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NOVEL DRUG DELIVERY AND DRUG TARGETING RECOMBINANT HUMAN ERYTHROPOETIN TO TREAT ANEMIA

Made Prita Artika*[1], Sirilus Deodatus Sawu[1], Ruliya Yunita Effendy[1], Aditya Nugaraha[1] and Dini Aprilia[1]

[1]Department of Clinical Pharmacy and Community, Faculty of Pharmacy Surabaya University, Surabaya, Indonesia.

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***Corresponding Author**
Made Prita Artika
Department of Clinical Pharmacy and Community, Faculty of Pharmacy Surabaya University, Surabaya, Indonesia.

ABSTRACT

Recombinant Human erythropoietin (RhEpo) has become an important discovery in the medical world related to biological products. The discovery of RhEpo is very helpful in handling anemia conditions that caused by CKD, cancer patients undergoing chemotherapy, HIV and patient who lose a lot of blood after surgery. Anemia condition make the body cannot produce normally endogenus erythropoietin. Erythropoietin helps in proliferation, differentiation and maturation so they can increase of normal red blood cells. The erythropoietin gene was isolated and produced known as Recombinant Erythropoietin. RhEpo has poor stability so the administration still uses the parenteral route to preventing aggregation and denaturation. Other developments still carried out to optimization the gene of human erythroid cells. This could be an apportunity for find targets, drug selection and use of gene therapy for several diseases related to another blood disorders. Knowledge regarding the use of RhEpo will be very helpful to optimization of therapeutic effects.

KEYWORDS: Erythropoetin, RhEpo, Anemia.

1. INTRODUCTION

Human recombinant erythropoietin (RhEpo) has become an important discovery in the medical world related to biological products. RhEpo's research began in 1905 by a professoe from Paris with his assistant. They managed to find a hemotropic factor called hemopoietin where hemopoietin plays a role in regulating the production of red blood cells. From this discovery then continued by subsequent studies that succeeded in finding a hemopoietic

substance called ‘erythropoietin gene was carried out by Lin et al and they succeeded in proving that this erythropoietin gene was instrument in coding the production of EPO from mammalian cells. The erythropoietin gene which wa isolated and produced was later known as Human recombinant erythropoietin (RhEpo).[1]

As discussed earlier, this erythropoietin gene works by encoding the EPO gene in the human body. EPO helps in the proliferation, differentiation and guarantee the survival of erythroid progenito cells so that they can increase and meet the needs of normal red bllod cells. Erythropoietin is produced from capillary epithelial cells around the kidney tubules nad by liver cells play a role in the production of red cells in the bone marrow. In the condition of endogenous eryhtropoietin from the body cannot produce normally then this RhEpo can be used to increase the production of red blood cells. As show in Figure 1, simply regulating EPo after meeting its receptor will activate homo-dimerazation and phosphorylation requiring the STAT/JAK system to be active and move towards the nucleus so as to fix it encoding genes and transcription of red blood cell precursor.[2,3]

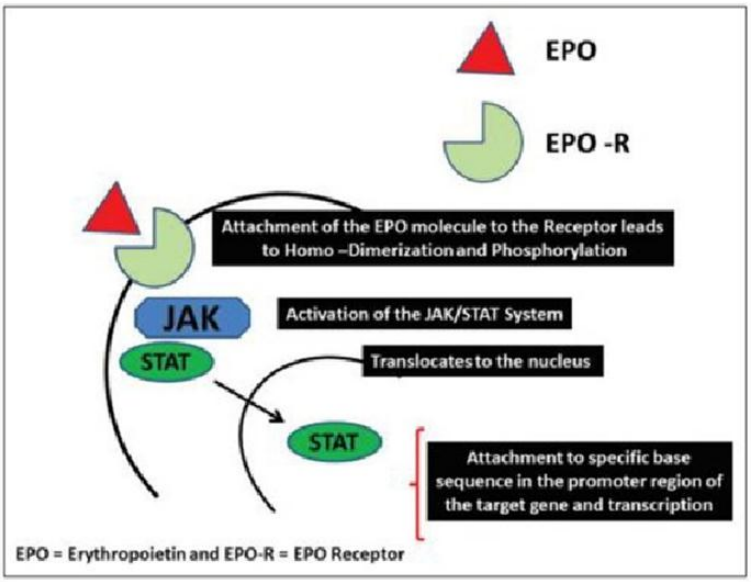

Figure 1. The mechanism of action of erythropoietin.

