

I Background and basic science

Summary

Lyonel G. Israels and Esther D. Israels

Erythropoiesis: an overview

This general discussion of erythropoiesis and description of some of the clinical manifestations associated with deregulation of the process are designed as an introduction to the subject. Red blood cell production is dynamic and highly regulated. The process starts with hematopoietic stem cells. Erythropoietin (EPO) is a glycoprotein humoral regulator of erythropoiesis. Binding of EPO to its receptor (EPOR) initiates a cascade of events leading to tyrosine kinase activation and transcription.

Key Words: Angiotensin II, apoptosis, BFU-E, CFU-E, EPO receptor, GATA-1, HIF-1, hypoxia, polycythemia, pure red cell aplasia, stem cell factor, transferrin, von Hippel-Lindau.

Summary

MaryAnn Foote

Studies of erythropoiesis and the discovery and cloning of recombinant human erythropoietin

The existence of erythropoietin (EPO) was postulated in the early 1800s, based on red blood cell mass studies. A series of elegant studies finally lead to its discovery, cloning and expression, and the commercial production of the recombinant human form (rHuEPO) approximately 180 years later. The availability of a steady supply of rHuEPO to augment the endogenous hormone has enabled physicians to ameliorate the anemia of kidney disease, chronic disease, and chemotherapy. Patients report that the quality of their lives is improved with rHuEPO therapy. This chapter traces the early work in erythropoiesis and the discovery and cloning of the *EPO* gene.

Key Words: Anemia, fatigue, hormone, kidney, medical history.

Summary

Timothy Osslund

Structural basis for the signal transduction of erythropoietin

The structures of recombinant human erythropoietin (rHuEPO) and its receptor (EPOR) have been studied and modeled using X-ray crystallography and other techniques. Dimerization of the extracellular portion of EPOR initiates signal transduction that culminates in production of erythroid colony-forming cells (CFU-E).

Key Words: Conformational changes, darbepoetin alfa, dimerization, epitopes, nuclear magnetic resonance, oligomerization, signal transduction, x-ray crystallography.

Summary

Christof Dame

Molecular biology of the erythropoietin receptor in hematopoietic and non-hematopoietic tissues

This article summarizes the current data on the molecular and cellular biology of the erythropoietin receptor (EPOR). EPOR deficiency terminates definitive erythropoiesis at the stage of erythroid colony-forming units. By binding to its receptor, EPO stimulates the proliferation of various hematopoietic cell types, increases the release of mature red blood cells from the bone marrow, and suppresses apoptosis. The expression level of EPOR regulates erythropoiesis by controlling the sensitivity of hematopoietic cells to EPO. Transcription of the EPOR gene in hematopoietic cells is controlled by GATA-1, Sp1, and helix-loop-helix proteins. Mutations in the cytoplasmic domain of the EPOR can cause erythrocytosis. EPOR is also expressed in various non-hematopoietic organs in a developmental-stage and tissues-specific manner. EPOR deficiency has the most significant effects on the normal development of the heart and the brain. Anti-apoptotic, proliferative, differentiative, and angiogenic effects of EPO in non-hematopoietic organs are mediated by functional EPOR. These data result in new concepts using recombinant EPO in acute or chronic neurological, retinal, or gastrointestinal disorders.

Key Words: Angiogenesis, apoptosis, central nervous system, development, erythrocytosis, erythropoietin, erythropoietin receptor, gastrointestinal tract, GATA-1, gene regulation, heart, neuron, retina, uterus.

Summary

Saghi Ghaffari, Lily Jun-shen Huang, Jing Zhang, and Harvey F. Lodish

Erythropoietin receptor signaling processes

Activation of erythropoietin receptor (EPOR) by erythropoietin (EPO) is essential for the survival, proliferation, and differentiation of red blood cells. EPOR is expressed in many organs including brain, heart, endothelium, and ovaries and may have physiological roles in these organs. Although studies are underway to establish the role of EPOR signaling in various organs, it is becoming increasingly apparent that red cells are not the only targets of EPO.

Many signaling pathways are activated in response to EPO stimulation of erythroid cells. Activation of STAT5 is required for erythroid survival. Specific roles of other EPOR-activated signaling pathways in erythroid development are being studied, as well as the nature and the role of signaling pathways activated in response to EPO in non-erythroid cells.

Key Words: AKT, friend virus-induced erythroleukemia, dimerization, JAK2 signaling, knock-out models, PI3-kinase, phosphorylation, R129C, SOCS, STAT5.

