Antibody-mediated pure red cell aplasia (PRCA) on switching from darbepoetin alfa to epoetin beta: what are the implications?

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Abstract

We report the development of antibody-mediated pure red cell aplasia (PRCA) in a 63-year-old man with end-stage renal disease following a switch from darbepoetin alfa to epoetin beta. Haemoglobin levels began to decrease 6 months after the switch. Increasing the epoetin beta dose produced no response and regular blood transfusions were required; PRCA was confirmed and epoetin beta was discontinued. The patient responded positively to immunosuppression; after 2 months on prednisone and cyclophosphamide, haemoglobin levels stabilized and no further transfusions were required. This case highlights the difficulty in establishing a cause-effect relationship where more than one erythropoiesis-stimulating agent is involved.

Keywords: darbepoetin alfa; epoetin beta; erythropoiesis-stimulating agents; pure red cell aplasia

Background

Anaemia is a serious complication of chronic kidney disease (CKD) and cancer therapy. Erythropoiesis-stimulating agents (ESAs), based on recombinant human erythropoietin (rHuEPO), are used to treat anaemia by raising haemoglobin (Hb) levels, alleviating its effects and reducing the need for blood transfusions. Available ESAs include epoetin alfa (Epogen®, Eprex® or Procrit®; Amgen, Johnson & Johnson and Ortho Biotech, respectively), epoetin beta (NeoRecormon®, Roche) and darbepoetin alfa (Aranesp®, Amgen), a super-sialylated analogue of epoetin alfa with a longer circulating half-life than epoetin alfa (NeoRecormon, Roche, manufactured in Mannheim, Germany Aranesp, Amgen, manufactured in Thousand Oaks, USA).

ESA use is associated with a risk of auto-antibody production [1] directed against rHuEPO and the native EPO molecule. This can cause development of a rare condition known as antibody-mediated pure red cell aplasia (PRCA) [2]. Patients with PRCA have erythroid precursor deficiency in the bone marrow and thus become resistant to rHuEPO treatment and dependent on blood transfusions for Hb maintenance.

We report the development and management of PRCA in a patient with CKD following a switch from darbepoetin alfa to epoetin beta.

Case report

A 63-year-old man with end-stage renal disease was started on intravenous (i.v.) darbepoetin alfa (20 µg Q 2 W ) for anaemia in January 2005 after transfer from another haemodialysis unit, where he had received this medication for at least 1 year. The patient had been receiving haemodialysis since 1999 and in December 2001 received a renal transplant, but hyperacute rejection caused immediate renal vein thrombosis.

During i.v. darbepoetin alfa treatment between January 2005 and February 2006, Hb levels varied between 10.9 g/dL and 12.5 g/dL (Figure 1). ESA doses were adjusted as necessary and ranged from 25 µg Q2W to 10 µg Q W . The patient was switched to subcutaneous (s.c.) epoetin beta (initial dose 2000 U/week) in February 2006. Hb remained stable, varying between 12.2 g/dL and 12.9 g/dL for 6 months, but then began to fall (Figure 1). The epoetin beta dose was progressively increased to 24 000 U/week, but the patient was unresponsive. By January 2007, Hb level was 7.1 g/dL and reticulocyte count 0.0 × 10³/µL, with normal white blood cell and platelet counts. A test for anti-EPO antibody in January 2007 was positive (964 ng/mL) and a bone marrow examination revealed the absence of erythroid precursors, confirming the suspected PRCA. Laboratory parameters at diagnosis of PRCA are summarized in Table 1. In addition, prostate-specific antigen, immunoglobulins IgG, IgA and IgM, complement proteins C3 and C4, anti-nuclear antibody, anti-DNA antibody, anti-neutrophil cytoplasmic antibodies and serum protein electrophoresis results were all normal.

Epoetin beta was discontinued at the end of January 2007; prednisone (1 mg/kg/day to 60 mg/day) and...
aspirate. 

