Introduction

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Current and Potential Applications for Erythropoietin

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Abstract

Erythropoietin (EPO) adjusts the red cell mass to the optimal size in order to satisfy the oxygen requirement of the body. The amount of circulating EPO is regulated by oxygen sensors in the kidney, which control the secretion of EPO through feedback signals. EPO stimulates the erythroid progenitor cells at different levels to develop into mature red blood cells. In anaemia, the serum EPO concentration, which is normally around 15 U/l, can increase 100-fold, or more. Patients with severe renal failure are unable to adapt the production of EPO in response to low haematocrit levels, and anaemia is due to a relative EPO deficiency. Studies have shown that recombinant human erythropoietin (r-HuEPO) could quickly correct anaemia in chronic renal failure by inducing a dose-dependent rise in haemoglobin and in the haematocrit level. r-HuEPO is now the standard treatment to correct severe anaemia in chronic renal failure. In recent years, r-HuEPO has been tested in other types of anaemia, some of which are fully discussed in this supplement together with various dosage regimens and routes of administration.

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The function of erythropoietin (EPO) is to adjust the red cell mass to the optimal size in order to satisfy the oxygen requirement of the body. The amount of circulating EPO is regulated by oxygen sensors in the kidney through feedback signals. EPO, which was thought to be produced in the proximal renal tubules, is now thought to be produced, at least in part or even exclusively, by the interstitial cells of the kidney, although this remains an area of controversy. EPO stimulates the erythroid progenitor cells at different levels to develop into mature erythrocytes, and late precursors of erythropoiesis are more sensitive to EPO than early precursors. For example, stimulation of early burst-forming unit-erythroid cells (BUF-E) requires 10 times the concentration of EPO required to stimulate late colony-forming unit-erythroid cells (CFU-E). In addition to its effects in erythropoiesis, EPO could also have some effects on megakaryopoiesis. It is well known that some patients with iron deficiency not only develop anaemia but also thrombocytopenia, and recombinant human erythropoietin (r-HuEPO) may have some potential in the therapy of hyperproliferative

thrombocytopenia. Some dialysis-dependent patients, when treated with r-HuEPO, show not only an increase in haemoglobin concentrations but also in platelet count.

In anaemia the serum EPO concentration, which is normally around 15 U/l, can increase 100-fold, or even more. Patients with polycythaemia vera typically have very low serum EPO concentrations. Patients with severe renal failure are unable to adapt the production of EPO in response to low haematocrit levels, and anaemia is due to a relative EPO deficiency. In 1986,

Winearls et al. [1] showed that r-HuEPO was able to quickly correct anaemia in chronic renal failure patients. In the majority of patients treated with r-HuEPO, clinical response is achieved during the first 4-6 weeks and is independent of red blood cell transfusions. After the study by Winearls et al. [1], Eschbach et al. [2] showed a dose-dependent rise in haemoglobin and haematocrit levels in the same setting and, since then, r-HuEPO has become the standard treatment to correct severe anaemia in chronic renal failure. During initial r-HuEPO therapy, the rate of rise of haematocrit levels appears to be dose-dependent. After attainment of the target haemoglobin/haematocrit, the r-HuEPO dose can be continually reduced while still maintaining a normal haemoglobin concentration.

Over the last few years r-HuEPO has been tested in other types of anaemia. It has been shown that r-HuEPO can correct the anaemia induced by azidothymidine (or zidovudine) therapy in HIV-infected patients, and it therefore allows continued treatment of AIDS patients despite the high toxicity of azidothymidine.

It is possible that in premature babies and patients with multiple myeloma who are anaemic because of low EPO production, intravenous or subcutaneous r-HuEPO may correct the anaemia and reduce the frequency of red blood cell transfusions. Other possible indications for r-HuEPO include its use before surgery to avoid the risks of transfusions and in cancer patients with chemotherapy-induced anaemia or with aplastic and dysplastic diseases of the bone marrow. However, the optimal dosage regimen and route of administration for r-HuEPO remain to be determined, as well as the minimal dose required to obtain meaningful effects in patients with neoplastic diseases.

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