Summary

Anne C. Heatherington

Clinical pharmacokinetic properties of rHuEPO: a review

The pharmacokinetic properties of recombinant human erythropoietin (rHuEPO) are one of the major factors that determine dosing regimens and mode of administration. This literature review focuses on the clinical studies that have determined the pharmacokinetic properties of

rHuEPO in various populations, including healthy volunteers and nephrology and oncology patients. For each population, dose-linearity and time-dependence are considered for both the intravenous and subcutaneous routes. Other issues, such as mode of dialysis, intraperitoneal dosing, site of injection, and type of rHuEPO, as well as the challenges in determining and comparing the pharmacokinetic properties are discussed. Clearance mechanisms and the role of organs such as kidney, liver, and bone marrow are reviewed.

Key Words: Dialysis, dosing regimens, literature review, mode of administration, nephrology patients, oncology patients, route of administration.

Summary

Graham Molineux

Biology of erythropoietin

Recombinant human erythropoietin (rHuEPO) has been in use since the late 1980s to treat the anemia associated with degeneration of the kidney. The effects of treatment with rHuEPO in this population are wide ranging, suggesting effects beyond mere replacement of the missing endogenous erythropoietin (EPO). Other anemias in oncology patients either in association with chemotherapy/radiotherapy treatment or indeed with only the cancer itself have also proven responsive to rHuEPO therapy. Different complications exist in the various diseases treated with rHuEPO, which in many cases have led to widely different usage patterns.

rHuEPO also has been shown to have numerous effects besides erythropoiesis and many of these non-anemic settings, such as use in stroke, neural injury, pre-adaptation to altitude, for example, are ripe for development of novel clinical approaches.

Keywords: Anemia, neural injury, oncology, receptor, response rates, stroke, therapy.

Summary

Alice S. Chuck, Rohini R. Deshpande, Adrian R. Distler, Shane A. Sander and James E. Seely

Commercial production of recombinant erythropoietins

Recombinant human erythropoietin (rHuEPO) can be produced using cells genetically engineered to secrete the protein. Production entails a series of steps, including cell-line development, cell bank formation, cell-culture processes, and recovery and purification of rHuEPO.

Key Words: Cell bank formation, cell culture processes, cell line development, purification, recovery.

II Clinical use of recombinant erythropoietins

Summary

Iain C. Macdougall

Use of recombinant erythropoietins in the setting of renal disease

Recombinant human erythropoietin (rHuEPO) has changed the way in which patients with renal disease are treated and has substantially improved their lives. rHuEPO is effective in the renal disease setting because it directly increases the amount of circulating hormone, the primary cause of anemia in patients with renal disease. While increase in red blood cells, hematocrit, and hemoglobin are the primary effects of rHuEPO therapy, other secondary benefits are found with the drug. These benefits include cardiovascular improvement, better quality of life, increased cognitive function, and increased sexual function. The side effects of rHuEPO therapy are minimal, and hematology parameters, for example neutrophil and platelet functions, are not adversely affected and may be beneficially enhanced. Recently, the rare disease of pure red cell aplasia has been found in some patients with kidney disease receiving rHuEPO, but the etiology is not understood.

Key Words: Cardiovascular function, coagulation factors, exercise capacity, gene therapy, hematocrit, hemoglobin, platelet function, pure red cell aplasia, quality of life, sexual function, vitamins.

Summary

John Glaspy

Erythropoietic therapy in the practice of oncology

Anemia is a common complication of cancer and is considered to be the anemia of chronic disease (ACD). Other causes of anemia in patients with cancer include myelosuppressive chemotherapy and radiation therapy, tumor infiltration, bleeding, and hemolysis. The use of recombinant human erythropoietin (rHuEPO) has allowed physicians to treat this anemia without red blood cell transfusions and has challenged long-held beliefs concerning the impact of anemia on the quality of life of patients with cancer.

Key Words: Anemia of chronic disease, darbepoetin alfa, phase III clinical studies, red blood cell transfusions.

Summary

Robert T. Means, Jr.

Use of recombinant erythropoietins for the treatment of anemia of chronic disease

The anemia of chronic disease (ACD) is one of the most common syndromes in clinical medicine. ACD is defined as a hypoproliferative anemia with a low serum or plasma iron concentration despite adequate reticuloendothelial iron stores. Typically, ACD occurs in patients with chronic infectious, inflammatory, or neoplastic diseases, although 40% of cases occur in patients without these diagnoses. It is generally accepted that ACD is a consequence of activation of the cytokines mediating the immune and inflammatory response, such as tumor necrosis factor (TNF), interleukin (IL)-1, and the interferons (IFN). The pathogenesis of ACD is characterized by both a blunting of the erythropoietin (EPO) response to anemia,

and a relative resistance to EPO. Although most patients with ACD have only a moderate degree of anemia, approximately 25% of patients are sufficiently anemic to potentially require transfusion. Clinical studies have demonstrated the efficacy of recombinant human erythropoietins (rHuEPO) in the management of ACD, and have established a role for iron therapy as an adjunct to rHuEPO in this syndrome.

