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Cyclosporine conversion from triple therapy

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SUMMARY

A pilot study of the role of cyclosporine conversion in triple therapy was undertaken in 30 renal transplant recipients. Actuarial patient survival at one year was 97 % and actuarial graft survival 79 %. Five grafts failed early, two patients were converted before 90 days because of poor graft function and 6 patients were excluded from conversion. Seventeen patients were thus converted at 90 days by increasing azathioprine to 2.5 mg/kg and then stopping cyclosporine over 14 days. Eight patients underwent rejection episodes after conversion, three suffered viral infections and four developed leucopenia requiring azathioprine dose reduction. Acute rejection after conversion occurred in none of the six HLA-DR matched and eight of the eleven — DR mismatched grafts ($p < 0.05$). Conversion from triple therapy can be successfully accomplished but the short term risks might outweigh the long term advantages in recipients of HLA-DR mismatched renal allografts.

Key words: ***Cyclosporine. Kidney transplant. Triple therapy.***

CONVERSION DE TRIPLE TERAPIA A CONVENCIONAL

RESUMEN

Se ha realizado un estudio piloto del papel de la conversión de triple terapia a convencional en 30 receptores de trasplante renal. La supervivencia actuarial del enfermo al año fue del 97 %, y la del injerto, del 79 %. Cinco injertos fallaron tempranamente, dos enfermos fueron convertidos antes de los noventa días por mala función del injerto y seis enfermos se excluyeron de la conversión. Diecisiete enfermos fueron convertidos a los noventa días, aumentando la azatioprina a 2,5 mg/kg., suspendiendo la ciclosporina en catorce días. Ocho enfermos presentaron episodios de rechazo después de la conversión, tres sufrieron infecciones virales y cuatro desarrollaron leucopenia, requiriendo reducción de la dosis de azatioprina. El rechazo agudo después de la conversión no se presentó en ninguno de los seis injertos HLA-DR compatibles, sino que tuvo lugar en los ocho de los once injertos DR no compatibles ($p < 0,05$). La conversión de la triple terapéutica puede realizarse con éxito, pero los riesgos a corto plazo podrían contrapesar las ventajas a largo plazo en receptores de injertos renales HLA-DR incompatibles.

Palabras clave: ***Ciclosporina. Trasplante renal. Triple terapia.***

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Introduction

Development of clinical protocols for the use of Cyclosporine in renal transplantation has been characterised by a trend towards lower dosage both in the short term and in the long term. Calne initially used a dose of 25 mg/kg/day but rapidly discovered how toxic cyclosporine was at that level [1], so the early studies largely used 17.5 mg/kg/day as a starting dose, tapering to 8-10 mg/kg/day by three months. Nephrotoxicity, lymphomas, hypertension, hypertrichosis and gingival hypertrophy were some of the side effects that emerged as reasons for further reduction of cyclosporine doses.

One approach to dose reduction has been conversion from cyclosporine, between one and six months after transplantation, to maintenance immunosuppression with azathioprine and prednisolone. Elective conversion at three months was pioneered in Oxford [2, 3] where two randomised controlled trials demonstrated the advantages and disadvantages of this approach. Further controlled trials have confirmed not only the efficacy of conversion, but also the major disadvantage of a 30 % incidence of acute allograft rejection [4, 5]. While almost all of these rejection episodes have been reversed, a small number of grafts have been lost [3]. Considerable experience in conversion has now accumulated from many centres suggesting that a two week overlap of therapies at conversion is sensible, and that elective conversion should not be undertaken in recipients of regrafts [6].

The second approach to dose reduction has been to combine cyclosporine at reduced dose with both azathioprine and prednisolone at low dose in triple therapy regimens [7, 8]. The major concern with triple therapy was that over-immunosuppression and infection would prove to be significant disadvantages. While at least one of the early pilot studies was truncated because of infection [9], the overall experience has not confirmed these fears and graft survival rates have been high [10].

We have undertaken a pilot study to combine the two approaches to total cyclosporine dose reduction. We have used a triple therapy regimen for the first 90 days followed by conversion to maintenance therapy with azathioprine and prednisolone.

Patients and methods

Thirty consecutive recipients of renal allografts commenced triple therapy immunosuppression. Three patients received single haplotype matched living related grafts and 27 received cadaver grafts allocated by the Australian organ sharing scheme on the basis of the best HLA-B and -DR match. Cyclosporine was started at 12.5 mg/kg/day, azathioprine at 1.5 mg/kg/day and prednisolone at 20 mg/day. During the first 90 days prednisolone doses were unchanged while azathioprine doses were changed only when the whole white cell count dropped. Cyclosporine was reduced to 10 mg/kg/day two weeks after transplantation and thereafter by 1 mg/kg at weekly intervals to achieve a dose of 5 mg/kg. Cyclosporine doses were adjusted on an individual basis to ensure whole blood trough cyclosporine levels within the range of 150 to 400 ng/ml (radioimmunoassay, Immunonuclear Corp., Waverly, Australia). Acute allograft rejection was treated with bolus doses of intravenous methylprednisolone. Acute or acute-on-chronic rejection following conversion was, in addition to methylprednisolone, treated with reinstitution of oral cyclosporine in the majority of cases.

