Case 1

The first patient is a 76-year-old man who was referred to the Nephrology Clinic with moderate-to-severe renal impairment with a serum creatinine level of ~300 µmol/l. Amongst other investigations, he underwent a renal biopsy in March 2001, which revealed a diagnosis of chronic mesangioproliferative glomerulonephritis. His past history included peptic ulcer disease, mild late-onset asthma, bronchiectasis and hypertension. In August 1999, he was enrolled in an 'Early Treatment of Anaemia in Chronic Renal Failure' research study. By June 2001, his haemoglobin had drifted down to 9.9 g/dl, and he was started on epoetin alfa (Eprex) 2000 units once weekly subcutaneously, as per the study protocol (Figure 1). He had a good initial response to this treatment, and by December 2001 his haemoglobin had risen to 11.0 g/dl.

Two months later, in February 2002, his haemoglobin had fallen quite sharply to 7.9 g/dl, and he was given a course of intravenous iron sucrose. His dose of epoetin alfa was also increased to 2000 units thrice weekly subcutaneously. In March 2002, his haemoglobin had drifted down to 9.9 g/dl, and he was started on epoetin alfa (Eprex) 2000 units once weekly subcutaneously, as per the study protocol (Figure 1). He had a good initial response to this treatment, and by December 2001 his haemoglobin had risen to 11.0 g/dl.

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he continued to be transfusion-dependent, and a serum sample was analysed in Professor Casadevall’s laboratory, which tested positive for anti-erythropoietin antibodies. There was some debate about the appropriate treatment for him, given the lack of experience reported in the medical literature and the concerns about using a nephrotoxic agent such as cyclosporin in a patient whose creatinine level was now between 400 and 500 μmol/l. The choice was between mycophenolate or anti-CD20 monoclonal antibody therapy, and on our haematologists’ advice he underwent a course of the latter treatment in July 2002. However, he remained transfusion-dependent up until March 2003, with a reticulocyte count of between 10 and 20 × 10⁹/l, and his haemoglobin (even with regular blood transfusions) remained between 8 and 10 g/dl. There was, however, a progressive fall in his titre of anti-erythropoietin antibodies as measured by radioimmune precipitation assay (Figure 2).

In March 2003, it was considered that he was at the point of reaching end-stage renal failure, and since he was due to start dialysis, he was commenced on cyclosporin 200 mg o.d. By now, he no longer required top-up blood transfusions, but since his haemoglobin...
remained <10 g/dl, and his anti-erythropoietin antibody levels were very low, he was started on epoetin beta (NeoRecormon) at a dose of 2000 units three times weekly subcutaneously, since he was destined for peritoneal dialysis (Figure 3). His reticulocyte count rose over the subsequent 3 or 4 months, and he became transfusion-independent. His haemoglobin, however, remained ~9–10 g/dl. His dose of epoetin beta was therefore increased to 4000 units thrice weekly subcutaneously at the beginning of August 2003, and following this his reticulocyte count increased to 86 × 10⁹/l (Figure 3), and his haemoglobin progressively increased to just over 13 g/dl. He has continued on cyclosporin 200 mg o.d. throughout this period, with his cyclosporin levels ranging from ~100 to ~180 mg/l. At the time of writing, he is clinically very well, with a haemoglobin of 13.2 g/dl. His anti-erythropoietin antibody levels are, however, still detectable by radio-immune precipitation assay, albeit at very low titres.

Case 2

Mr L. is a 79-year-old man who was diagnosed as having advanced renal impairment due to vascular nephropathy in February 2000 (serum creatinine 520 μmol/l, estimated GFR 10 ml/min). In April 2000, his creatinine level had risen to 600 μmol/l (estimated GFR 8.5 ml/min), and his haemoglobin was between 10 and 11 g/dl. He was therefore started on epoetin alfa (Eprex) at a dose of 4000 IU/week (60 IU/kg/week), increasing to 6000 IU/week (90 IU/kg/week) in June 2000. Following this, his haemoglobin concentration increased to between 12 and 13 g/dl, but in December 2000, there was a rapid fall in his haemoglobin to 6.5 g/dl. Gastroscopy revealed a bleeding peptic ulcer, and he was treated with omeprazole and blood transfusions. His dose of epoetin alfa was increased to 9000 IU/week (135 IU/kg/week). At this point, he was deemed to have reached end-stage renal failure, and haemodialysis was started in January 2001. For no obvious reason, his epoetin alfa was replaced by epoetin beta subcutaneously.

His anaemia persisted, with a low reticulocyte count of 2 × 10⁹/l, and normal platelet (160 × 10⁹/l) and white cell (6.9 × 10⁹/l) counts. A bone marrow examination was diagnostic of pure red cell aplasia, and the patient remained heavily transfusion-dependent, receiving 74 units of blood between December 2000 and January 2001.
2002. At the time of his bone marrow aspirate, his serum ferritin was 1767 μg/l and his transferrin saturation was 84%. A serum sample from May 2001 was positive for anti-erythropoietin antibodies, and his epoetin beta was stopped in early June 2001.

He then commenced treatment with intravenous immunoglobulin (0.4 g/kg/day for 5 days), and further courses were given in August and September that year. He remained transfusion-dependent with a reticulocyte count of <10 x 10^9/l. In October 2001, he was treated with oral corticosteroids at a dose of 70 mg/day, along with two pulses of intravenous cyclophosphamide (0.5 g/m²) in October and December 2001. Following this, his transfusion requirements rapidly decreased, and his reticulocyte count improved to ~40–50 x 10^9/l. His anti-erythropoietin antibody titres also declined, becoming barely detectable from February 2002, and becoming completely negative from May 2003 onwards.

