Recovery from anti-recombinant-human-erythropoietin associated pure red cell aplasia in end-stage renal disease patients after renal transplantation

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Introduction

Since 1990, recombinant human erythropoietin (r-HuEPO) has been used for the treatment of anaemia of chronic renal failure (CRF). Correction of anaemia may improve cardiovascular as well as non-cardiovascular morbidity and mortality. Despite these potentially beneficial effects of r-HuEPO, some CRF patients who have previously or are currently using r-HuEPO have been reported to display suspected or confirmed pure red cell aplasia (PRCA) [1,2]. These patients developed an unexplained sudden decrease in their haemoglobin (Hgb) level. Anti-r-HuEPO antibody (Ab), which has been demonstrated in several studies [3–5], seems to be the proximate cause of the PRCA. Currently, there is no firmly established management of anti-r-HuEPO associated with PRCA in CRF patients. Cyclophosphamide and prednisolone appear to be ineffective [6]. We report here that anti-r-HuEPO associated PRCA in end-stage renal disease (ESRD) patients was reversible after kidney transplantation.

Case report

Four Thai end-stage renal disease patients undergoing chronic hemodialysis were a mean age of 41 years [15, 44, 52 and 53 years]. Two patients had received alpha and two patients received beta r-HuEPO therapy with initially satisfactory responses to a subcutaneous mean dose of 120 u/kg/week (range 113–140 u/kg/week). Despite an increase to a mean r-HuEPO dose of 267.25 u/kg/week (range 206–338 u/kg/week), they subsequently developed refractory anemia (Figure 1). A switch from alpha to beta or beta to alpha forms of r-HuEPO, which was performed before this manoeuvre had been shown to be ineffective, failed to increase responsiveness to the treatment (Figure 1A and B). To rule out other causes of persistent anaemia, patients underwent endoscopy. Additional investigations included iron studies, serum vitamin B12, folate level, thyroid function tests, haemolytic screen and C-reactive protein were all normal. The reticulocytopenia was incongruent with the degree of anaemia (reticulocyte count <10 000 cells/mm³; Figure 2). Furthermore, subsequent bone marrow examinations demonstrated PRCA based upon the absence of erythroid precursor in an otherwise normocellular marrow. ELISA tests to detect anti-r-HuEPO was performed as previously described [7] showing positive reactions for IgG but not IgM in all patients. Quantitative in vitro analysis for colony forming unit-erythroid (CFU-E) [8] revealed that each patients’ serum (but not healthy control) inhibited the proliferation of cultured healthy donor bone marrow erythroid progenitor cells despite the presence of as much as 10 units of erythropoietin/ml. The effect of all the sera to inhibit erythroid progenitor cell growth was not evident on granulocytic colonies. The average length of r-HuEPO treatment prior to the development of PRCA was 23 months: namely patient A 14 months, patient B 30 months, patient C 22 months, patient D 26 months. After the development of anti-r-HuEPO associated PRCA, all patients became blood transfusion-dependent. Specifically, they required average monthly blood transfusions of 3 units of packed red cell
(PRC: range 2.5–3.4 unit per month) to alleviate anaemic symptoms. The time course of development of anti-r-HuEPO associated PRCA and the blood transfusion requirement are shown in Figure 1. Three patients received more than 30 units PRC in aggregate. Despite treatment with decadurabolin 50 mg/week for 9 weeks, prednisolone 80 mg/day tapered over 12 weeks, and oral cyclophosphamide 100 mg/day for 8 weeks, patient A showed no increase in responsiveness to r-HuEPO and no change in anti-r-HuEPO antibody. All patients received cadaveric kidneys transplantation based upon a national organ allocation scheme using HLA matching and panel reactive antibody levels. The mean duration of anti-r-HuEPO associated PRCA
before kidney transplantation was 8.25 months (range 3–11 months). Patients’ immediate sera before transplantation were positive for anti-r-HuEPO. HLA typing of patients showed no predilection except that all patients displayed HLA DR B1*9. After induction therapy with Daclizumab 50 mg day 0 and day 14 post-transplant, all patients were treated with cyclosporine, azathioprin and prednisolone. Cyclosporine level was aimed for 1500 ng/ml 2 h post-dose for 1 month and 1500–1300 ng/ml for 1–3 months. Following kidney transplantation, the haemoglobin (Hgb) levels in all patients returned to more than 10.0 g/dl at 12, 8, 12, 10 weeks post-transplantation, respectively. The reticulocyte count increased after the transplantation (Figure 2). At 4 week post-transplant, anti-r-HuEPO was negative.
Discussion

Four patients displayed remission of anti-r-HuEPO associated PRCA after renal transplantation. The average time to Hgb >10.0 g/dl was 10.5 weeks. None of the patients required a blood transfusion post-transplantation.

Treatment of non-anti-r-HuEPO-associated PRCA with steroids, cytotoxic agents, intravenous immunoglobulin (IVIG) or cyclosporine [9] yields response rates ranging from 30 to 55%. Presently, the optimal therapy for anti-r-HuEPO associated PRCA is uncertain; previous data have shown that failures are common. Also there is no report of a spontaneous recovery of anti-r-HuEPO associated PRCA. In our series, decadurabolin, an anabolic steroid previously used to treat renal anaemia in pre-r-HuEPO era, failed to raise the Hgb of one patient. Furthermore, high doses of prednisolone for 12 weeks and cyclophosphamide for 8 weeks did not improve the anaemia, this patient required continued transfusions. A switch from the alpha to the beta, or vice versa, forms of r-HuEPO also showed no significant increase in responsiveness to treatment.

Interestingly, all patients displayed HLA DR B1*9, an allele present in 8.7% of the general Thai population. Considering the low incidence of anti-r-HuEPO associated PRCA and the prevalence of HLA B1*9 in this subset of patients, we speculate that there may be a role of MHC encoded proteins that relates to immune recognition and production of anti-r-HuEPO. This hypothesis may explain the variable occurrence of anti-r-HuEPO associated PRCA among different countries, a speculation that needs more study for confirmation.

In conclusion, four patients displayed disappearance of anti-r-HuEPO and reversion of the anti-r-HuEPO associated PRCA after the kidney transplantation. These findings suggest that a trial of immunosuppressive therapy should be considered for CRF patients experiencing anti-r-HuEPO associated PRCA.

Conflict of interest statement. We (Praditpornsilpa K, Buranasot S, Bhokaisuwan N, Avihingsanon Y, Pisitkul T, Kansanabuch T, Eiam-Ong S, Intarakumtornchai T, Tungsanga K) declare no conflict of interest in this study.

References


Fig. 2. Reticulocyte count of each patient during the development and the recovery of anti-r-HuEPO associated PRCA post-renal transplantation.


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