Conversion from triple to double therapy was undertaken 90 days after transplantation by increasing the azathioprine dose to 2.5 mg/kg for one week. The cyclosporine dose was then halved for one week before stopping, so that conversion to azathioprine and prednisolone was planned to take two weeks. Prednisolone doses were subsequently reduced by 1 mg per fortnight to a maintenance level of 10 mg per day.

Prospective assessment of all patients included clinical history and examination, serum biochemistry and routine haematology indices. Renal biopsies were performed routinely 10 days, 90 days and one year after transplantation as well as for the diagnosis of renal dysfunction. The mean length of follow-up after transplantation was 484 days (range 213-679), and after conversion was 396 days (range 120-592).

Statistical analyses were performed by paired t-test, two sample t-test, two way analysis of variance, Fisher's exact test and Kaplan Meier survival curves as appropriate.

Results

The ages, HLA matching and degree of humoral sensitisation of the 30 renal transplant recipients are detailed in Table I. Five grafts were lost before 90 days (Table II). Two patients were successfully converted from cyclosporine before 90 days because of prolonged initial non-function. Six patients were not converted because the decision was taken not to convert recipients of regrafts, patients whose follow-up after conversion would have been inadequate, or those with pre-existing skin cancers contraindicating full dose azathioprine. Thus 17 patients were converted according to protocol. Those who were converted did not differ significantly from the whole group in the characteristics analysed before transplantation (Table I).

Table I. Details of patients at transplantation and the subgroup that was electively converted from triple therapy to azathioprine and prednisolone

Patients, at transplantation (n = 30)

	Mean	SD	Range
Age (years)	44	17	14-66
AB mismatches	1.76	1.15	0-4
DR mismatches	0.66	0.55	0-2
Cadaver 1st graft	n = 25		
Cadaver 2nd graft	n = 2		
Living related donor	n = 3		
Unsensitised	n = 23		
Sensitised (PRA Peak %)	n = 7		(5-70)

Converted patients

	Mean	SD	Range
Age (years)	44	17	14-66
AB mismatches	1.35	0.93	0-3
DR mismatches	0.71	0.59	0-2
Cadaver 1st graft	n = 16		
Living related donor	n = 1		
Unsensitised	n = 13		
Sensitised (PRA Peak %)	n = 4		(5-20)

Table II. Outcome following transplantation in 30 patients commenced on triple therapy

	n
Grafts lost before 90 days	5
Patients converted early	2
Patients not converted	6
Patients converted by protocol	17
Total	30

Overall actuarial one year patient survival was 97 % and graft survival was 79 % (Fig. 1). The single patient death was sudden and unexpected, occuring at home three weeks after graft nephrectomy, and was presumed to be cardiac in origin. Graft loss before 90 days was due to technical problems in two, hyperacute rejection in one, and vascular rejection in two, one of which was complicated by renal artery stenosis.

Actual immunosuppressive therapy in the 17 patients undergoing conversion was close to the protocol design. The mean (± SD) initial dose of cyclosporine was 12.0 mg/kg/day (± 1.2) and azathioprine was 1.6 mg/kg/day (± 0.2). On the day before conversion the mean cyclosporine dose was 4.3 ± 0.8 mg/kg/day with trough whole blood levels of 284 ± 102 ng/ml. Conversion started a mean of 88 ± 11 days after transplantation and was achieved over 14 ± 6 days in

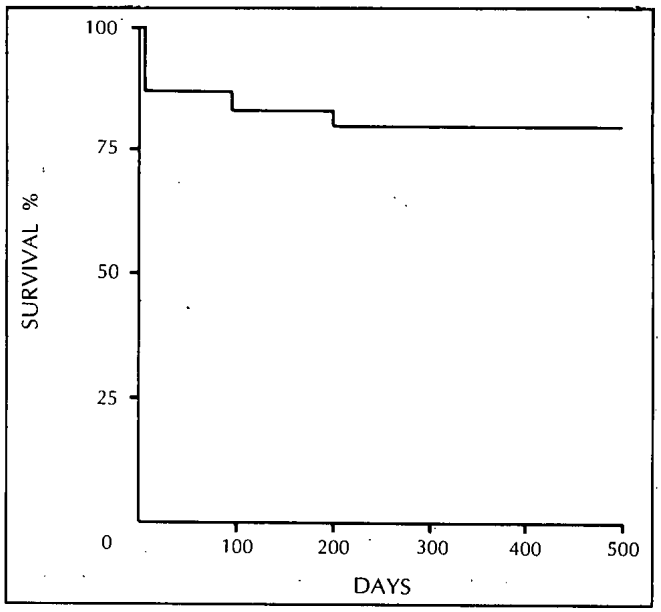

Fig. 1.—Actuarial graft survival in 30 patients commenced on triple therapy with the intention to convert to azathioprine and prednisolone 90 days after transplantation.

