Recombinant Human Erythropoietin:  
A Review of Pharmacology and Therapeutic Potential in Anemias

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Abstract: Epoetin alfa (EPO) is a biosynthetic form of the glycoprotein hormone. Erythropoietin has been shown to be highly effective in prevention of anemia, i.e anemia due to renal failure, anemia of AIDS and anemia of cancer with patients responding with increase in hematocrit, Hb levels and improvement in quality of life. Various clinical trials have shown to be effective in anemia of prematurity, treatment of postural hypotension in anemic type 1 diabetic patients with autonomic neuropathy, treatment of anemia in inflammatory bowel disease, the anemia of primary autonomic failure, hematopoietic stem cell disorders, and acceleration of erythroid repopulation after bone marrow transplantation (BMT). This review discusses pharmacological and therapeutic potential of recombinant human erythropoietin in anemias. 
Key words: Recombinant Human Erythropoietin, pharmacology, anemia
Eritropoetin Manusia Rekombinan:
Tinjauan Farmakologi dan Potensi Terapeutik pada Anemia

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Kata kunci: Eritropoetin Manusia Rekombinan, farmakologi, anemia.

Introduction

Erythropoietin is a naturally occurring hormone, produced by the kidneys, which stimulates the body to produce red blood cells. It is used to treat anemia, which can be a disease in its own right or a symptom of another disease, like kidney failure. It can be given to people with cancer who have anemia, either because of the disease or their chemotherapy treatment. It has also become more widely known as a drug used by athletes to increase their hemoglobin levels (blood-doping) and improve performance; but its use in sport is illegal and it can be detected by drug tests.1

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 1989.2 A synthetic form of Erythropoietin (EPO), human recombinant EPO, has been successfully used to treat anemia in patients with chronic renal failure and AIDS. EPO has also been used in anemia related to cancer.1

Erythropoietin Production

EPO is primarily synthesized by the kidney under the control of a single gene on human chromosome 7.1 Endogenous human erythropoietin, a growth factor, is a glycosylated protein hormone that appears to be secreted principally by renal peritubular interstitial cells outside the tubular basement membrane in the cortex and outer medulla of the kidney; however approximately 10% is produced in the liver and possibly at other extrarenal sites in adults. Fetal erythropoietin production occurs mainly in the liver. Secretion of the hormone occurs principally in response to reductions in arterial and/or venous oxygen tension and tissue oxygenation in the kidney.

With anemia or hypoxemia, renal synthesis of EPO rapidly increases 100-fold or more, serum EPO levels rise and marrow progenitor cell survival, proliferation and maturation are dramatically increased.1 Factors other than tissue hypoxia might also 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 chemotherapy3 and during vitamin B12 or iron replacement therapy.4

Chemistry

Epoetin alfa is a biosynthetic form of the glycoprotein hormone erythropoietin. The amino acid sequence and biologic properties of epoetin alfa are identical to those of endogenous human erythropoietin extracted from the urine of patients with aplastic anemia. The drug is prepared from cultures of genetically modified mammalian (Chinese hamster ovary) cells using recombinant DNA technology.1 The molecular weight of the functional, 165-amino acid erythropoietin protein (excluding carbohydrate moieties) is approximately 18,400 daltons. Epoetin alfa contains two internal disulfide bonds linking positions 7 and 161 and positions 29 and 33; these bonds are necessary for the hormone’s biologic activity.5
Pharmacology

Mechanism of Action

Erythropoietin induces the production of erythrocytes (i.e., stimulates erythropoiesis) principally by stimulating the proliferation and differentiation of committed erythroid precursors (i.e., burst-forming units-erythroid [BFU-E], colony-forming units-erythroid [CFU-E]). Other marrow precursors, including colony-forming units: CFU-megakaryocytic (CFU-MK), CFU-granulocytic-monocytic (CFU-GM), and pluripotent stem cells may also be increased with in vivo administration of erythropoietin. Stimulation of CFU-E and BFU-E appears to be direct, while stimulation of CFU-MK and CFU-GM may occur as indirect feedback responses.