1.1 Prevalence

It is known that one of the complications that arise due to CKD is anemia and this occurs in about 25% of CKD patients and thus requires blood transfusion. With the discovery of Recombinant Human Erythropoietin (RhEpo) is very helpful in handling anemia conditions that are not only caused by CKD but some other conditions such as cancer patients udergoing chemotherapy, HIV and patients who lose a lot of blood after surgery.[4,5]

2. CHARACTERISTICS RHEPO

RhEpo is produced from Chinese hamster ovary (CHO) cells that have been genetically engineered to produce heterogeneous structures similar to the body's endogenous erythropoietin. Erythropoietin is a gycoprotein with a molecular weight of about 30,4 kDa. This erythropoietin molecule consists of 2 disulfide bonds to stabilize the amino acid polypeptide chain. Chanes in disulfide bonds wills caues a reduction in even loss of erythropoietin pharmacological activity (Figure 2). One of the disulfide bonds located between positions 7 and 161 has an important role related to the pharmacodynamics of erythropoietin, which is to maintain the structure of the molecular configuration to bind to the EPO-R receptor.[6,7]

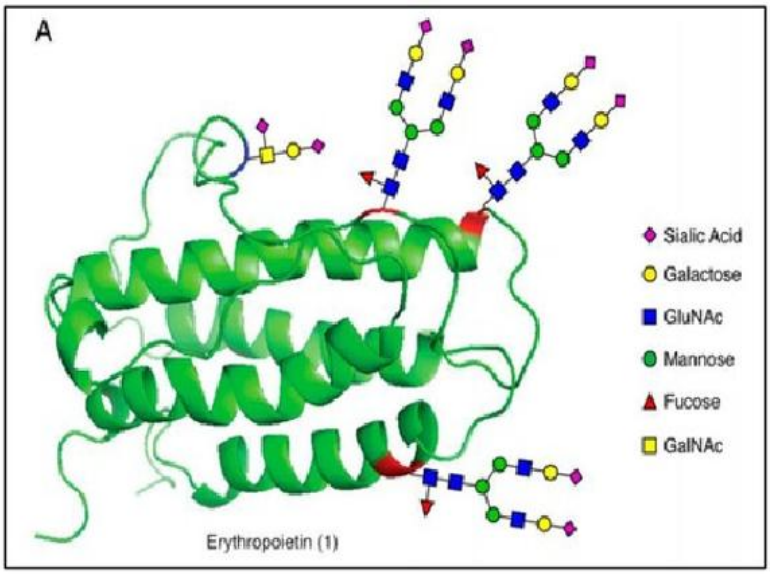

Figure 2. Erythropoietin structure.

Erythropoietin has poor stability in water, where erythropoietin will become easily degraded. It is also known that in storage using a syringe, erythropoietin absorbs into the syringe wall, causing aggregation and denaturation. This aggregation and denaturation can cause serius problems because they are irreversible and can cause hypersensitivity reactions.[8] One effort to prevent this problem is by using a syringe made from polypropylene which is known from the research results does not change the stability of the protein after repacking. In addition it can also by the addition of surfactants and amino acids which have a role as erythropoietin protectors. Due to the problem of stability in poor water is also finally made erythropoietin preparations in the form of dry powder or isotonic solution containing hydrochloric acid/citric acid for IV and SC administration.[4,8]

3. RECOMBINANT HUMAN ERYTHROPOIETIN (RHEPO)

3.1 EPO Formulations

At present many RhEpo preparations have been circulating in the market by using different formulations for each factory. From previous studies, RhEpo formulations typically contain erythropoietin as active ingredients, mannitol, glycine, leucine, arginine, glutamic acid, tween 20 and human serum albumin (HSA). One of the RhEpo formulations which contains the active ingredient alpha epoietin has the following formulation[9]:

rHuEPO	2000IU
Polysorbate 80	0.15 mg
NaCl	2.192 mg
NaH2PO4.2H2O	0.580 mg
Na2HPO4.2H2O	1.115 mg
Glycine	2.50 mg

