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Importance of biologic follow-ons: experience with EPO

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The importance of recombinant human erythropoietin (epoetin) therapy has been clearly demonstrated in patients with anemia due to chronic kidney disease. The use of biopharmaceuticals to replace endogenous proteins, which may be inadequately low, carries the risk of stimulating the immune system to develop autoantibodies. Although these proteins are designed to closely mimic the endogenous proteins, they may have potential immunogenic properties. Erythropoietin produced by recombinant DNA technology is the most successful and efficacious agent for treating anemia. It was initially used in treating anemia in chronic kidney disease patients. Pure red cell aplasia (PRCA) ensuing from production of neutralizing anti-erythropoietin antibodies occurred very rarely with epoetin treatment. This agent was initially administered intravenously, but the mode of administration was progressively altered to subcutaneous without apparent increase in immune reaction. However, between 1998 and 2001, a sharp increase in the number of PRCA cases was seen. PRCA had been a very rare complication until this time. All of these patients had high affinity neutralizing anti-erythropoietin antibodies. This observation was made primarily in cases where one brand of epoetin, Eprex®, was administered subcutaneously to patients with chronic kidney disease treated outside the United States, although a small number of cases among chronic kidney disease patients treated solely with epoetin beta were also identified. The marked increase in the number of Eprex® cases was attributed to a change in the stabilizers, storage, and route of administration of Eprex® to patients with chronic kidney disease. Since then changes have been made to the route of administration, storage, and handling of Eprex®, and more recently to the rubber stoppers used in the prefilled syringes. Eprex® was administered intravenously to chronic kidney disease patients and, with improved storage and handling, there was a subsequent dramatic reduction in the number of cases. More recently, the rubber stoppers have been replaced by Teflon-coated ones to prevent interactions with stabilizers and release of chemicals that have adjuvant properties. However, this concern is still relevant in the new generation of epoetin agents

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and generic formulations of epoetins. Epoetin treatment for anemia requires regular follow-up of hemoglobin levels but also of reticulocyte counts in chronic kidney disease patients.

Key words: epoetin; pure red cell aplasia; chronic kidney disease.

Pure red cell aplasia (PRCA) is a severe isolated anemia with sudden onset. It is a rare hematologic disorder accompanied by an almost complete absence of red cell precursors in the marrow.[1] These patients show normal platelet and leukocyte counts, but reticulocytes are $< 10\,000/mm^3$ in the peripheral blood and bone marrow contains less than 5% erythroblasts with a block of maturation. This loss of erythrocyte production results in a drop in the hemoglobin count 0.1 g/dL/day. Since serum iron is not consumed in new erythrocyte production, serum iron and ferritin levels rise sharply. Affected patients require frequent transfusions of packed red cells. In the case of epoetin-induced PRCA, the syndrome is caused by neutralizing anti-erythropoietin antibodies, but PRCA may also occur among individuals with lymphoproliferative disorders, parvovirus B19 infection, systemic lupus, rheumatoid arthritis, autoimmune hepatitis, thymoma, or treatment with drugs such as chloramphenicol.[2,3] Furthermore, in about half of the cases, no etiology is identified. In patients who lack appreciable levels of anti-erythropoietin antibodies, serum erythropoietin levels are increased. In contrast, free serum erythropoietin levels are extremely low in PRCA due to neutralizing antibodies and may be undetectable by standard radio-immuno assay (RIA).[4]

Red blood cell production is controlled by erythropoietin, which is primarily produced in the kidney. Unlike other hematopoietic growth factors, a single organ produces erythropoietin and its effect on red cell production is regulated by classic feedback control mechanism.[5] The liver is a secondary site of production that is by far not as active. Erythropoietin stimulates erythropoiesis after binding its receptor on erythroid progenitor cells. Erythropoiesis also is controlled by interleukin-3, granulocyte macrophage colony-stimulating factor, and stem cell factor.[6,7] Anemia is a frequent complication both in chronic kidney disease and in hematologic malignancies, especially in chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and myeloma. In these cases, patients have been treated with recombinant human erythropoietin to alleviate symptoms of anemia. The clinical rationale for epoetin use has been based on serum levels of erythropoietin.[8]

DNA technology has facilitated the syntheses of proteins to treat disease. One of these, epoetin, is used to stimulate red cell growth in patients with low levels of endogenous erythropoietin and replaces transfusion dependence. The use of epoetin is standard for anemia related to chronic kidney disease. It has a very high therapeutic index. The use of a new protein therapy always has the potential of developing neutralizing antibodies even though the protein introduced closely mimics the endogenous protein. It is important to monitor these treatments carefully for the occurrence of antibody-related events. In the case of epoetin, between 1998 and 2003, over 200 patients treated for chronic kidney disease have developed clinical and pathological features of PRCA worldwide.[9] When this observation was made, almost all of the chronic kidney disease patients who developed epoetin-induced PRCA were receiving epoetin subcutaneously, and the prescribed medication was mainly epoetin alpha (Eprex®, Ortho Biotech). The median delay between the start of therapy and the occurrence of symptoms was about 11 months for chronic kidney disease patients who had received Eprex®.[8–11] The cases with NeoRecormon and Epogen were sporadic