Pharmacokinetics

Epoetin alfa cannot be given orally as it is destroyed in the GI tract because of its protein nature, and must be administered parenterally (i.e., via IV infusion, subcutaneous injection, intra peritoneal injection). Systemic absorption of epoetin alfa is delayed and incomplete following subcutaneous injection or intra peritoneal injection. However, while serum concentrations peak sooner and are substantially higher with IV than subcutaneous injection of epoetin alfa, they are less sustained, and the IV route of administration generally offers no clinical advantage over the subcutaneous route.

The distribution of epoetin alfa and the endogenous hormone in humans remains to be fully elucidated. Epoetin alfa appears to distribute into a single compartment with an apparent volume of distribution that approximates or slightly exceeds plasma volume (about 4–5% of body weight).

The elimination characteristics of epoetin alfa and endogenous erythropoietin in humans remain to be fully established. Subcutaneous administration of rHuEpo induces lower peak plasma EPO concentrations, with an elimination half-life of about 19 to 22 hours compared to the 4 to 5 hours of IV rHuEpo. Subcutaneous 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 subcutaneously.

Indications

Recombinant human erythropoietin can be effective in a number of anemias. EPO has been shown to be highly effective in prevention of anemia, i.e. anemia due to renal failure, anemia of AIDS and anemia of cancer. Various clinical trials have shown to be effective in anemia of prematurity, treatment of postural hypotension in anemic type 1 diabetic patients with autonomic neuropathy, treatment of anemia in inflammatory bowel disease, the anemia of primary autonomic patients with autonomic neuropathy, treatment of anemia in type 1 diabetic 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.

Prevention of Anemia

Patients facing surgery or cancer chemotherapy are at a risk of developing anemia. Some of these patients may benefit from the prophylactic use of rHuEpo. 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.

Anemia due to Renal Failure

Epoetin alfa has been used for the treatment of anemia associated with chronic renal failure. Clinical studies indicate that the drug increases and/or maintains hemoglobin concentrations and hematocrit and decreases the need for transfusions in dialysis-dependent patients with chronic renal failure as well as in those who do not yet require maintenance dialysis (predialysis patients). Therapy with epoetin alfa is also associated with subjective improvements in these patients, including a perceived general increase in feeling of well-being and quality of life. Many clinicians currently consider epoetin alfa as first-line therapy for anemia of chronic renal failure. Therapy with epoetin alfa may eliminate the need for maintenance red blood cell transfusions, though it should not be used as a substitute for emergency transfusion. The speed and level of response depends on the individual patient and the level of iron supply. Although iron absorption can increase several folds when rHuEpo is used, oral iron supplementation may be insufficient in matching iron demands by the rHuEpo-expanded erythroid marrow.

Anemia Caused by AIDS

Anemia is found in about two thirds of patients with acquired immunodeficiency syndrome (AIDS) and generally worsens during treatment with zidovudine. Dosages of rHuEpo of 100 to 300 IU/kg administered IV or SC three times a week induce increase in hematocrit and reduction of transfusion requirements in patients with baseline serum Epo levels less than 500 mU/mL. HIV-infected patients with endogenous pretreatment (pretransfusion) serum erythropoietin concentrations of up to 500 mU/mL who are receiving weekly cumulative zidovudine dosages of 4.2 g or less are more likely to respond to epoetin alfa therapy than patients with higher endogenous pretreatment erythropoietin concentrations (i.e., exceeding 500 mU/mL). During the initial eight weeks of therapy with epoetin alfa, the hematocrit should be monitored weekly and dosage of epoetin alfa adjusted accordingly.

