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The Cardiovascular Protective Effects of Erythropoietin Stimulating Agents

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EDITORIAL

Erythropoietin (EPO) is a member of the class I family of cytokines with a strong ability to stimulate erythropoiesis. The endogenous EPO is mainly synthesized and secreted by the kidney, and the recombinant EPO is utilized in patients suffering from different kinds of anemia [1-3]. EPO influences erythropoiesis by binding to its specific receptor which is expressed on the surface of immature erythroblasts [4]. However, several studies have demonstrated that EPO and EPO receptors are not only expressed in erythroblasts but also in a number of cell types including those within the cardiovascular and nervous system, suggesting that the effects of EPO extend beyond regulation of erythropoiesis. There are different kinds of EPO, namely, epoetin alfa, epoetin beta, and epoetin gamma, which are analogues of recombinant human EPO (rhEPO) derived from a cloned human erythropoietin gene. All of them have the same 165 amino acid sequence with a molecular weight of 30,400 daltons and have the same pharmacological actions as native EPO [1]. The normal serum concentrations of EPO for individuals with normal hematocrit range from 4-27 mU/mL. However, in certain conditions of anemia and hypoxia, EPO levels can be increased 100-1000 times the normal serum EPO concentration [1]. Moreover, the subcutaneous administration of a single 600 U/kg dose of epoetin alfa to healthy volunteers produced a peak serum concentration of over 1000 mU/mL after 24 hours [5].

A second generation drug, namely, darbepoetin has a threefold longer circulating half-life than rhEPO. It was shown that darbepoetin alfa is 3.6-fold more potent than rhEPO in increasing the hematocrit when each is administered thrice weekly, but when the administration frequency is reduced to once weekly, darbepoetin alfa is approximately 13-fold higher in vivo potency than rhEPO [6, 7]. A third-generation EPO-related molecule called continuous EPO receptor activator (CERA) has been manufactured. The elimination half-life of CERA in humans is considerably increased to about 130 hours maintaining a stable control of hemoglobin levels with a monthly interval dose [8-10]. The tissue protective effects of EPO, beyond the hematopoietic system, is mediated by activation of homodimeric EPO receptor, but is also believed to be mediated by its actions on the heterotrimeric complex consisting of EPO receptor and the β-common receptor [8]. Nitric oxide (NO) is a potent vasodilator formed in endothelial cells, and plays a key role in control of the cardiovascular system. It was shown that EPO can exert non-erythropoietic effects in vascular endothelium and is increasingly regarded as a potent tissue protective cytokine. Several studies demonstrated that EPO decreases tissue damage by inhibition of apoptosis and reduction of inflammatory cytokines [11-14]. In-vitro treatment with low dose of rhEPO increased endothelial nitric oxide synthase (eNOS) protein expression in cultured endothelial cells [15-17]. On the other hand, incubation of human coronary artery endothelial cells with high dose of rhEPO for 24 hours inhibited eNOS expression and NO production suggesting that high dose of EPO may have detrimental effects on endothelial function [18, 19].

EPO has a vast variety of cardiovascular effects. It exerts its effects on cardiac as well as the vascular tissues since EPO receptors are expressed in cardiomyocytes, vascular endothelial cells and smooth muscle cells [20-22]. The clinical dosage required to observe EPO-induced tissue protection is much higher than that required for hematopoietic effects [20-22]. There is robust experimental evidence of beneficial effects with the use of EPO in the cardiovascular system. However, all the plausible mechanisms should be tested in clinical situations to properly evaluate clinical outcomes. There are some adverse events data described in clinical trials in patients with heart failure,

kidney disease, myocardial infarction, and stroke [23-26]. The adverse side effects associated with EPO therapy were due to its pleiotropic effects mainly in the cardiovascular system including hypertension, thrombosis and augmented tumor angiogenesis [27-29]. Single-center studies have shown that EPO therapy of anemia in patients with heart failure was associated with improvement in exercise capacity, improved cardiac and renal function and reduced use of diuretics [30, 31]. Other trials evaluated the safety and efficacy of darbepoetin alfa at a dosage of 0.75μg/kg once every 2 weeks in symptomatic heart failure patients [32, 33]. It was demonstrated that the incidence of adverse events in these trials was similar between placebo- and darbepoetin alfa-treated patients [34]. However, the significant increase in hemoglobin shown with darbepoetin alfa therapy correlated well with improved health-related quality of life. The results from pre-clinical studies attribute multiple mechanisms of protection by EPO against myocardial disorders besides anemia treatment. Treatment with EPO may decrease apoptosis of myocytes, induce neovascularization by promoting myocardial angiogenesis increasing collateral vessels, reduce collagen deposition in ischemic myocardium, as well as, improve left ventricular function. However, large clinical trials did not demonstrate those benefits [23, 24]. Similarly, trials in patients with anemia and heart failure did not demonstrate improved clinical outcomes and raise concerns about increased complications [25, 26]. It is highly possible that EPO may have failed in these clinical trials because of the employment of insufficient dose. Preclinical studies have frequently used doses in the range of 1,000 to 5,000 IU/kg, while just a dose of 300 IU/kg were utilized in many large clinical trials. Although this lower dose is adequate for the EPO receptors in the erythroblasts, the EPO receptors found on multiple cell types responsible for cardiovascular protection are different [27-29]. However, the explanation may not be that simple. There is a complex interplay between vascular abnormalities and inflammatory mediators. There are several different cell types involved, and, within each individual cell, there are complex interactions among multiple signaling pathways. On the other hand, the use of higher doses of EPO in those large clinical trials might have had developed adverse effects such as thrombosis and hypertension.

In conclusion, experimental and clinical studies have demonstrated that EPO does not only affect the hematopoietic system, but also plays important role in control of the cardiovascular system. EPO has been shown to produce cardiovascular protection by exerting its effects on the endothelial cells and vascular smooth muscle cells. Tissue protective effects of EPO on the vasculature are mediated by decreasing apoptosis of myocytes, by inducing neovascularization, by promoting myocardial angiogenesis increasing collateral vessels, by reducing collagen deposition in ischemic myocardium, and by stimulating endothelial nitric oxide production and vasodilatation. However, these beneficial effects were not demonstrated in large clinical trials, a fact that makes clear the need for insights in this yet developing field. In order to effectively utilize EPO for cardiovascular protection in diseased patients, it will be required a better understanding of the ideal dosage to maximize effectiveness and minimize adverse effects of novel manufactured variations of EPO stimulating agents. There is a necessity of increasing our knowledge of the relevant processes that occur at the cellular level, and to individualize patients for relevant factors that may affect clinical outcome.

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