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BRIEF REPORT

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Conversion from cyclosporin to tacrolimus in a patient with prolonged acute tubular necrosis

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Abstract Acute tubular necrosis (ATN) is a common condition following cadaveric renal transplantation with an incidence in many series of nearly 50 %. The aetiology is uncertain; however, it would appear to be related to damage to the transplant kidney either prior to retrieval, during cold preservation or during re-warming of the kidney at the time of anastamotic construction. There is no specific therapy for ATN and treatment is comprised of an expectant policy with supportive dialysis and fluid restriction. Renal function improves in the majority of cases, though there may be delayed function for several weeks. We report a case of dialysis-dependent ATN that had persisted for 5 months following transplantation. Following conversion to tacrolimus there was immediate improvement in renal function, and after a month of tacrolimus therapy the patient was dialysis-independent.

Key words Acute tubular necrosis, tacrolimus, cyclosporin · Tacrolimus, ATN, cyclosporin · Cyclosporin, ATN, tacrolimus · Conversion, cyclosporin, tacrolimus

Introduction

Tacrolimus (Prograf) has been shown in clinical trials to be effective both as primary immunosuppression therapy and in the treatment of refractory rejection [5,9]. We have recently had success with tacrolimus in the treatment of a patient with primary non-function secondary to acute tubular necrosis (ATN) that had persisted for 5 months following transplantation.

Case report

A 41-year-old gentleman underwent cadaveric renal transplantation in October 1995 for hypertensive nephropathy. The donor was a young male who had died from a cerebral haemorrhage. The human leucocyte antigen (HLA) mismatch was 1:2:0. Whilst on the intensive care unit the donor experienced a single hypotensive episode lasting 30 min; however, he maintained a good urine output throughout. The kidney was preserved in University of Wisconsin preservation solution and the cold ischaemia time was 16 h and 55 min.

A small lower pole artery that had been damaged at the time of retrieval was anastamosed end-to-side to the main renal artery, and the anastamosis time for the renal-iliac anastamosis was 40 min. At the time of the recipient operation, the lower pole of the kidney was noted to be poorly perfused.

The patient was commenced on triple therapy immunosuppression consisting of cyclosporin 8 mg/kg per day, azathioprine 1.5 mg/kg per day and prednisolone 0.3 mg/kg per day. Dosing of cyclosporin (Neoral) was based on 12-h trough levels that aimed to maintain blood concentrations of 80–200 ng/ml (Emit assay). The dose of azathioprine and steroids remained constant. The patient also received the standard supplementary therapy that included nifedipine 10 mg twice daily, ranitidine 150 mg once daily, co-trimoxazole 480 mg twice daily and amphotericin lozenges 4 per day.

The transplant kidney exhibited primary non-function and the patient remained anuric. A duplex ultrasound scan demonstrated thrombosis of the lower pole renal artery with approximately 10 % of the kidney being under-perfused. This was confirmed by a ^{99m}Tc mercaptoacetyl triglycerine (MAG3) isotope scan of the kidney. An ultrasound-guided renal transplant biopsy on the 10th post-transplant day revealed acute tubular necrosis (ATN). The patient was re-commenced on CAPD and maintained a stable creatinine on dialysis of between 470 and 520 μmol/l. Repeat biopsies were performed at 1, 2 and 3 months post-transplant and were con-

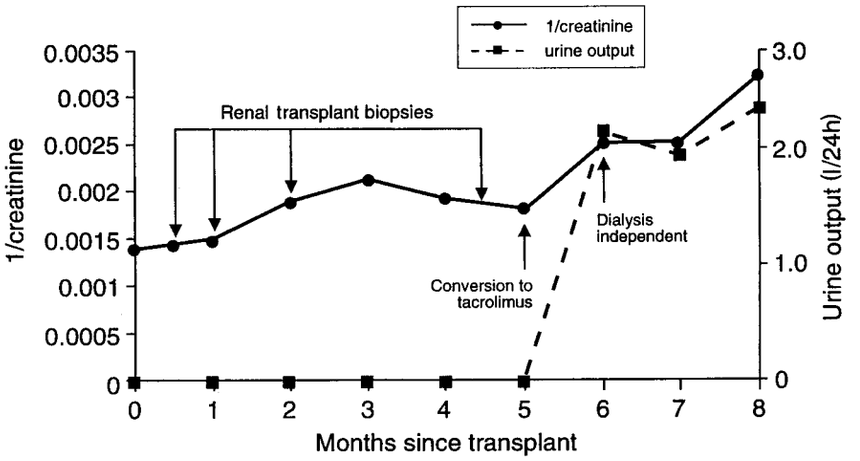

Fig. 1 Graph demonstrating clinical course pre- and post-conversion to tacrolimus

sistent in showing ATN with ischaemic changes but no evidence of acute rejection.

