s,[1,2] and the recombinant form was developed shortly thereafter. Hematocrit and the concentration of hemoglobin in blood are normally maintained constant. About 1% of the red cell mass is renewed each day. Anemic people suffer from tissue hypoxia. Severe cases can require transfusion of red cells from blood donors. Transfusion therapy with allogenic blood components may cause immunologic reactions and infections. In addition, repeated red blood cell transfusions can lead to iron overload. Therefore, the availability of recombinant human erythropoietin (rHuEPO) as an antianemic drug has been an important medical progress.

Initial trails of the replacement therapy with rHuEPO to restore the hematocrit in patients with end-stage renal failure

* *Corresponding author*. Tel.: +91 9003311921.
E-mail address: svijaya_kumar2579@rediff.com (S.V. Kumar).
Abbreviations: rHuEPO, recombinant human erythropoietin.
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were reported 20 years ago,[3,4] which then lent a new impetus to studies of the pathophysiology and pharmacology of EPO.[5] As soon as rHuEPO was made available for human trial, a series of clinical studies were promptly conducted to assess its effectiveness in correcting anemia of chronic renal disease. The initial results demonstrated that rHuEPO could restore the packed cell volume, abrogate the necessity of regular blood transfusion in patients requiring dialysis, and improve the overall well-being.[3,4,6] This review provides an overview of pharmacologic use of recombinant erythropoietin in various nonuremic conditions and other potential applications of recombinant erythropoietin in clinical practice.

2. rHuEPO

2.1. *Production and biological characteristics*

The preparation of pure human urinary EPO enabled the identification of the amino acid sequence of a tryptic fragment of the protein and synthesis of EPO DNA probes for the isolation and cloning of the EPO gene. Mammalian cells transferred with the EPO gene linked to an expression vector ("recombinant DNA") produce rHuEPO in vitro. Chinese hamster ovary (CHO) cells deficient in the dihydrofolate reductase gene are most commonly used for the large-scale manufacture of the drug, because in such cells EPO gene amplification can be achieved by coselection in the methotrexate.[7–9] The extent of microhetergeneity of CHO cell expressed rHuEPO has been studied by mass spectroscopy and NMR spectroscopy.

Human urinary EPO and rHuEPO are identical with regard to their amino acid sequence, position of the α-disulfide bridges and 4 glycosylation sites, and their secondary structure. The peptide consists of 165 amino acids. The molecular mass of the glycoprotein entity is 30 kDa. The carbohydrate portion (40%) is essential for molecular stability and full in vivo biological activity. There are quantitative differences in glycosylation, which may also explain the fact that the specific in vivo biological activity of purified human urinary EPO is lower (70,000 IU/mg peptide) than that of the purified recombinant product (about 200,000 IU/mg peptide).

Two brands of CHO cell-derived EPOs, termed epoetin alfa and epoetin beta, are currently used for treatment of EPO-deficiency anemia and for support in autologous blood collection programs. Both of these types of rHuEPO are produced in CHO cultures and act on the same erythropoietin receptor, and there are some variations on the degree of glycosylation,[10] which lead to the differences in the pharmacokinetics and pharmacodynamics among the rHuEPOs.

As the N-glycosylation confers the biological activity of RHuEPO, an increase in the number of glycosylation sites may enhance its activity. A hyperglycosylated rHuEPO, known as NESP (Novel Erythropoiesis Stimulating Protein; Darbepoetin-alfa), has recently been introduced.[11]

Compared with the rHuEPOs, NESP has a higher negative charge and a threefold longer half-life and requires a less frequent dosing schedule and produces a similar clinical outcome and safety profile as rHuEPOs in treating anemia of chronic renal disease and of malignancy.[12–14]

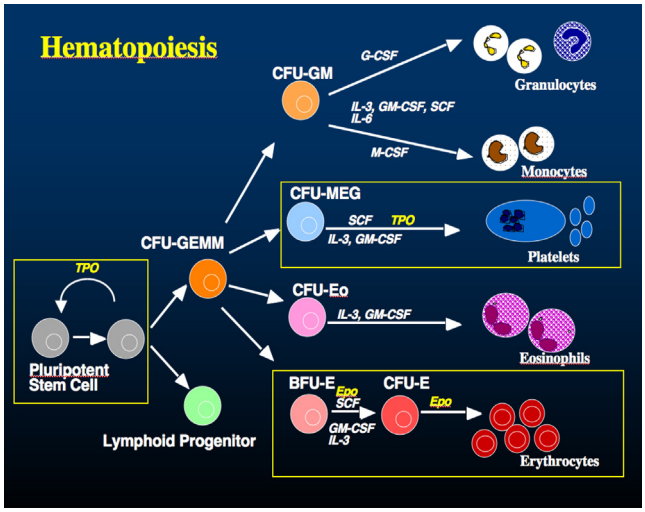

Fig. 1 – Hematopoiesis.

2.2. *Mechanism of action*

Erythropoietin is essential for the proliferation, differentiation, and maturation of RBCs in bone marrow (Fig. 1). Erythropoietin is critical for the survival of RBC progenitors in bone marrow and may also have immune modulatory activity.[15,16] Erythropoietin functions by binding to the erythropoietin receptor, which is a member of the superfamily of cytokine receptors.[17] The number of erythropoietin receptors varies during RBC differentiation, with its peak presentation at the colony-forming unit erythroid/proerythroblastic stage and the level being undetectable at the reticulocytes (Fig. 2). The binding of erythropoietin to its receptor results in homodimerization of the receptor, followed by activation of several signal transduction pathways: JAK2/STAT5 system, G-protein (RAS), calcium channel, and kinases.

rHuEPO has revolutionized the treatment of patients with anemia of chronic renal failure. Moreover, rHuEPO has been shown to be effective in connecting anemia associated with various nonuremic conditions (Table 1).

3. rHuEPO therapy in renal failure

rHuEPO as an antianemic drug for treatment of patients suffering from chronic renal failure was introduced 20 years ago.[3,4] Given intravenously or subcutaneously,[18] it is now routinely used in patients on regular hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as well as in many predialysis patients.[19,20] rHuEPO raises hematocrit and blood hemoglobin concentration in a dose-dependent and predictable way, and it abolishes the need for red cell transfusions with its risks of incompatibility reactions, viral infections, and iron overload. In previously anemic patients, rHuEPO therapy reverses the hyperdynamic cardiac state and restores the impaired brain function. The well-being and exercise tolerance of the patients are greatly increased (Table 2).

rHuEPO can correct the anemia in practically patients with renal failure, but the dose needed is variable (Table 3). The