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Clinical characteristics of erythropoietin-associated pure red cell aplasia

Kenneth R. Carson MD

Andrew M. Evens DO, MS

Charles L. Bennett* MD, PhD

Division of Hematology/Oncology, Department of Medicine, Northwestern University Feinberg School of Medicine and the Robert H Lurie Comprehensive Cancer Center, Chicago, IL, USA

Departmentof Internal Medicine, Hematology/Oncology, Veterans Administration Chicago Healthcare Systems-Lakeside Division, Chicago, IL, USA

Stefano Luminari MD

Dipartimento di Oncologia ed Ematologia, Centro Oncologico Modenese, Università di Modena e Reggio Emilia, Modena, Italy

Recombinant human erythropoietin (epoetin) was first used for the treatment of anemia resulting from renal disease in 1986. During the first 10 years of its use, there were only three cases of epoetin-induced antibodies reported, which resulted in pure red cell aplasia (PRCA). Between 1998 and 2002, 191 chronic kidney disease patients developed PRCA during the course of epoetin treatment. Clinical characteristics of patients with PRCA include an absolute resistance to epoetin therapy, with a rapid development of severe anemia and very low reticulocyte count. In addition, patients developed high titre, high affinity neutralizing antibodies, which are detectable by immunoassays. The diagnosis of PRCA requires the onset of severe anemia, erythropoietin neutralizing antibodies in circulation, the lack of red cell precursors in the bone marrow aspirate, and normal to elevated transferrin saturation. Patients require blood transfusions to maintain an acceptable level of hemoglobin. Cessation of epoetin treatment alone does not improve PRCA. Patients have required immunosuppressive treatment. However, the most efficacious treatment has been kidney transplantation accompanied by immunosuppressive agents that prevent organ rejection. Evaluating patients receiving recombinant epeoetin therapy who experience a sudden loss of epoetin efficacy for the possibility of antibody-mediated PRCA is crucial. Timely identification and treatment of this rare syndrome can prevent the development of

* Corresponding author. Tel.: +1 312 469 4410; Fax: +1 312 469 4441.
E-mail address: cbenne@northwestern.edu (C.L. Bennett).

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severe red blood cell transfusion requirements and the potential complications of iron overload, which results from these transfusions.

Key words: PRCA; epoetin; autoantibodies.

The widespread use of recombinant proteins in treating diseases over the past two decades is supported in large part by the proven biologic safety of these agents in comparison to the previously used products, which were derived primarily from animal or human sources. Recombinant proteins are very similar in structure to their endogenous counterparts, but do not have the associated risks of viral contamination. However, there is always the potential and in some cases the actual occurrence of autoantibodies that develop from use of these proteins. The mechanism of antibody generation is not well understood and there are several examples of administered proteins such as insulin, human growth hormone, human granulocyte macrophage colony-stimulating factor, coagulation factor VIII, interferon-α and -β and more recently erythropoietin engendering antibodies against them.[1]

Anemia is a universal complication of chronic kidney failure. The kidney is the major source of native erythropoietin, a protein that stimulates red cell growth and development. Anemia reduces one's quality of life and cognitive and physical function and also increases the risk of developing left ventricular hypertrophy.[2] Fortunately, the occurrence of severe anemia has been prevented among patients with chronic kidney disease by universal use of recombinant erythropoietin (epoetin). Treatment with epoetin for patients with chronic kidney disease is standard treatment because of its high therapeutic index.[3–5] With respect to the possibility of epoetin inducing autoantibodies, between 1988 and 1998 this was found to be a theoretical but not actual concern. During this time period, despite use of epoetin by millions of patients with chronic kidney disease, only three individuals were reported to have developed epoetin-associated autoantibodies. These individuals were identified as a result of a clinical and laboratory diagnosis of the rare syndrome, pure red cell aplasia (PRCA). However, between 1998 and 2002, there was a sharp increase in the number of chronic kidney disease patients with epoetin-associated PRCA.[6] PRCA is characterized by severe anemia, very low reticulocyte counts, and the absence of red cell precursors in the marrow. The chronic kidney disease patients who developed PRCA had been treated primarily with the Eprex™/Erypo™ brand (Ortho Biotech) of epoetin alfa, but there were also a few cases in which chronic kidney disease patients in Europe had been receiving epoetin beta (NeoRecormon™, Roche) or in the United States had been receiving the Epogen™ (Amgen) formulation of epoetin alfa. Almost all had received the drug subcutaneously.[6,7] None of the patients had a diagnosis of cancer.

DIAGNOSIS OF PATIENTS WITH EPOETIN-ASSOCIATED PRCA

The first report of patients with this syndrome described 13 French and British chronic kidney disease patients in the years 1998 to 2001 who had developed antibody-mediated PRCA following subcutaneous treatment primarily with the human serum albumin-free formulation of epoetin.[6,8] Severe transfusion-dependent anemia, very low levels of reticulocytes ($< 10\,000/mm^3$), and the absence of red blood cell precursors in normal-appearing marrow supported the diagnosis of PRCA.[9] The neutralizing