Key Words: Cytokines, hypoproliferative anemia, immune and inflammatory responses, interferon, interleukin, iron concentrations.

Summary

Fred D. Cushner

Use of erythropoietins in the surgical setting

Blood loss is inherent to the surgical setting. Despite meticulous surgical technique, blood loss still occurs, resulting in decreased hemoglobin concentrations and hematocrit levels, as well as a significant allogeneic transfusion rate. Using the orthopedic surgery model, this chapter focuses on the use of recombinant human erythropoietin (rHuEPO) to not only decrease allogeneic transfusions but also to maximize blood parameters, such as hematocrit and hemoglobin concentration, during the peri-operative period.

Key Words: allogeneic transfusions, blood, hematocrit, hemoglobin, orthopedic surgery, PAD, predonated autologous blood, rHuEPO.

Summary

Don H. Catlin, Caroline K. Hatton, and Françoise Lasne

Abuse of recombinant erythropoietins by athletes

Athletes have practiced doping, or the use of substances to increase athletic endurance and achievement, for centuries. In the past few decades, however, financial gains for elite athletes have exacerbated the problem. Elite endurance athletes in sport such as cross-country skiing, cycling, and track and field, closely follow medical research and have illegally used products and procedures developed for patients with anemia. The use of recombinant human erythropoiesis-stimulating proteins is a great concern. Several tests have been developed for detection of these proteins.

Key Words: Blood transfusion, erythropoietin, detection, doping, darbepoetin alfa, epoetin alfa, epoetin beta, exercise, isoelectric focusing, sports medicine, urine.

Summary

Patrick Mayeux and Nicole Casadevall

Antibodies to endogenous and recombinant erythropoietin

Recombinant human erythropoietin (rHuEPO) has been used for more than 12 years for the treatment of anemia associated with various diseases. During this time, thousands of patients have been successively treated with rHuEPO and at least up to 1998, this treatment has induced only a very few number of cases of neutralizing antibodies leading to pure red cell aplasia (PRCA). Moreover, auto-antibodies to erythropoietin (EPO) are rare in people who have never been treated with rHuEPO. From these observations, it is generally believed that

EPO is weakly immunogenic, although some results suggest that EPO immunogenicity could have been underestimated. The situation has suddenly changed from 1998, with a dramatic increase of pure red cell aplasia cases due to anti-EPO antibodies reported in patients treated with rHuEPO for anemia due to chronic renal failure. This article reviews the methods for anti-EPO detection and measurement, the characteristics of anti-EPO antibodies and the possible causes responsible for the sudden appearance of such antibodies.

Key Words: Chronic renal failure, neutralizing antibodies, pure red cell aplasia, recombinant product.

Summary

Steven G. Elliott

New molecules and formulations of recombinant human erythropoietin

Recombinant human erythropoietin (rHuEPO) is a breakthrough therapeutic with uses in the treatment of anemia associated with kidney disease, cancer, HIV infection, inflammatory disease, and for blood loss associated with surgery or trauma. Although rHuEPO is safe and effective, improvements in the properties of the molecule or methods of delivery are desirable. The excellent safety profile of rHuEPO sets a high standard, making this endeavor a challenge. Current approaches include construction of analogs to stabilize or increase activity, chemical modification of rHuEPO, gene delivery, and development of slow-release formulations. One successful strategy is glycoengineering of rHuEPO, which involves construction of glycosylation analogs with increased content of sialic acid-containing carbohydrate. One such glycoengineered molecule, darbepoetin alfa has been approved for marketing in the United States, the European Union, Australia, and Canada. The rate of clearance of darbepoetin alfa is reduced relative to rHuEPO, increasing its *in vivo* biologic activity. Darbepoetin alfa has a similar safety profile to rHuEPO and can be administered with more flexible modes of administration including extended dosing intervals.

Key Words: Immunogenicity, Aranesp[®], darbepoetin alfa, EPO mimetic, extended dosing interval, gene therapy, glycoengineering, glycosylation, pegylation, rHuEPO, serum half-life.

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