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G. Morris-Stiff
D. Talbot
V. Balaji
K. Baboolal
K. Callanan
J. Hails
R. Moore
D. Manas
R. Lord
W. A. Jurewicz

Conversion of renal transplant recipients from cyclosporin (Neoral) to tacrolimus (Prograf) for haemolytic uraemic syndrome

G. Morris-Stiff · V. Balaji · K. Baboolal · R. Moore · R. Lord · W. A. Jurewicz (✉)
Department of Transplant Surgery, University Hospital of Wales, Cardiff, CF4 4XN, UK
Tel. 01222 746536; Fax 01222 761623

D. Talbot · K. Callanan · J. Hails · D. Manas
Department of Transplant Surgery, Freeman Hospital, Newcastle Upon Tyne, NE7 7DN, UK

Abstract Five patients with cyclosporin-related haemolytic uraemic syndrome (HUS) following cadaveric renal transplantation were converted from cyclosporin- to tacrolimus-based immunosuppression. All patients had biochemical, haematological and biopsy evidence of HUS at the time of conversion. Four of the patients showed complete resolution of the syndrome within 1 week of conversion with normalisation of haemoglobin, platelets and lactate dehydrogenase levels. In the fifth patient renal function stabilised with slow resolution of the haematological and biochemical parameters. Four of the five patients are still taking tacrolimus, one having converted back to cyclosporin due to marked hair loss. We conclude that conversion to tacrolimus appears to be an effective treatment for cyclosporin-related HUS following renal transplantation.

Key words Tacrolimus · Cyclosporin · Haemolytic uraemic syndrome · Renal transplantation

Introduction

Haemolytic uraemic syndrome (HUS) is an uncommon complication following cadaveric renal transplantation, which is characterised by the presence of a microangiopathic haemolytic anaemia, thrombocytopenia and renal failure [6]. The treatment of HUS involves removal of the causative agent together with correction of biochemical and haematological abnormalities and supportive therapy for the renal failure. The introduction of tacrolimus has allowed the opportunity for conversion of the primary immunosuppressive agent when cyclosporin is believed to be the cause of HUS. We report our experience in the treatment of five patients with cyclosporin-induced HUS who were successfully treated by conversion to tacrolimus.

Patients and methods

During the period from January 1994 to April 1996, five patients developing HUS whilst on cyclosporin-based regimens were converted to tacrolimus. The group consisted of four females and one male with a median age of 24 years (range 20–52). The HUS was diagnosed on biochemical and haematological grounds and all patients underwent ultrasound-guided transplant biopsies to confirm the diagnosis. None of the patients had HUS as an indication for transplantation. Pan cultures were also performed to eliminate infective causes of HUS such as CMV, *Shigella*, *Streptococcus pneumoniae* and *Escherichia coli* (O 157).

Patients were converted at a median period of 14 days (range 10–29) following transplantation. The median initial dose of tacrolimus was 0.24 mg/kg per day (range 0.1–0.4) which was administered in two divided doses commencing 12 h after cessation of cyclosporin. Doses were adjusted according to clinical response and 12-h trough levels as assessed by IMX assay which aimed to maintain tacrolimus blood levels of 5–10 ng/ml.

Results

In all cases the diagnosis of HUS was based on haematological and biochemical criteria including the presence of anaemia, thrombocytopenia, reticulocytosis and evidence of haemolysis including fragmentation and schistocytes on the blood film with a negative direct Coombs test. Biochemical abnormalities included elevated se-

rum creatinine, elevated lactate dehydrogenase and increased levels of unconjugated bilirubin. In all cases the diagnosis was confirmed by light microscopic examination of the biopsy specimens which showed the characteristic features of ischaemic damage secondary to microvascular hyaline thrombi. No infective agents were identified in these patients as a possible cause for the HUS.

Following the switch to tacrolimus, four patients demonstrated a marked improvement in renal function and the fifth stabilised without any further deterioration. At a median follow up of 12 months (range 1–18), the median creatinine was 123 μmol/l (range 65–236) ($t < 0.001$, Student's paired t-test). Other biochemical and haematological markers including platelet count, haemoglobin and lactate dehydrogenase also returned to normal levels within 1 week of commencing tacrolimus. At the time of follow up, four of the five patients still remain on tacrolimus. One patient reconverted to cyclosporin due to tacrolimus-related alopecia.

Discussion

HUS is a well-recognised complication of bone marrow transplantation although it is much rarer in solid organ transplantation occurring in between 0.5 and 3.4% of renal transplant recipients [2, 3]. Until recently the condition was associated with a high incidence of graft loss and a considerable patient mortality [6]. The basic pathological lesion of HUS is that of an arteriopathy with hyaline thrombosis and intimal proliferation of small renal vessels resulting in glomerular ischaemia and subsequent sclerosis [6]. Immunosuppressive therapy is believed to play a major role in HUS. In renal transplant recipients, Singh and colleagues [6] noted cyclosporin therapy to be the aetiological factor in around 50% of cases. In 22% of renal transplant patients, post-transplant HUS was a recurrence of the preoperative disease although this was not the case in this series.

Treatment options for HUS arising in the transplant patient involve the exclusion of both rejection and an infective aetiology followed by dose-reduction or discontinuation of the suspected causative drug and administration of alternative immunosuppression [6]. The role of tacrolimus as an alternative immunosuppressive therapy for patients with HUS has previously been documented in kidney [1, 5, 6] and kidney/pancreas graft recipients [4]. In both cases reported in the literature, a successful outcome was achieved through discontinuation of cyclosporin and conversion to tacrolimus. We conclude that conversion from cyclosporin-based therapy to tacrolimus-based immunosuppression offers an effective treatment for patients developing HUS following cadaveric renal transplantation which does not compromise the effectiveness of the patient's immunosuppressive medications.

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