Anti-epoetin-antibody-induced anemia in a child with chronic renal failure

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Sirs,

Recombinant human erythropoietin was introduced in 1988 for the treatment of anemia in chronic kidney disease (CKD). The development of antibodies against epoetin was a rare complication during the first decade of its use. However, in 1998 there was a sudden increase in epoetin-induced antibodies associated with pure red cell aplasia (PRCA) in patients with CKD who had been using Eprex, a subcutaneous epoetin-alfa product marketed in Europe [1, 2]. Although the recombinant epoetin products differ in glycosylation, the increase in PRCA was probably caused by a change in the formulation of Eprex in which human serum albumin was replaced by glycine and polysorbate 80 [3]. Switching patients from subcutaneous to intravenous administration and adding Teflon to the rubber stopper of prefilled Eprex syringes subsequently eliminated nearly all antibody formation. For epoetin-beta, antibody-associated PRCA is even rarer, as evidenced by the very few cases that have been published. We present here the first report of a child who developed antibody-associated PRCA elicited by the use of epoetin-beta.

The patient was born on the Dutch Antilles. In 2004, at the age of 5 years, he developed renal failure due to persistent obstructive uropathy. His CKD-related anemia was treated with epoetin-beta subcutaneously from 2004 onwards (2×2000 IE/week). After 1.5 year of use, he developed a progressive transfusion-dependent anemia unresponsive to recombinant epoetin-beta (Neorecormon: maximum 5×2000 IE/week) and presented at our hospital (Fig. 1). An increase in the epoetin-beta dose to 5×6000 IE/week had no effect on the reticulocyte count, demonstrating that the anemia was unresponsive to epoetin-beta.

Laboratory testing revealed the following: hemoglobin (Hb), 2.8 mmol/L; reticulocyt count, <0.1%; MCV, 83; white blood cells (WBC), 11.7×10⁹/L; platelet count, 228×10⁹/L. There were no signs of hemolysis: lactate dehydrogenase, 184 U/L; haptoglobin, 0.99 g/L. The combination of anemia, low reticulocyte count, and normal leukocyte and trombocyte count with the use of epoetin-beta suggested a diagnosis of antibody-mediated PRCA. Anti-epoetin immunoglobulin (Ig) G antibodies identified by means of an antigen binding assay, essentially as described by Aalberse et al. [4], were indeed elevated. Treatment was initiated with one pulse methylprednisolone (15 mg/kg), followed by prednisone 1 mg/kg/day, and cyclosporine 4 mg/kg/day (trough levels 50–100 mg/L). Within days of starting this treatment, anti-epoetin-antibodies levels declined and were undetectable after 2 months of treatment (Fig. 1). The reticulocyte count increased to 2% after 3 months, and from then on Hb remained at acceptable levels between 5 and 7 mmol/L without the need for blood transfusions (Fig. 1). After 3 months, the prednisone dosage was reduced to 7.5 mg (0.3 mg/kg/day) and the cyclosporine dosage to 3 mg/kg/day until transplantation. One year later a successful family
Kidney transplantation was performed, and Hb was stable at 6.5 mmol/L 4 months after transplantation (Fig. 1).

This 5-year-old boy developed PRCA caused by anti-epoetin-antibodies following exclusive treatment with epoetin-beta subcutaneously. The subcutaneous administration of epoetin may have rendered the immune system of this boy more susceptible to antibody formation.

Treatment options for antibody-associated PRCA are invariably based on case reports or case-series. Several immunosuppressive drugs have been tried: corticosteroids alone, cyclophosphamide, cyclosporine, mycophenolate mofetil, intravenous immunoglobulin, and anti-CD20 monoclonal antibodies, with or without corticosteroid treatment. Although the results of different strategies vary, all patients who had a kidney transplant showed a full recovery of erythropoiesis [5]. Our patient responded well to a pulse of methylprednisolone followed by prednisone and low-dose cyclosporine. After this treatment the Hb remained stable, indicating the permanent disappearance of antibodies. No side-effects of our treatment were noted, and a successful renal transplantation was ultimately performed.

In conclusion, the combination of prednisone and cyclosporine in a low dose was successful in the treatment of anti-epoetin-antibody-induced anemia in a child with chronic renal failure.

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