.. Recheck the count per week in order to maintain adequate Hb. Other signs are

.. In suspected or confirmed PRCA cases, ESAs should be discontinued and immunosuppressive therapy, for example cyclophosphamide combined with prednisone, should be initiated.

.. There are more reported PRCA cases following s.c., compared with i.v., ESA administration. Whereas the vast majority of reports of recombinant EPO-related PRCA have been attributable to treatment with Eprex®, cases attributable to other recombinant EPOs have been reported [4–6].

.. The number of antibody-mediated PRCA cases in CKD patients treated with s.c. Eprex® injections from single-use syringes increased between 1998 and 2002 [7]. This coincided with changes in the formulation and packaging of Eprex®. Human serum albumin stabilizer was replaced with glycine and polysorbate 80 in 1998 [2], due to concerns over Creutzfeld–Jakob prions in blood-derived products. Formation of micelles between polysorbate 80 and epoetin alfa [8] has been proposed as a possible cause of increased immunogenicity. It should be noted that other ESAs besides Eprex® use polysorbate stabilization. NeoRecormon® is stabilized by polysorbate 80 and Aranesp® by polysorbate 20, glycine, a 5-amino-acid complex, calcium chloride and urea. Another suggested cause is leaching of organic compounds by polysorbate 80 from the uncoated rubber stoppers used in Eprex® syringes [9]. The variation in post-translational modifications, aggregation, dose, treatment duration and patient genetic characteristics may also influence immunogenicity [10].

.. Physicians should be aware of the characteristics indicative of PRCA development, and the potential impact of switching between similar biopharmaceuticals. It is important to note that switching a patient between available ESAs may lead to difficulties in attributing the development of PRCA to one particular ESA.

.. To monitor potential ESA immunogenicity and achieve the highest levels of patient safety, pharmacovigilance is essential. Concerns over PRCA will become more prominent given the imminent market introduction of biosimilar recombinant EPOs. The routine practice, in some countries, of switching biopharmaceuticals for similar products does not allow pharmacovigilance and may delay diagnosis of complications such as PRCA in CKD patients.

.. Identification of anti-EPO antibodies is critical for PRCA diagnosis. Radio-immunoprecipitation assays or enzyme-linked immunosorbent assays are used to determine the presence of EPO-binding antibodies. Bioassays, in which patient serum or immunoglobulin inhibits red blood cell precursor growth in bone marrow or cell line cultures, are used to determine the presence of EPO-neutralizing antibodies. In suspected or confirmed PRCA cases, ESAs should be discontinued and immunosuppressive therapy, for example cyclophosphamide combined with prednisone, should be initiated.

.. We report the development of PRCA in a patient with CKD 6 months after a switch from i.v. darbepoetin alfa Q2W to s.c. epoetin beta QW.

.. PRCA is a rare, but serious complication requiring multiple blood transfusions. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative anaemia guidelines [3] suggest that anti-EPO antibody-induced PRCA should be considered and further evaluated in a previously responsive patient who, after at least 4 weeks of ESA therapy, displays a rapid decline in Hb level (>0.5–1 g/dL per week) or a transfusion requirement of ≥1–2 units per week in order to maintain adequate Hb. Other signs are a reticulocyte count <10 000/µL with normal white blood cell and platelet counts and severe erythroid hypoplasia, with <5% red blood cell precursors in the bone marrow aspirate.

.. Cyclophosphamide (50 mg/day) treatment was started to repress antibody formation. Hb values were variable but slowly increased in response to immunosuppressive therapy (Figure 1). By May 2007 the anti-EPO antibody titre had fallen to 51.9 ng/mL. Reticulocyte count on follow-up in February 2007 had increased to 4.0 × 10³/µL, but was still below the normal range. Twelve blood transfusions were required between 19 December 2006 and 19 March 2007. The patient committed suicide on 27 May 2007.

.. Discussion

.. We report the development of PRCA in a patient with CKD 6 months after a switch from i.v. darbepoetin alfa Q2W to s.c. epoetin beta QW.

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