Anemia of Cancer

Anemia is a frequent occurrence in patients with cancer and may be due to different causes. In untreated subjects, the most common type is anemia of chronic disease, which is...
Anemia of Prematurity

Prematurely born infants, who are otherwise healthy, undergo an exaggerated decrease in hemoglobin 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 1000 g. In infants weighing less than 1000 g or requiring artificial ventilation, the reduction in transfusion needs is less impressive, which may be due to poor Epo responsiveness or insufficient iron supplements. There is no benefit in using rHuEpo for infants weighing more than 1300 g, because they rarely require transfusion.

Treatment of Postural Hypotension in Patients with Autonomic Neuropathy

Postural hypotension is a feature of autonomic failure that may result from various causes and can be very difficult to treat. It has been shown that some patients with severe symptomatic autonomic neuropathy from type 1 diabetes have a normocytic anemia associated with erythropoietin (EPO) deficiency. The treatment of these patients with EPO rapidly corrects their anemia and improves their overall well-being.

Treatment of Anemia in Inflammatory Bowel Disease

Some patients with inflammatory bowel disease have anemia that is not responsive to iron administration and not due to folate or B12 deficiency. One hypothesis is that inflammatory cytokines decrease erythropoietin production and create resistance to the effect of erythropoietin, leading to a relative deficiency of this hormone. Studies have shown that rHuEpo treatment can increase Hb levels in patients with inflammatory bowel disease and anemia refractory to treatment with oral iron and vitamins.

The Anemia of Primary Autonomic Failure

The sympathetic nervous system stimulates erythropoiesis in humans because anemia is a frequent occurrence in patients with severe autonomic failure and is associated with a blunted erythropoietin response. This anemia has been shown to be improved with rHuEPO administration.

Anemia of Hematopoietic Stem Cell Disorders

Anemia is a major clinical problem in conditions such as aplastic anemia, sickle cell anemia, myelodysplastic syndromes (MDS), and idiopathic myelofibrosis. Many patients are adversely affected by transfusion-dependency and secondary hemochromatosis. 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. 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.

Acceleration of Erythroid Repopulation After Bone Marrow Transplantation (BMT)

Endogenous Epo production is frequently inadequate in recipients of allogenic 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.

Adverse Effect Profile

Hypertension

The most frequent adverse effect observed in patients receiving epoetin alfa for anemia of chronic renal failure is development or exacerbation of hypertension. The risk of hypertensive episodes appears to be low to nonexistent in patients with normal renal function compared with that in patients receiving the drug for anemia of chronic renal failure.

Hematologic Effects

Increased in partial or complete clotting at the site of vascular access has been observed in renal dialysis patients receiving epoetin alfa. Patients with chronic renal failure (both dialysis and predialysis patients) experience other types of thrombotic events like myocardial infarction, cerebrovascular accident, transient ischemic attacks.

Nervous System Effects

Seizures [tonic-clonic (grand mal)] have been reported occasionally in patients receiving epoetin alfa. Hypertensive encephalopathy also has been observed. Seizures also have been reported in HIV-infected patients receiving epoetin alfa for the treatment of anemia associated with zidovudine therapy; however, seizure activity in these patients appears to be related to underlying pathology (e.g., meningitis, cerebral neoplasm) or other concomitant drug therapy rather than to therapy with epoetin alfa.
Renal and Electrolyte Effects

Predisialysis increases in serum concentrations of potassium, blood urea nitrogen (BUN), creatinine, uric acid, and phosphate have been reported with erythropoietin therapy. Severe, recurrent hyperkalemia has been reported infrequently with epoetin alfa. An increase in calcium-phosphate product associated with joint pain, inflammation, swelling, and periarticular calcification has also been observed.\textsuperscript{18}

Flu-like Syndrome

A flu-like syndrome has been reported rarely in patients receiving epoetin alfa, principally with IV infusion of the drug, but also with subcutaneous administration. This flu-like syndrome is characterized by the development of transient diaphoresis, chills, shivering, malaise, feeling of cold or warmth, myalgia, bone pain and arthralgia of the limbs and pelvis, generalized aches and pains (including chest, back, and/or flank pain), fever, paresthesias, and/or abdominal pain/cramps. The reaction generally is self-limiting and does not require dosage modification or preclude continued administration of the drug.\textsuperscript{18}

