Transpl Int (1998) 11 [Suppl 1]: S322–S324

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A randomised, prospective study on the conversion from cyclosporine–prednisone to cyclosporine–azathioprine at 6 months after renal transplantation

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Abstract In a randomised prospective trial, we studied the effects of replacement of prednisone (Pred) by azathioprine (Aza), 6 months after transplantation, in stable renal allograft recipients on cyclosporine and prednisone (CsA+Pred). Out of 83 patients, 42 started treatment with CsA+Aza and 41 continued therapy with CsA+Pred. CsA was dosed to achieve a level of 150 ng/ml, the Aza dose was 3 mg/kg per day and the Pred dose was 0.15 mg/kg per day. Eighteen months after randomisation, in the CsA+Aza group 18 of the 42 patients were effectively treated with CsA+Aza. In the main, anaemia, leuco- and thrombocytopenia, and hypocorticism necessitated the reintroduction of Pred in the remaining 24 patients. Compared to the continuation of CsA+Pred, conversion of Pred to Aza resulted in a reduced number of antihypertensive drugs needed, and in lower serum total, LDL and HDL cholesterol levels; the incidence of acute rejections and graft losses was no different. In conclusion, conversion of CsA+Pred to CsA+Aza is a safe option in renal transplant patients with contraindications to long-term corticosteroid treatment.

Key words Renal transplantation · Immunosuppressive agents · Cyclosporin · Azathioprine · Prednisone

Introduction

Nowadays, the combination of cyclosporin (CsA) and prednisone (Pred), sometimes supplemented by azathioprine (Aza), is the standard immunosuppressive drug regimen after renal transplantation. With the use of these drugs, graft survival rates are satisfactory. Major concern remains regarding the side effects of these drugs, especially when they are used chronically. Pred is feared for its effects on bone metabolism and skin, and its contribution to hypertension and hyperlipidaemia after transplantation [1, 2, 3]. Previous studies have demonstrated that withdrawal of steroids, resulting in CsA monotherapy, increases the risk of acute rejection [4]. Therefore, other strategies to minimise the long-term side effects of Pred have to be explored. The combination of Csa with Aza was recently shown to provide excellent graft survival [1] and the side effects of Aza are less feared. Based on these considerations, we performed a randomised, prospective trial to study the effects of conversion from Pred to Aza in stable renal transplant patients treated with CsA+Pred at 6 months after transplantation. This paper describes the preliminary results in patients with sufficient length of follow up.

Patients and methods

Patient population

Adult recipients of a first or second renal allograft were eligible for this study if they had stable graft function and were treated with CsA+Pred at 6 months after renal transplantation. The exclusion criteria were: more than two rejections in the first 6 months after transplantation, elevated liver enzymes, leucocytopenia or thrombocytopenia, azathioprine allergy, aged under 18 years, a contrain-

dication to long-term corticosteroid treatment, and receipt of the kidney from an HLA-identical living related donor.

Study design

After they had given informed consent, patients were randomised at 6 months after transplantation to start Aza and gradually stop Pred over a period of 8 weeks or to continue treatment with Pred. Aza was started at a dose of 3 mg/kg per day. The Pred dose before randomisation was 0.15 mg/kg per day; in the CsA+Pred-treated group this dose was left unchanged. In both groups, CsA was dosed to achieve a trough level of 150 ng/ml. If anaemia (haemoglobin < 6 mmol/l), leucocytopenia ($< 3*10^9$/l) or thrombocytopenia ($< 50*10^9$/l) occurred, the Aza dose was adjusted to a minimum of 1.5 mg/kg per day. If, none-the-less, the haematological abnormalities persisted, Aza was stopped and Pred was restarted at a dose of 0.15 mg/kg per day. Patients visited the outpatient clinic at least monthly for the first 6 months after randomisation. Afterwards this frequency was tapered gradually.

Analysis

Clinical and laboratory examinations were carried out as part of routine posttransplant patient care. The results are given as means with standard deviations. Analysis was performed on an intention-to-treat basis, using data collected at 6, 12 and 24 months after transplantation. Unpaired and paired comparisons of numerical data were carried out with Wilcoxon's rank-sum and signed ranks tests. Proportions were compared with chi-squared analysis using continuity correction. A P value less than 0.05 was considered significant. Calculations were performed with the SAS system, version 6.12 (SAS Institute, Cary, N.C., USA).

Results

Eighty-three patients were included in the study and completed a follow up of 18 months. Forty-two patients were allocated to treatment with CsA+and Aza and forty-one patients to continuation of treatment with CsA+Pred. There were no significant differences in clinical characteristics of the patients at the time of randomisation (Table 1). After randomisation, an acute rejection occurred in 1 patient in the CsA+Aza group and in 4 patients in the CsA+Pred group. The latter 4 patients eventually lost their grafts due to chronic rejection, while no graft loss occurred in the CsA+Aza group (NS). Eighteen months after randomisation, 18 of the 42 patients in the CsA+Aza group were still on their originally assigned treatment. The average dose of Aza in these patients was 2.1 mg/kg per day. In 22 of the 42 patients in the CsA+Aza group, treatment had to be changed to CsA+Pred because of anaemia, leucocytopenia or thrombocytopenia (12 patients), symptoms suggestive of hypocorticism (2 patients), a combination of these problems (4 patients) or other reasons (4 patients). Two patients were treated with the combination of CsA + Pred and a relatively low dose of Aza. In the patients of the CsA+Pred group with a functioning graft, no changes in treatment were required. No differences were found between the two treatment groups regarding graft function, haemoglobin, weight and CsA level. In the CsA+Aza group the number of antihypertensive drugs necessary to control blood pressure was lower than in the CsA+Pred group (Table 2). There was a significant

