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Conversion of renal transplant recipients from cyclosporin to low-dose tacrolimus for refractory rejection

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Abstract Twenty-five patients with refractory rejection following renal transplantation were converted from cyclosporin to tacrolimus in an attempt to salvage the allografts. All patients had received two or three pulses of methylprednisolone, 6 had OKT3, 14 had antithymocyte globulin (ATG) and 2 had both OKT3 and ATG prior to conversion. The median time from transplantation to conversion to tacrolimus was 32 days (range 12–322). Patients underwent a simple switch from cyclosporin- to tacrolimusbased therapy with tacrolimus administered at a median dose of 0.15 mg/kg per day. Doses were adjusted according to clinical response and trough blood levels. Twenty-one of the 25 patients (84%) with refractory rejection showed evidence of reversal of rejection as indicated by a significant reduction in serum creatinine (Student's paired t-test, $P < 0.05$) following conversion to tacrolimus. None of these patients had further episodes of rejection. Three patients had ongoing rejection and returned to dialysis, and 1 patient showed deteriorating renal function associated with a cytomegalovirus infection. Of 18 patients currently on tacrolimus, 15 have improved renal function and 3 have shown no further deterioration. We conclude that low-dose tacrolimus appears to be effective in salvaging renal allografts with resistant rejection.

Key words Kidney transplantation · Tacrolimus · Cyclosporin · Rejection · Steroid-resistant rejection

Introduction

Tacrolimus is a macrolide lactone, derived from the fungus *Streptomyces tsukubaensis*, which has been shown to possess potent immunosuppressive activity both in vitro and in vivo in animal models [8, 12]. Initial studies on the use of tacrolimus in humans confirmed its safety as a rescue therapy for resistant hepatic graft rejection [4, 13] and large multicentre clinical studies have since supported the use of tacrolimus in primary liver allografting [7, 11, 14]. The use of Prograf in kidney transplantation is at present less widespread. However, there is now mounting evidence of its effectiveness in rescue therapy of renal allografts with resistant rejection [1–3, 6, 9]. This paper reports the experience of the Cardiff and Newcastle Renal Transplant Units in conversion of renal allograft recipients with refractory rejection from cyclosporin immunosuppression to tacrolimus-based therapy.

Materials and methods

During the 28-month period from January 1994 to April 1996, 25 renal transplant recipients were converted from cyclosporin-based (Neoral, Sandoz) immunosuppression to tacrolimus (Prograf, Fujisawa) as rescue therapy for refractory rejection. The group consisted of 16 males and nine females, with a median age of 34 years (range 20–58). The initial causes of renal failure are shown in Table 1. Twenty-one patients had received a first kidney transplant (22 cadaveric donor and 3 living related donor) whilst 4 patients

Table 1 Indications for transplantation ($n = 25$)

Cause of renal failure	Number of cases
Chronic glomerulonephritis	5
Diabetic nephropathy	3
Reflux nephropathy	3
Chronic pyelonephritis	3
Focal segmental glomerulosclerosis	2
Polycystic kidney disease	1
Systemic lupus erythematosis	1
IgA nephropathy	1
Chronic tubulointerstitial nephritis	1
Dents disease	1
Toxaemia of pregnancy	1
von Hippel-Lindau disease	1
Unknown	4

were on their second renal allograft. Six patients had greater than 50% panel-reactive cytotoxic antibodies (PRA), the remainder had a PRA less than 30% at the time of transplantation.

Eighteen patients were commenced on standard triple therapy, consisting of cyclosporin 8 mg/kg per day, azathioprine 1.5 mg/kg per day and prednisolone 0.3 mg/kg per day. Three had dual therapy (cyclosporin 8 mg/kg per day and prednisolone 20 mg/day) and 4 patients received cyclosporin monotherapy (8 mg/kg per day). All patients had biopsy-proven acute cellular rejection according to the Banff criteria [10], and changes of vascular rejection were present in 9 patients. The median time of onset of the first rejection episode was 8 days (range 3–63) posttransplantation.

All patients with refractory rejection received methylprednisolone pulse therapy prior to conversion. In addition, 6 of the patients received OKT3, 14 had antithymocyte globulin (ATG) and 2 patients received both OKT3 and ATG. A simple switch was carried out in all patients and tacrolimus was introduced in divided doses starting 12 h after cessation of cyclosporin. The doses were adjusted according to a clinical response and 12-h blood trough levels were measured by the IMX assay [5]. A level above 15 ng/ml was regarded as potentially toxic, particularly in the presence of a low haematocrit and hypoalbuminaemia.

Statistical analysis was carried out using the Student's t-test to detect a difference between pre- and postconversion groups, with significance taken at the 5% level.

Results

The median time from transplantation to conversion to tacrolimus was 32 days (range 12–322) and the median follow-up time postconversion is 9 months (range 1.5–26). The median creatinine at the time of conversion was 488 μmol/l (range 150–1110) and the median current creatinine for all patients is 241 μmol/l (115–1500). Twenty-one of the patients (84%) responded to conversion with either improvement or stabilisation of renal function (Student's t-test) $P < 0.05$). The median reduction in serum creatinine for this group was 196 μmol/l (range 23–688). Four patients (16%) exhibited a deterioration in graft function. Three patients experienced ongoing rejection and returned to dialysis and a 4th patient developed a cytomegalovirus (CMV) infection with associated deterioration in renal function following conversion to tacrolimus.