Water fro injection to complete 0.5 ml

3.2 Delivery System

RhEpo administration until now still uses the parenteral route. The study of alternative assistance through other channels is still in furteher reseach related to the risk of erythropoietin. RhEpo can be given via intravenous and subcutaneous route injection 2-3 times a coversation tailored to the patient. It can be argued that IV and SC assistance is preferable also because of the need for rapid pharmacological action to meet the needs of red blood cells in the body which reduce the increased deficiency of erythropoietin producton.[10]

3.3 Stage of Drug Development

The development of RhEpo is of concern to many reseacher today, namely finding alternative routes other than by parenteral administration, namely through the oral route. Of course thus us a big challenge where erythropoietin has poor biovailability, the size of macromolecular proteins is also a challenge which is certainly not easy because with a large size it will be difficult to penetrate the intestinal epithelial layer and enter the blood vessels. The polymer nanocarrier approach is an attempt to overcome this compression through the use of polymeric materials it is expected to modulate the release of erythropoietin and encrease its absorption in the gastrointestinal tract.[11]

Other development are also known to have carried out ex vivo optimization efforts to see the gene/protein profile of human erythroid cells. This could be an opportunity for the health

world to find targets, drug selection and use of gene therapy for several disease related to other blood disorders such as thalassemia or crescent anemia.[12]

3.4 Pharmacokinetics

The rapid administration of RhEpo intravenously will experience elimination in normal patients due to the very rapid distribution phase by following the rate of first-order kinetics. In general, RhEpo bioavailability through the intravenous route is 100% with an elimination half-life in the blood circulation of abaout 4-11 hours. Distribution volume is 40-90 mL/kg with total clearance of 4-15 mL/hour per kg to reach peak concentration in the blood, intravenous administration is faster than subcutaneous administration. Bioavaibility in subcutaneous administration ranged from 36-39% with the time reaching peak concentrations in the blood aroun 12-18 hours and elimination half-life around 12-18 hours and elimination half-life around 24-79 hours. Erythropoietin is dergaded by reticuloendothelial scavenging pathways or lymphatic systems.[13]

Some preparations of RhEpo that are currently available for use include erythropoietin alpha, erythropoietin and darbepoetin alpha. The differences in these preparations can be seen in Table 1.[2]

3.5 Pharmacodynamics

Erythropoietin receptors are protein belonging to the superfamily cytokine reseptor. Erythropoietin binding to the erythropoietin receptor triggers homodimerization and phosphorylation which then cause the activation of several signal transduction pathways such as the JAK2/STAT5 system, G-protein (RAS), calcium channels, and kinases with the activation of the JAK/STAT system STAT translocation occurs into the nucleus and attaches to the target gene promoter and transcription. Erythropoietin has important activities in poliferation, differentiation, and maturation of RBCs in bone marrow.[2,14]

3.6 Administration

In clinical use, RhEpo is a mainstay for kidney failure patient with dialysis and not dialysis, cancer patient receiving cytostatic drugs such as nonmyeloid malignancy, low-risk myelodysplastic syndrome (MDS) and acquired immune deficiency syndrome (AIDS and Zidovudine effects).[12] However, side effects are substantial, including hypertention, thromboembolism, stroke, and the potential worsening of certain cancers. A single dose over at least 1 minute IV or SC. RhEpo store in carton with cool temparure of 2^{o}-8^{o}C, not in the

freezer and must be protected by light. RhEpo is more cost-effectiveness and produces an additional cost per QALY around US $18.800.[13,15]

Table 1: Comparison of varius types of erythropoietin.

Parameter	EPO-alpha	EPO-beta	Darbepoetin alpha	CERA
MW (Daltons)	30.000	30.000	37.000	60.000
Polyethylene glycol conjugation	Absent	Absent	Absent	Present
Glycosylation sites	3	3	5	-
Routes of administration	SC, IV, IP	SC, IV, IP	SC, IV	SC, IV
Half-life (SC admn;hours)	19	20	73	139
Bioavailability after SC administration	20	23-42	37	62
Dose	50-150 IU/kg	20-80 IU/kg	0.45 mcg/kg	0.6-1.2 mcg/kg
Dosing schedule	1-3 times/week	1-3 times/week	Once a week or once in 2 weeks	Once in 2 weeks to once a month

*SD: Standart Deviation with three replication of treatment

4. CONCLUSION

The use of RhEpo in the treatment of anemia bocomes very important especially in conditions where the production of red blood cells does not occur normally. The clinician's knowledge regarding the use of RhEpo will be vary helpful in achieving optimal therapeutic effects.

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