The successful conversion to Tacrolimus (FK506) of a renal transplant recipient with cyclosporin-induced haemolytic–uraemic syndrome

D. Richardson, C. H. Jones, C. G. Newstead, E. J. Will and J. P. Lodge

Departments of Renal Medicine and Transplant Surgery, St James’s University Hospital, Leeds, UK

Case report

A 45-year-old hypertensive woman with end-stage renal failure of unknown cause had been maintained on CAPD for 3 years when she was admitted for her first renal allograft. Cytotoxic antibodies had been negative on serial testing and HLA match was excellent (0,0,0 mismatch). The graft showed primary function with a prompt fall in blood urea and serum creatinine. A conventional triple-therapy regime of immunosuppression was given, with prednisolone (20 mg/day), azathioprine (2 mg/kg/day) and cyclosporin A (7.5 mg/kg/day). From day 3 post-transplant the platelet count began to fall, and at day 6 deterioration in renal function occurred (Figure 1). Examination of a renal transplant biopsy at this time demonstrated focal mild protein insudation in two arterioles. Four of 16 glomeruli showed small intracapillary thrombi containing platelets. Platelet adhesion was seen in nine of 16 glomeruli. No tubular microvacuolation, microcalcification, or vascular smooth-muscle cell damage was identified. There was no evidence of tubulointerstitial infiltrate or vascular rejection. At the time of biopsy these findings were felt to be consistent with cyclosporin toxicity. Whole-blood 12-h trough cyclosporin level by monoclonal specific antibody (Abbott) was raised at 525 ng/l (target range 200–250 ng/l) and the dose was reduced to 4.5 mg/kg/day. Azathioprine was withheld because of thrombocytopenia. On day 7 renal function continued to worsen and haemoglobin decreased from 8 to 6 g/dl despite a 4-unit packed cell transfusion (Figure 2). Platelet count fell to 30 x 10⁹/l. Serum bilirubin increased to 69 μmol/l (normal range 3–15). A blood film showed cell fragments compatible with intravascular haemolysis. A direct Coombs test was negative. Doppler ultrasound of the renal allograft and vessels was normal. The clinical picture of intravascular haemolysis, thrombocytopenia, and worsening renal function was most compatible with a diagnosis of cyclosporin-induced haemolytic–uraemic syndrome. Cyclosporin was discontinued on day 7 and 0.5 g of intravenous methylprednisolone administered as a single dose. Oral prednisolone was increased to 100 mg/day. Neither plasmapheresis nor fresh frozen...
plasma were employed. Cyclosporin level by monoclonal specific antibody (Abbott) decreased (Figure 1). At day 11, renal function continued to deteriorate and three further 0.5 g doses of intravenous methylprednisolone were given on consecutive days. Tacrolimus was begun at a dose of 2 mg b.d. Platelet count, haemoglobin concentration, and graft function subsequently improved. Azathioprine was reintroduced once the platelet count exceeded $100 \times 10^9$/l. Tacrolimus level was 5 ng/l (monoclonal antibody assay, Abbott) and dose increased to 4 mg b.d., with the achieved objective of obtaining blood levels of >5, <10 ng/l. Graft function at 1 year was normal, with serum creatinine at 89 umol/l.

**Discussion**

An association between haemolytic–uraemic syndrome and cyclosporin has been described [1–3]. Cyclosporin-induced HUS most frequently occurs within 1 month of transplantation [5,8] and has been associated with graft loss in 57%, and patient death in 20%, of cases [7]. Reduction of cyclosporin dosage can be associated with graft rejection [3]. The pathogenesis of cyclosporin-induced HUS is not known, although the co-occurrence of acute rejection has been identified [6].

The optimal management of this syndrome is not defined. Reduction of cyclosporin dose alone has been advocated [8]. The risk of graft loss with such an approach has led to more aggressive therapies, including intensification of immunosuppression. Case reports of a beneficial response to plasma exchange with fresh frozen plasma replacement in renal [5] and combined renal/pancreas transplantation [6] have been published. Pooled gammaglobulin has been used in combination with plasma exchange [6] and alone [7].

However, patient numbers are small and no controlled studies have been performed. These procedures may be potentially hazardous, particularly in the immuno-suppressed, thrombocytopenic patient.

Tacrolimus is a macrolide with a similar mechanism of action to cyclosporin A and can be effective in reversing cyclosporin-resistant renal allograft rejection [9]. Substitution of Tacrolimus for cyclosporin A in patients with HUS has been described following liver transplantation [10] and in an isolated kidney [11] and a combined kidney-pancreas [6] transplant. As reported here, withdrawal of cyclosporin was followed by resolution of HUS, which had been resistant to plasma exchange in the kidney recipient. HUS has, however, also been described in a patient receiving Tacrolimus [12]. Successful immunosuppression with RS 61443 (mycophenolate) following cyclosporin-induced haemolytic syndrome has been described in a heart transplant patient [4], although renal failure persisted. This approach has not been described with a renal graft.

We describe HUS occurring early in the post-transplant course. Renal transplant biopsy performed prior to the appearance of any clinical manifestations of HUS was felt to be consistent with cyclosporin toxicity. In retrospect, these changes would also be compatible with HUS. Complete resolution occurred with salvage of normal graft function following cyclosporin withdrawal. Four days after cyclosporin withdrawal, graft function remained abnormal and thrombocytopenia persisted. Cyclosporin was still detected in whole blood at that time, albeit at subtherapeutic levels (Figure 1). Renal biopsy was not possible because of thrombocytopenia and, in view of the known association of cyclosporin-induced HUS and rejection [6], methylprednisolone was administered. Whilst the reintroduction of cyclosporin following resolution of HUS has been described, the persistence of graft dysfunction and thrombocytopenia, with low levels of cyclosporin still detectable, led us to seek an alternative immunosuppressive strategy. Tacrolimus was introduced with return of good graft function and without recurrence of haemolysis.

From our experience, it is not possible to be certain which therapy led to resolution of HUS. Cyclosporin withdrawal alone may have been sufficient in this patient. However persistent thrombocytopenia and graft dysfunction led us to introduce Tacrolimus on day 11, following which the situation improved. Fresh frozen plasma, plasmapheresis and pooled gammaglobulin were not required. Our experience therefore suggests that withdrawal of cyclosporin alone may result in recovery of graft function with resolution of intravascular haemolysis. However, the possibility of precipitating acute rejection necessitates the use of alternative immunosuppression and tacrolimus was used without a recurrence of HUS in this case.

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