In March 1996, 5 months post-transplant, the patient was still dialysis-dependent and anuric. His creatinine was 548 μmol/l and the cyclosporin dose was 4 mg/kg per day, maintaining trough levels of 156 ng/ml. He was converted to tacrolimus at a dose of 0.15 mg/kg, which was adjusted on the basis of 12-h trough levels (IMX assay) with the aim of maintaining a tacrolimus level of 5–10 ng/ml. Within the 1st week of commencing tacrolimus the creatinine started to fall; urine output increased to around 2 l/day and was maintained at this level. At the end of the 1st month of tacrolimus therapy, creatinine had fallen to 394 μmol/l and the patient's peritoneal dialysis was discontinued. At 4 months post-conversion his creatinine is now 312 μmol/l. His current tacrolimus dose is 0.13 mg/kg per day with a 12-h trough level of 5.6 ng/ml. The clinical course is illustrated in Fig. 1.

Discussion

Acute tubular necrosis (ATN) is a condition of multifactorial aetiology that occurs following ischaemic damage to the transplant kidney either prior to retrieval, during cold preservation or during the re-warming of the kidney at the time of anastamotic construction. The incidence of ATN in cadaveric renal transplantation shows significant variation but would appear to be between 30 % and 50 % [8,11]. A number of factors have been identified as being associated with a high incidence of ATN. They include choice of preservation fluid, donor age, intracerebral haemorrhage as a cause of donor death, donor oliguria, prolonged cold ischaemia time, anastamotic time, number of HLA-DR mismatches, high recipient antibody titres and the requirement of perioperative blood transfusions [1, 2, 4, 6, 7].

The "gold standard" for the diagnosis of ATN is graft ultrasound-guided percutaneous biopsy. Ultrasonographic features suggestive of ATN include a swollen graft with an elevated resistive index and reverse diastolic flow; however, these features may not differentiate from other forms of graft dysfunction. Therefore, a biopsy should be performed as this allows differentiation from rejection and immunosuppression-related nephrotoxicity [6].

The management of ATN relies upon dialysis support and fluid restriction. The period of ATN may last several weeks, during which function is poor. However, with an expectant policy, 65 % of initially oliguric grafts regain function [12]. Several studies have confirmed the role of tacrolimus, both as primary immunosuppression and as rescue therapy in grafts exhibiting refractory rejection [5,9]. However, conversion from cyclosporin to tacrolimus as treatment of ATN has not previously been reported.

The nephrotoxicity of cyclosporin due to renal vasoconstriction and subsequent reduction in glomerular filtration rate is well documented [3]; however, the long-term effects of tacrolimus on renal function are uncertain. A study of systemic and renal haemodynamics in liver transplant recipients treated with either cyclosporin or tacrolimus showed that whilst systemic hypertension was significantly reduced in the tacrolimus-treated patients, there was no difference in the effects of the two drugs on renal blood flow [10]. It is possible that the low drug levels used in this case (0.15 mg/kg per day), which is significantly less than the 0.2–0.3 mg/kg per day used in the early studies of tacrolimus in renal transplantation, may in fact be less nephrotoxic than the standard dose of cyclosporin (4–8 mg/kg per day) used in renal transplant recipients.

This case has illustrated that severe prolonged ATN may resolve spontaneously after several months of careful management. Conversion from cyclosporin to low-dose tacrolimus may have been beneficial in the resolution of the ATN by discontinuing the vasoconstrictive effect of cyclosporin on the renal vasculature. This case also illustrates the importance of an expectant policy for patients with dialysis-dependent primary graft non-

function secondary to ATN. The immediate improvement in serum creatinine following conversion from cyclosporin to low-dose tacrolimus and the subsequent independence from dialysis within a month of changing therapy suggest a potential role for this new immunosuppressive agent in the treatment of patients with prolonged primary non-function who would otherwise be heading towards a nephrectomy. Further prospective trials are required to assess the role of tacrolimus in this setting.

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