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Prospective randomised study comparing tacrolimus (Prograf) and cyclosporin (Neoral) as primary immunosuppression in cadaveric renal transplants at a single institution: interim report of the first 80 cases

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Abstract As part of an ongoing study, 80 patients undergoing cadaveric renal transplantation were randomised to receive either Prograf [PTT (patients receiving Prograf); $n = 40$]- or Neoral [NTT (patients receiving Neoral); $n = 40$]-based immunosuppression as part of a triple therapy regimen. Prograf was commenced at a dose of 0.2 mg/kg per day and Neoral at 8 mg/kg per day. Both groups received identical azathioprine and corticosteroid regimens. Trough levels for Prograf were maintained between 5 and 15 ng/ml and for Neoral between 100 and 200 ng/ml. During the 3-month follow up 40% of PTT and 33% of NTT experienced biopsy-proven acute rejection. In each group 81% of rejection episodes were classified as either borderline or grade 1. The median 3-month serum creatinine levels were 128 μmol/l and 135 μmol/l, respectively, for PTT and NTT. Six grafts were lost in the NTT group including three deaths with functioning grafts whilst none were lost in the PTT group (χ^2, $P < 0.02$). The prevalence of other complications was similar for the two groups. We conclude that Prograf represents an effective and safe therapy as a primary immunosuppressive agent following cadaveric renal transplantation and appears to have a similar side-effect profile to Neoral.

Key words Cyclosporin · Tacrolimus · Kidney transplantation

Introduction

The short-term results of renal transplantation have improved steadily over the past decade, this being attributable to a fall in acute rejection episodes and infectious deaths [5]. However, the annual attrition rate after the first year has changed very little in the "cyclosporin era" and over 25% of grafts are still being lost between 1 and 5 years in the UK [11]. Extensive investigation of tacrolimus in the late 1980's including both in vitro [3, 10] and in vivo studies led to its first reported use by Starzl and colleagues in cadaveric renal transplantation in 1989 [8]. Several multicentre trials [2, 4] have demonstrated tacrolimus (Prograf) to be superior to cyclosporin (Sandimmun) in terms of reduction in the incidence of steroid-resistant acute rejection. However, no study has compared tacrolimus to the new microemulsion formulation of cyclosporin (Neoral). This paper reports the interim results of a prospective randomised controlled trial comparing Prograf and Neoral in cadaveric renal transplant recipients.

Materials and methods

The study is an ongoing open, randomised study, conducted at a single institution, which began in 1996. All patients aged over 16 years of age were eligible for inclusion. During the 14-month period from January 1996 to February 1997, 80 consecutive adult patients underwent cadaveric renal transplantation and were randomised to receive either Prograf (PTT) or Neoral (NTT). Approval was obtained from the local ethics committee and informed consent was obtained prior to transplantation.

In the PTT group, Prograf was administered at a dose of 0.2 mg/kg per day and in the NTT group Neoral was introduced at

8 mg/kg per day with both drugs administered in two divided doses with doses adjusted in accordance with clinical response and 12-h blood trough levels using the IMX assay for Prograf and Emit assay for Neoral. Whole blood trough levels for Prograf were maintained between 5 and 15 ng/ml and for Neoral between 100 and 200 ng/ml. In addition all patients received azathioprine (1.5 mg/kg per day) and prednisolone (20 mg/day). The steroid dose was tapered gradually over a period of 3 months. Rejection episodes were diagnosed clinically according to a 20% deterioration in renal function as assessed by serum creatinine and were confirmed by ultrasound-guided renal allograft biopsy with histological assessment according to the Banff criteria [7].

Statistical analysis was performed using Student's *t*-test to assess differences in the means and the Chi-squared test to detect differences in proportions.

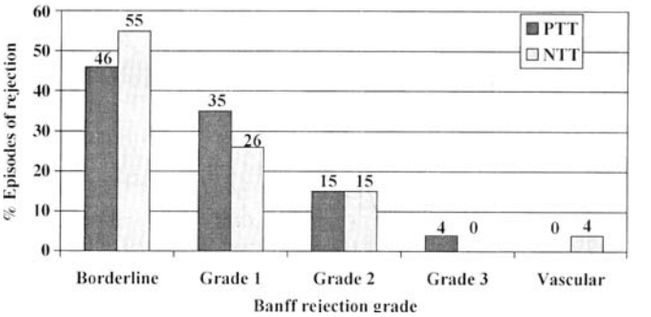

Fig. 1 Distribution of grades of rejection for Prograf *(PTT)* and Neoral *(NTT)* treatment groups

Results

Eighty patients have been included in this interim analysis. Forty were entered into the PTT arm and 40 into the NTT arm of the trial. The two groups were similar for recipient age (median: 44 years versus 48 years), HLA antigen mismatch (median: 2 versus 2), total ischaemic time (median: 18.75 h versus 18.2 h) and there was no difference in the prevalence of delayed graft function between the groups (12% versus 17%). Thirty-two patients were undergoing a first transplantation in the PTT group compared with 34 in the NTT group. The numbers of second (7 versus 5) and third transplants (1 versus 1) were also similar.

