Case Report

Successful re-introduction of recombinant human erythropoietin following antibody induced pure red cell aplasia

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Introduction

Reports of pure red cell aplasia (PRCA) secondary to recombinant human erythropoietin (rHuEPO), predominantly following the administration of subcutaneous (s.c.) epoetin alfa, have increased dramatically over the past 3 years. Treatment with immunosuppressive agents has been partially successful in some patients, rendering them transfusion independent. To date there are no reports describing the re-introduction of rHuEPO.

We discuss the case of an 81-year-old man on maintenance haemodialysis who developed PRCA, with positive anti-EPO antibodies (Abs) whilst receiving s.c. epoetin alfa. The epoetin alfa was stopped, cyclosporine (CyA) started and regular transfusions prescribed when symptomatically anaemic. After receiving CyA therapy for 4 months he became anti-EPO Ab negative. One year after starting CyA he was re-challenged with rHuEPO-intravenous (i.v.) darbepoetin alfa. Re-introduction has been successful; with a significant, sustained rise in haemoglobin (Hb), becoming transfusion independent.

Case

The patient was first presented to nephrology care in May 1997 when he presented with a 7-month history of bilateral leg swelling, hypoalbuminaemia, proteinuria and renal impairment. A diagnosis of membranous nephropathy was made on renal biopsy. He was started on immunosuppressive therapy (steroids), which he continued until December 2000 when progressive renal impairment led to the start of haemodialysis. He was commenced on s.c. epoetin alfa in October 2000. His Hb was measured at 8.6 g/dl and a dose of 2000 IU, three times weekly, was initiated.

His initial response to EPO was excellent; his Hb was successfully maintained (10.9–13.2 g/dl) on the original starting dose and he did not require any blood transfusions.

In January 2002 he was first noted to be anaemic, his Hb was recorded at 8.3 g/dl, demonstrating a rapid decrease. Despite increasing his epoetin alfa to 4000, 6000 and then 10 000 IU three times weekly there was no improvement in his Hb. In February 2002 he required blood transfusions to support his symptomatic anaemia. Regular iron infusions (Venofer) were continued and his ferritin level was maintained above 500 ng/ml. Despite iron replacement and increased rHuEPO replacement he required regular blood transfusions—53 U over 11 months in 2002 and 41 U over 9 months in 2003. With failure to respond to an increasing dosing regime of rHuEPO, this was stopped in April 2002.

All investigations into other causes of rHuEPO resistance, including computerized tomography scans of the chest, abdomen and pelvis, and viral serology tests failed to identify a recognized cause. Immunoprecipitation test for the presence of anti-EPO Abs was positive in May 2002 (PPD Development CLIA Immunochemistry Laboratory Richmond VA). A bone marrow biopsy performed showed a lack of erythroid precursors consistent with the diagnosis of PRCA.

Despite stopping his rHuEPO, his anti-EPO Abs continued to be positive and so in September 2002 it was decided to start immunosuppressive treatment—CyA 100 mg twice daily. On CyA treatment an increase in his reticulocyte count was noted. Whilst this did decrease the need for transfusion it did not obviate the need for blood transfusions (Figure 1). On CyA therapy his anti-EPO Abs became negative in December 2002 and remained negative on all subsequent testing.

In October 2003, because of his persistent anaemia and transfusion requirements, it was decided to re-

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introduce rHuEPO therapy. Darbepoetin alfa, at a dose of 10 μg/week was chosen because of its longer half-life, requiring less frequent dosing and the paucity of association with PRCA. The initiation of darbepoetin alfa did correspond with a significant rise in the reticulocyte count, which may partially explain the prompt rise in Hb and transfusion independence.

Discussion

The use of rHuEPO for the treatment of renal anaemia has become widespread since its first use in 1986. Initially few problems were associated with its use and prior to 1998 only scattered cases are found describing PRCA [1,2]. Since then there has been a dramatic increase in the occurrence and in December 2002, 142 patients had been diagnosed with Ab-positive PRCA. These patients present with a severe rHuEPO resistant anaemia, very low reticulocyte counts, a paucity of erythroid precursors on bone marrow, an absence of other causes of rHuEPO resistance and positive anti-EPO Abs.

Regular blood transfusions are often required to maintain adequate Hb levels. The majority of patients who developed PRCA were administered s.c. epoetin alfa, there are selected reports of patients on epoetin beta developing PRCA.

To date there are no reports of patients on darbepoetin alfa developing PRCA, or of exclusive i.v. rHuEPO therapy leading to the development of PRCA. The increase in cases of PRCA coincides with product changes, removing human serum albumin from the ex-US formulation of epoetin alfa, to comply with new European regulations [3].

There is consensus in the literature that it is essential to stop rHuEPO after the development of PRCA [3,4,8,9]. In addition, various immunosuppressive regimes have been used with some success. Casadavell et al. [3,4] reported the fate of 42 patients with Ab-positive PRCA observed for 1 year. A 72% success rate, defined as the disappearance of Abs and a reticulocyte count >10 000/mm³, was observed for the patients who received immunosuppression. CyA has been successfully used in PRCA in a number of different clinical scenarios [5–7].

Although immunosuppressive agents may render the patients transfusion independent, they will, in all likelihood remain anaemic and subject to the usual morbidity and mortality associated with this anaemia. Despite improvements in their reticulocyte counts it is likely that they will have too little circulating erythropoietin to sustain an adequate Hb. To date there are no reports of re-challenging these patients with rHuEPO.

A recommendation was made by the manufacturers of epoetin alfa (Ortho Biotech [8]) to discontinue therapy with rHuEPO rather than to switch patients to alternative products. Support for this statement was found in the paper by Casadavell et al. [4] who had found anti-EPO Abs to cross-react with all commer-

![Graph showing Haemoglobin values, reticulocyte counts and transfusion requirements during the study period.](https://academic.oup.com/ndt/article-abstract/19/8/2137/1918391)
cially available rHuEPO products (epoetin alfa, epoetin beta and darbepoetin alfa). A recent report has lent further support to this argument, describing the case of a patient who developed weals at the site of s.c. rHuEPO injections [9]. When given i.v. rHuEPO (epoetin alfa and darbepoetin alfa) the patient developed skin reactions at the site of former s.c. injections and eventually a systemic anaphylactoid response. In addition, it has been strongly suggested that the skin plays an important role in immune reactions and the development of anti-EPO Abs [9].

We argued that by treating the patient with an immunosuppressant drug, CyA, and rendering the anti-EPO Abs negative we had reduced the possibility of this potential reaction.

i.v. darbepoetin alfa was chosen because of the reasons mentioned above. It remains to be elucidated how long immunosuppression should be continued for and how soon after the commencement of immunosuppression could you safely re-challenge with rHuEPO.

**Conclusion**

We report the case of a haemodialysis patient who developed PRCA secondary to epoetin alfa. After treatment with immunosuppressives (CyA) for 1 year, and becoming anti-EPO Ab-negative, he was re-challenged with rHuEPO (darbepoetin alfa).

Four months later his Hb is satisfactory and he remains transfusion independent. We postulate that rHuEPO can be safely re-introduced after a period of immunosuppression to reverse anti-EPO Abs.

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**References**


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