Eighteen of the patients are currently still on tacrolimus. Fifteen (72%) of these patients have demonstrated a significant reduction in creatinine levels and 3 (12%) have stable renal function with no further deterioration. Of those not currently taking tacrolimus there was a single mortality, an obese diabetic who died suddenly of a pulmonary embolism. Her renal function had improved considerably following the switch to tacrolimus and her creatinine levels had fallen from 721 μmol/l at the time of conversion to 219 μmol/l prior to her death. Four patients failed to respond to conversion (3 ongoing rejection, 1 CMV). One patient with an underlying renal diagnosis of focal segmental glomerular sclerosis and biopsy-proven rejection responded to conversion, but later developed recurrent disease with no evidence of residual rejection on the repeat biopsy. The final patient responded to therapy, but returned to cyclosporin-based immunosuppression because of concerns with regards the cost of the new medication.

No patients have received further pulses of methylprednisolone or antibody treatment following conversion to tacrolimus. Seven patients developed CMV disease following conversion which responded to treatment with gancyclovir in all cases. No other viral or bacterial complications occurred. No non-diabetic patients developed diabetes and blood sugar control posed no problems in the diabetic patients. The median dose of tacrolimus at the time of conversion was 0.15 mg/kg per day (range 0.08–0.37). The current median tacrolimus dose is 0.1 mg/kg per day (range 0.02–0.4) and the current median trough tacrolimus level is 7.6 ng/ml (range 5.2–16).

Discussion

Extensive investigation of tacrolimus in the late 1980's including both in vitro and in vivo studies [8, 12] confirmed its potent immunosuppressive properties and led to its evaluation in the clinical setting. Initial studies examined the role of tacrolimus as rescue therapy in resistant hepatic graft rejection and found it to be successful in salvaging the grafts in 70% of cases [4]. These results were confirmed by a US multicentre study which showed a reduction in the incidence of resistant rejection compared with cyclosporin [13]. The University of Pittsburgh was the first centre to report the use of tacrolimus in the treatment of refractory rejection following renal transplantation [11]. Their experience with the long-term follow up of 169 patients over a 5-year period has shown that tacrolimus was successful in rescuing allografts in 74% of cases [7]. The Kidney Transplanta-

Table 2 The relative costs of tacrolimus (Prograf) and cyclosporin (Neoral) as maintenance therapy in renal transplant recipients (based on median dose levels)

Drug	Dose mg/kg per day	Cost per year for a 75 kg patient
Prograf	0.1	£ 5228.63
Neoral	6.0	£ 4911.08

tion Rescue Study Group recently reported improvement in 78% of cases and stabilisation of renal function in 11% following conversion to tacrolimus [14]. However, a Scandinavian multicentre analysis reported only 52% graft survival in patients converted for refractory acute rejection [3]. Several other centres have also reported their results with varying degrees of success [1, 2, 6, 9].

This study has confirmed the role of tacrolimus in the rescue therapy of resistant renal allograft rejection. Twenty-one of the 25 patients (84%) showed evidence of reversal of rejection as indicated by improvement/stabilisation in renal function following commencement on tacrolimus and 18 of these patients are still maintained on the drug. Of the 18 patients currently on tacrolimus, the drug successfully reversed rejection in 15 patients and has prevented any further deterioration in the other 3 patients. The initial median dosage of tacrolimus was 0.15 mg/kg per day achieving measured drug levels of between 5 and 15 ng/ml and these levels appeared effective in controlling the rejection and preventing further episodes. This dose regimen is significantly lower than the 0.3 mg/kg per day used in some of the previous studies of tacrolimus in renal transplantation and though, in comparison, our study is small we believe that by reducing the trough levels many of the neurological side-effects may be prevented without jeopardising graft function.

Initially there was concern about the cost implications of changing patients to Prograf and indeed 1 patient had their medication switched back to cyclosporin because of financial restrictions. We have found, however, that patients required low maintenance doses averaging 0.1 mg/kg per day, which represents a comparable cost to cyclosporin at our usual maintenance doses of 6 mg/kg per day (Table 2). Interestingly, one of the patients who suffers from long-standing liver cirrhosis secondary to hepatitis C, is currently maintaining his creatinine at 140 μmol/l, having fallen from 710 μmol/l, on a dose of 0.02 mg/kg per day.

In conclusion, this small experience confirms the results of other series in which tacrolimus has been used as a rescue therapy, in that rejection was reversed in 21 out of 25 (84%) patients with severe ongoing renal allograft rejection. We recommend administering a maintenance tacrolimus dose of 0.1 mg/kg per day and not to exceed trough levels above 10 nmol/l since these levels were associated with a significant improvement in renal function without any evidence of FK506-related toxicity and at a cost which is comparable with cyclosporin.

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