Because of symptomatic angina, a decision was made to restart erythropoietic therapy, and in October 2003 he was commenced on darbepoetin alpha (50 μg once weekly intravenously) under cyclosporin cover (50 mg/day). He had a good response to this, and the patient has not been transfused since. His anti-erythropoietin antibodies remain completely undetectable, and his reticulocyte count varies between 100 and 140 x 10^9/l. Indeed, his dose of darbepoetin alfa was able to be reduced to 30 μg weekly because of haemoglobin levels in excess of 13 g/dl. His cyclosporin was stopped in mid-January 2004.

**Case 3**

Mrs H. is a 75-year-old lady who had a left nephrectomy in 1967 for recurrent pyelonephritis. This also affected her right kidney, and her renal function slowly deteriorated. In October 1998, her haemoglobin was ~10 g/dl, and she was started on epoetin alfa (Eprex) subcutaneously. She finally reached end-stage renal failure in January 1989 and was started on regular haemodialysis. In June 1999, her haemoglobin concentrations began to decrease, despite increasing her dose of epoetin alfa up to 15 000 IU/week. In October 1999, her haemoglobin concentration was 6.4 g/dl with a reticulocyte count of 2 x 10^9/l, and a diagnosis of pure red cell aplasia was confirmed. The patient was heavily transfusion-dependent at that time and anti-erythropoietin antibodies were strongly positive in March 2000. Her epoetin alfa was subsequently stopped, and she was treated with two doses of intravenous immunoglobulins (1 g/kg) in March 2000. No response was seen, and in June 2000 she was started on oral corticosteroids (0.5 mg/kg) along with intravenous cyclophosphamide (0.5 g/m²). Her anti-erythropoietin antibody levels subsequently decreased, and her last blood transfusion was in December 2000.

She moved to another haemodialysis unit in May 2002, and she was inadvertently started back on epoetin alfa in April 2003 because of persistent anaemia, initially receiving this intravenously (10 000 IU/week), and then switching to epoetin beta intravenously (6000 IU/week) in October 2003. Since then her haemoglobin has been stable ~11.5–12 g/dl. Before being re-challenged with epoetin, her anti-erythropoietin antibody levels were at the lower limit of detection (0.1 U/ml). Six months after re-challenge, her anti-EPO antibody titre was stable at 0.1 U/ml, although in December 2003 the titre had very slightly increased to 0.2 U/ml. At that time her haemoglobin was 11.4 g/dl with a reticulocyte count of 62 x 10^9/l. In February 2004, her haemoglobin was 11.3 g/dl with a reticulocyte count of 80 x 10^9/l. Her anti-erythropoietin antibody titre was stable at ~0.2 U/ml.

**Discussion**

As far as we are aware, these are the first reported cases of patients with epoetin-associated pure red cell aplasia being actively re-challenged with erythropoietic therapy. Many nephrologists seem to be nervous about re-instituting erythropoietic treatment since the antibodies are known to cross-react with all available therapeutic agents [3,6]. Successful outcomes following epoetin-associated pure red cell aplasia have, however, been reported after renal transplantation, when the graft produces endogenous erythropoietin while the patient is maintained on immunosuppressive therapy [4]. The first patient was considered to be rather too old to be included on the UK Transplant list, and yet leaving him with a haemoglobin of between 8 and 10 g/dl would have adverse consequences on his quality-of-life, exercise capacity, and cardiac function. Since at that time he was in the transition phase between remaining dialysis-independent and starting peritoneal dialysis, the subcutaneous route was the only practical one to use for erythropoietic therapy. Since the exact cause of epoetin-associated pure red cell aplasia is not known, it is also not clear whether patients who have produced antibodies as a result of epoetin alfa therapy would also be more predisposed to do likewise with epoetin beta therapy. Nevertheless, the risks were considered small compared with the adverse consequences of leaving him anaemic, and he was treated with increasing doses of epoetin beta (NeoRecormon), with good effect.

It is impossible to say from the first case whether the monoclonal antibody therapy helped to reduce his levels of anti-erythropoietin antibodies. The antibody levels seemed to be falling even before the anti-CD20 monoclonal antibody therapy was introduced, and it is not possible to comment on whether this treatment accelerated the decline. Other immunosuppressive regimens have also been given to patients suffering from this condition, and despite the lack of controlled data, it is generally believed that immunosuppression accelerates the recovery from this condition compared with no such treatment [4]. The main point of case 1, however, is not whether his immunosuppressive therapy helped to reduce his levels of anti-erythropoietin antibodies,
but more that when his levels were low, it was possible to re-introduce erythropoietic therapy under cyclosporin cover.

Cases 2 and 3 both responded to corticosteroids and pulsed intravenous cyclophosphamide, and both were successfully re-challenged with intravenous erythropoietic therapy (darbepoetin alfa for case 2, and epoetin alfa/epoetin beta for case 3). Initially, case 1 was started on peritoneal dialysis, and so the option of giving erythropoietic therapy intravenously was not an option. He has subsequently switched to haemodialysis, but has remained on subcutaneous therapy.

In summary, all three patients with epoetin-associated PRCA were successfully re-challenged with erythropoietic therapy. One has always to be cautious about over-interpreting data from a few isolated case reports, but it is hoped that the experience with these three patients may encourage other nephrologists to attempt re-challenge in patients who have developed epoetin-associated PRCA once their anti-erythropoietin antibody levels are at a low titre.

Conflict of interest statement. None declared.

References


Received for publication: 10.1.04
Accepted in revised form: 25.5.04

Since this report was accepted for publication, the authors have become aware of two additional published Case Reports of re-challenge with epoetin (Summers et al Nephrol Dial. Transplant 2004; 19: 2137–2139) and darbepoetin alfa (Asari & Gokal, J Am Soc Nephrol 2004; 14: 2204–2207)