Other Adverse Effects

Nausea, vomiting, diarrhea, edema, arthralgias, and fatigue have been reported in more than 5\% of chronic renal failure patients receiving epoetin alfa. Tachycardia, cramps, night sweats, visual disturbances, exacerbation of acne, skin rash and urticaria, petechial purpura, pruritus, transient local pain and/or stinging at the subcutaneous injection site, volume overload, shortness of breath, and conjunctival inflammation, redness, and/or injection have been reported infrequently.\textsuperscript{18} Aggravation of splenomegaly has been reported occasionally in patients receiving the drug for anemia of myeloproliferative disorders.\textsuperscript{16} Adverse effects reported with epoetin alfa in HIV-infected individuals include pyrexia, headache, cough, rash, respiratory congestion, nausea, vomiting, diarrhea, shortness of breath, hypertension, fatigue, peripheral neuropathy, joint pain, pruritus, seizures, myalgia, palpitation, and local reaction (e.g., burning, pain) at the site of injection.\textsuperscript{19} Adverse effects reported with epoetin alfa in cancer patients with chemotherapy-induced anemia include pyrexia, diarrhea, nausea, vomiting, edema, asthenia, paresthesia, fatigue, shortness of breath, upper respiratory infection, dizziness, and trunk pain.\textsuperscript{16}

Drug Interactions

Androgens

Androgens have been shown to increase the sensitivity of erythroid progenitors to endogenous erythropoietin and possibly stimulate residual endogenous erythropoietin secretion. these drugs have been used as an adjunct to epoetin alfa therapy in a few patients to decrease the total amount of epoetin alfa required for the amelioration of anemia.\textsuperscript{20}

Desmopressin

Concurrent therapy with epoetin alfa and desmopressin has resulted in an additive effect in reducing the bleeding time in a patient with end-stage renal disease who was receiving epoetin alfa for correction of uremia-induced increased bleeding time and epistaxis.\textsuperscript{21}

Probenecid

Probenecid has been shown to inhibit renal tubular secretion of endogenous erythropoietin in animals.\textsuperscript{22}

Precautions and Contraindications

The safety and efficacy of epoetin alfa have not been established in patients with a preexisting seizure disorder, and the drug should be used with caution in such patients.\textsuperscript{18} All patients receiving epoetin alfa should be observed closely for signs of declining neurologic status, especially during the first 3 months of therapy. Frequent, periodic monitoring of blood pressure (up to 3 times weekly) is indicated in all patients receiving epoetin alfa, including dialysis and nondialysis patients and cancer patients, since development of hypertension may be associated with the rate or extent of increase in hematocrit. Blood pressure monitoring is particularly important in patients with an underlying history of hypertension or cardiovascular disease.\textsuperscript{23} Therapy with epoetin alfa should be discontinued immediately and appropriate therapy initiated if an anaphylactoid reaction should occur.

Stimulation of oncogenic hematologic cell lines by epoetin alfa has not been documented to date; however, the drug, like other growth factors, should be used with caution in patients with a known neoplasm or leukemic disease.\textsuperscript{23} Renal function (as evaluated by measurement of BUN and serum creatinine concentration) and fluid and electrolyte balance (as determined by results of blood chemistry tests, especially serum potassium, phosphate, and uric acid) should be monitored in all chronic renal failure patients receiving epoetin alfa. This precaution may be particularly important in patients predisposed to hyperkalemia (e.g., chronic renal failure patients).\textsuperscript{24} Compliance with concurrent drug therapy (especially antihypertensive therapy), dietary restrictions, and dialysis schedules should be encouraged in chronic renal failure patients receiving epoetin alfa therapy.