Sixteen patients (40%) in the PTT group experienced an acute rejection episode compared with 13 (33%) in the NTT group. All rejection episodes were confirmed by ultrasound-guided biopsy and reported according to the Banff criteria [7]. Patients experiencing rejection in the PTT group suffered a mean of 1.6 episodes per patient compared with 1.8 episodes per patient for the NTT group. The severity of rejection episodes was similar for both groups (Fig. 1) with 81% of patients in each group suffering either a borderline or grade 1 rejection episode. The 3-month serum creatinine levels for PTT and NTT were not significantly different at 128 μmol/l vs 135 μmol/l. Complications were seen more commonly in the cyclosporin group. There were six graft losses in the NTT group and none in the PTT arm. The causes of graft loss included three patients deaths with functioning graft (left ventricular failure, myocardial infarct and pulmonary embolus), one renal artery stenosis, one renal vein thrombosis and one refractory rejection (χ^2, $P < 0.02$).

Infection with cytomegalovirus was seen more frequently in the NTT group (4 vs 0), but not significantly so. The prevalence of postoperative diabetes mellitus was similar for the two groups. In the PTT group, 3 patients developed non-insulin-dependent diabetes mellitus (NIDDM) whilst in the NTT group, 1 patient developed NIDDM and 1 patient now requires insulin for blood sugar control. The 3-month serum cholesterol was lower in the PTT group, but not significantly so (5.6 mmol/l vs 6.6 mmol/l) and there was no difference in blood pressure control as assessed by the antihypertensive index [9] with values of 1.9 for PTT and 1.95 for NTT.

At a follow up of 3 months, 39 out of 40 patients are still receiving tacrolimus, 1 having converted to cyclosporin due to tacrolimus enteropathy. Five patients in the cyclosporin group were converted to tacrolimus due to refractory rejection with a satisfactory outcome in 4 patients and one graft failure.

Discussion

This paper reports the interim results of a single centre randomised study comparing Neoral- and Prograf-based triple therapy immunosuppression in cadaveric renal transplantation. Previous studies had shown that Prograf significantly reduced the prevalence of acute rejection episodes when compared to the Sandimmun formulation of cyclosporin [2, 4], however, no studies had compared Prograf with the microemulsion formulation, Neoral.

The starting dose of 0.2 mg/kg per day in this study is the same as that used in the American multicentre trial [2], but lower than the 0.3 mg/kg per day used in the European study [4] and in the Pittsburgh and Japanese prospective studies of Prograf [1, 6]. In addition, our target trough levels of 5–15 ng/ml, which were the same throughout the study, were less than those recommended in previous studies. These parameters were chosen in an attempt to maximise the immunosuppressive properties of tacrolimus whilst reducing the adverse events.

In the current study we have shown that these two agents have similar results in terms of the 3-month serum creatinine levels and in both the number and severity of acute rejection episodes. The vast majority (81%) of rejection episodes in both the PTT and NTT

groups were either borderline or grade 1 as assessed by the Banff criteria [7]. Previous studies had demonstrated significantly lower acute rejection rates for Prograf compared with Sandimmun. The American multicentre study [2] reported 30.7% vs 46.4%, and the preliminary data from the European study [4] noted acute rejection rates of 19.4% vs 31.3%. The lack of statistical difference in our series (40% vs 33%) may be a reflection of the better absorption of the new microemulsion formulation of cyclosporin.

There was a significantly greater prevalence of graft losses in the Neoral group compared with patients receiving Prograf. There were three deaths with functioning grafts and three grafts were lost, one each to refractory rejection, renal artery stenosis and renal vein thrombosis. The overall graft and patient survival at 3 months for the NTT group was 85% and 93%, respectively, and for the PTT group was 100% in each case. These results are not dissimilar to previously reported series [1, 2, 4, 6] for patients undergoing cadaveric renal transplantation under tacrolimus- and cyclosporin-based immunosuppression.

Whilst the prevalence of acute rejection episodes in the Prograf group was a little higher than in previous studies using higher doses, we did not see any of the dose-related side effects such as neuropsychiatric events. In addition, there was no significant difference in the prevalence of new onset diabetes mellitus in the two groups. Infective complications were observed more commonly in the NTT group with four patients developing cytomegalovirus infections compared with none in the PTT group. Whilst some studies have suggested that Prograf reduces the serum cholesterol levels and improves blood pressure control, neither of these features were demonstrated in this study. We conclude that primary immunosuppression with Prograf starting at a dose of 0.2 mg/kg per day and with target trough levels of 5–15 ng/ml is an effective and safe therapy following cadaveric renal transplantation with a comparable side-effect profile to Neoral.

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