Table 1 Patient characteristics at entry into the study (*CsA* cyclosporin, *Aza* azathioprine, *Pred* prednisone, *NS* not significant, *LRD* living related donor)

	CsA+Aza	CsA+Pred	*P*
No. of patients	42	41	
Age (years)	43 ± 15	47 ± 14	NS
Male/female	31/11	21/20	NS
Weight (kg)	79 ± 14	79 ± 15	NS
LRD/cadaveric	10/32	9/32	NS
Patients with rejections	11	14	NS
Creatinine (μmol/l)	134 ± 33	135 ± 50	NS
Haemoglobin (mmol/l)	8.0 ± 1.2	8.0 ± 0.9	NS
CsA level (ng/ml)	170 ± 60	185 ± 48	NS
Cholesterol (mmol/l)	6.5 ± 1.7	7.0 ± 1.4	NS
MAP (mm Hg)	110 ± 13	114 ± 11	NS
No. of antihypertensive drugs	1.5 ± 0.9	1.4 ± 0.9	NS

Table 2 Results at 24 months after transplantation (intention-to-treat analysis)

	CsA+Aza	CsA+Pred	*P*
No. of patients	42	37	
Creatinine (μmol/l)	144 ± 38	131 ± 28	NS
Haemoglobin (mmol/l)	8.1 ± 1.3	8.5 ± 1.1	NS
Weight (kg)	80 ± 16	83 ± 18	NS
CsA level (ng/ml)	171 ± 54	165 ± 28	NS
MAP (mm Hg)	107 ± 10	111 ± 10	NS
No. of antihypertensive drugs	1.4 ± 1.0	1.9 ± 1.0	< 0.05

Table 3 Lipid profile in CsA+Aza Group (n = 23)

	6 Months	12 Months	*P*
Cholesterol (mmol/l)	6.3 ± 1.7	5.5 ± 1.8	< 0.05
Triglycerides (mmol/l)	1.9 ± 0.8	2.3 ± 1.1	NS
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.1 ± 0.4	< 0.01
LDL cholesterol (mmol/l)	4.2 ± 1.4	3.5 ± 1.5	< 0.05
Ratio cholesterol/HDL	5.3 ± 1.9	5.8 ± 2.2	NS

Table 4 Lipid profile in CsA+Pred Group (n = 25)

	6 Months	12 Months	*P*
Cholesterol (mmol/l)	7.1 ± 1.5	7.4 ± 2.0	NS
Triglycerides (mmol/l)	2.4 ± 1.1	3.0 ± 1.6	NS
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.3 ± 0.4	NS
LDL cholesterol (mmol/l)	4.8 ± 1.3	4.9 ± 1.5	NS
Ratio cholesterol/HDL	5.8 ± 2.1	6.3 ± 2.6	NS

decrease in total, LDL and HDL cholesterol in the CsA+Aza group, but the ratio of total to HDL cholesterol did not change (Tables 3, 4).

Discussion

Our data indicate that in patients treated with CsA+Pred, replacement of Pred by Aza at 6 months after renal transplantation is a safe policy with respect to graft function. This is in accordance with the data of Opelz [1] who demonstrated that graft survival in patients treated with CsA+Aza was equal to or even superior to graft survival in CsA+Pred-treated patients. As cardiovascular events form a major clinical problem after renal transplantation, the observed effects of stopping Pred on several risk factors for cardiovascular disease may be important [5]. Firstly, a significantly lower amount of antihypertensive drugs was used in the CsA+Aza group. Secondly, the levels of total and LDL cholesterol were diminished, which should reduce the risk of cardiovascular diseases. However, these beneficial changes were accompanied by a similar decrease in HDL cholesterol. Since the latter lipoprotein is generally regarded as playing a protective role against atherosclerosis, it remains unclear to what degree the observed cholesterol-lowering effects of Pred withdrawal are beneficial with respect to the cardiovascular risk profile. Unfortunately the design of the study does not allow a detailed comparison of bone metabolism and skin abnormalities between the study groups. With a longer follow up, attention will be paid to the number of symptomatic bone fractures and the incidence of osteonecrosis.

The choice of the initial dose of Aza (3 mg/kg per day) was based on our previous experience with this drug when it was given in combination with Pred [6]. In the current study the combination of the same dose of Aza with CsA resulted in an unexpectedly high incidence of bone marrow depression. Reduction of the Aza dose was necessary in nearly all patients, and in 38% of the patients treatment was discontinued because of anaemia, leucocytopenia or thrombocytopenia. After discontinuation of Aza these signs of bone marrow depression were reversible in all cases. The effectively realised dose of Aza in our study is still somewhat higher than in other studies, where the mean Aza dose is 1.0–1.5 mg/kg per day in CsA+Aza-treated patients [7, 8]. This could account for the lower rejection frequency after steroid withdrawal in our group. One may consider that CsA+Aza is a more potent immunosuppressive regimen than CsA+Pred, and thus might give rise to more infections and malignancies in the long term. We did not find any difference in infection rate between the two groups (data not shown). The follow-up period in this study is too short and the incidence too low to draw any conclusions regarding the malignancy rate. However, no differences in malignancy rate have been described between patients treated with CsA+Pred or with CsA+Pred+Aza. In conclusion, conversion from CsA+Pred to CsA+Aza in renal transplant patients with stable graft function is feasible. In about half of the cases it is a good alternative for patients with contraindications to long-term corticosteroid treatment.

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