Conditions that may diminish or block the effects of epoetin alfa include states of acute or chronic inflammation, infection, neoplastic disease or malignancy, underlying myelodysplastic disorders, marrow suppression from uremia, aluminum overload (possibly by interfering with iron bioavailability), hyperparathyroidism/osteitis fibrosa cystica, hypersplenism, acute or chronic blood loss, erythrocyte en-
zyme abnormalities (e.g., pyruvate kinase deficiency), and/or folic acid or vitamin B12 deficiency. It is especially important to consider the possibility of diminished response in patients with an acute or chronic infection or in those undergoing surgery, both states of acute inflammation.25

**Precautions in Pregnancy, Fertility, and Lactation**

Although there are no adequate and controlled studies to date in humans, epoetin alfa has been shown to be teratogenic in rats when given IV at 5 times the usual human dosage. Epoetin alfa should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. A decrease in body weight gain, delayed appearance of abdominal hair, delayed eyelid opening, delayed ossification, and a decrease in the number of caudal vertebrae in first-generation fetuses has been observed in animal experiments.26

**Precautions in Pediatric Patients**

Safety and efficacy of epoetin alfa in children have not been established. However, the drug has been used for the treatment of anemia (e.g., anemia of chronic renal failure, anemia of prematurity) in a limited number of children younger than 12 years of age. Results of studies in patients 2.5–18 years of age and in premature neonates suggest that the safety and efficacy of the hormone are similar to those in adults.27

**Precautions in Geriatric Patients**

While safety and efficacy of epoetin alfa have not been established specifically in geriatric patients, a large proportion of patients treated with the drug for anemia associated with chronic renal failure have been 65 years of age or older. Although no special precautions are necessary, however, careful monitoring of blood chemistry and blood pressure may be necessary.28

**Dosage recommendations**

**Prevention of Anemia**

When epoetin alfa is used preoperatively to reduce the need for allogeneic blood transfusions in anemic patients, who are scheduled to undergo elective noncardiac, nonvascular surgery with hemoglobin concentration between 10 to 13 g/dL, the recommended dosage is 300 units/kg given by subcutaneous injection once daily for 10 days prior to surgery, on the day of surgery, and for 4 days after surgery.29

**Anemia of Renal Failure**

A majority of dialysis dependent patients given a dose of erythropoietin of 50 to 150 U/kg three times a week by subcutaneous or intravenous injection show a gradual increase in their hemoglobin levels to 10 to 12 g/dL. The maintenance dose is usually 75 U/kg three times a week. Iron supplementation (200 mg of oral elemental iron daily, i.e., 900 mg of iron sulfate) should be administered routinely during the first 4 to 6 weeks of rHuEpo treatment to all patients except those with increased serum iron and transferrin saturation.30

**Anemia of Cancer**

It has been shown that rHuEpo at a dose of 100 to 150 IU/kg three times weekly corrects chemotherapy-induced anemia and reduces transfusion requirements.1

**Anemia of Prematurity**

The dosages of rHuEpo used for the treatment of anemia of prematurity have been in the range of 75 to 1,200 IU/kg/wk. 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) should be given along with rHuEpo.11

**Postural Hypotension in Autonomic Neuropathy**

Dose of recombinant human EPO for the treatment of postural hypotension in autonomic neuropathy is 25 IU/kg s.c. thrice weekly.12

**The Anemia of Primary Autonomic Failure**

Erythropoietin in low doses (25 to 50 units/kg body weight, subcutaneously, three times a week) has been used to treat anemia of primary autonomic failure.14

**Conclusion**

The use of rHuEPO has undoubtedly altered the traditional management of renal anemia. Its therapeutic benefit has been explored in other clinical areas also. Treatment with EPO is expensive and not every patient can benefit from it. One has to be very judicious in the use of erythropoietin. Iron supplementation is recommended as rHuEPO therapy accelerates erythropoesis causing a functional iron deficiency. In future new developments are likely, which optimize and maximize erythropoiesis, making the management of anemia more effective.

**References**