16 of the patients. One patient failed to convert fully because of leucopenia when the dose of azathioprine was increased. Myelosuppression was a major problem in three further patients after they had stopped cyclosporine. Of these four patients, two returned to standard triple therapy and two stopped azathioprine entirely remaining on cyclosporine and prednisolone in the long term.

Allograft rejection was encountered in a surprisingly high proportion of the patients (Table III). Eight patients (47 %) had evidence of allograft rejection after conversion. Rejection was diagnosed on clinical criteria alone in one patient and supported by renal transplant biopsy in six. Clinical indication of rejection comprised a progressive rise in serum creatinine in all patients, but the classical syndrome of malaise, pyrexia, hypertension, graft swelling and tenderness did not occur. In one patient routine renal biopsy at one year revealed diffuse focal cellular infiltration indicative of active rejection.

The diagnosis of rejection was made a mean of 113 (± 103, range 27-323) days after conversion. The earliest rejection, at 27 days, occurred in a man who discontinued azathioprine temporarily because of myelosuppression. The majority of the rejection episodes were experienced within three months of conversion, but two were more than six months after apparently successful conversion. Intravenous methylprednisolone was given in three boluses of 0,5 gm to five of the eight patients while oral corticosteroids were increased in two. Cyclosporine was reintroduced in seven of the patients but withheld from one because of a prompt response to methylprednisolone and a biopsy showing moderate interstitial fibrosis.

Table III. Problems associated with conversion in 17 patients converted according to protocol from triple therapy to azathioprine and prednisolone. Patients are listed in order of transplantation date

Patient	Leucopenia Requiring Aza Dose Reduction	Infection After Conversion	Allograft Rejection	Uncomplicated Conversion
1				+
2			+	
3			+	
4			+	
5				+
6	+			
7			+	
8				+
9				+
10				+
11		+		
12			+	
13	+	+		
14	+	+	+	
15				+
16	+		+	
17			+	

One patient (no. 11, Table III) lost her graft after conversion but this was attributed to venous damage from thrombosis and severe vascular rejection occurring during the first 90 days and thus before conversion. The decision to convert the patient was pursued according to the protocol in the hope that cyclosporine nephrotoxicity contributed significantly to allograft dysfunction, but the patient went on to lose her graft. No grafts were lost in the seven patients with good allograft function at the time of conversion but who experienced rejection after conversion. There was no correlation between the number of rejection episodes before conversion and rejection after conversion. Despite the small numbers there was a statistically significant effect of HLA-DR matching. None of the six DR matched grafts were rejected after conversion, while eight of the eleven DR mismatched kidneys did suffer rejection episodes ($p < 0.05$).

Viral infections were seen in three of the seventeen patients after conversion. Cytomegalovirus infection led to self limiting pyrexia and malaise in two patients but the third patient required artificial ventilation for three weeks because of *Influenza pneumonitis.* No patients developed *Pneumocystis carinii* infection at any stage and bacterial sepsis did not complicate conversion in any patients.

Serum creatinine before and after conversion was compared in those patients who successfully stopped cyclosporine, to assess whether conversion from triple therapy affected renal function. The change in mean creatinine for the group (Fig. 2) showed a trend to improvement during the month following conversion ($p < 0.04$, two way analysis of variance; $p < 0.08$, paired t-test day 0 and 28). The renal function in patients converted successfully appeared to be better than in those who continued with maintenance cyclosporine (mean serum creatinine 114 ± 20 µmol/l at six months and 97 ± 24 at one year, compared with 164 ± 78 µmol/l at six months and 148 ± 64 at one year) but these differences were not statistically significant. It was thus possible to discern only a small effect of low dose cyclosporine on renal function at 90 days.

Discussion

The decision to stop the cyclosporine component of triple therapy electively and replace it by immunosuppression with full dose azathioprine and prednisolone balances risks with benefits. The risks tend to be short term and the benefits largely long term and so early follow-up of both controlled and uncontrolled studies must be viewed in that context. In this pilot study of 30 patients, 77 % were eligible for conversion, the remaining 23 % either failing or requiring early conversion. The decision was taken not to convert a group of patients who reached 90 days on triple therapy, thus 56 % were electively converted. Only 20 % were however converted without infection, rejection or myelosuppression.

The penalties of converting from established triple therapy have not been widely examined. The Helsinki group are conducting an interesting study of converting from triple therapy to double therapy with one of the four limbs involving conversion to azathioprine and prednisolone. The preliminary results presented, but not published, at the 3rd congress of the European Society of Organ Transplantation (Gothenberg, 1987) suggested a 33 % incidence of acute rejection when cyclosporine was stopped. From our experience (47 %) we would agree that there is a high incidence of acute or acute-on-chronic rejection following conversion from triple therapy. These figures are as high as or higher than comparable studies where cyclosporine therapy is replaced by azathioprine and prednisolone [11, 12]. The majority of acute rejection episodes reported after conversion from cyclosporine monotherapy have been encountered in the subsequent few weeks, though one report has emphasised poor long term results because of late rejection episodes [13]. It is not clear why there should be a disparity between long term results in Groningen and in the Oxford conversion trials where late rejection was not seen [3, 14]. In our study, rejection experienced after conversion from triple therapy was distinguished not only by the long period between

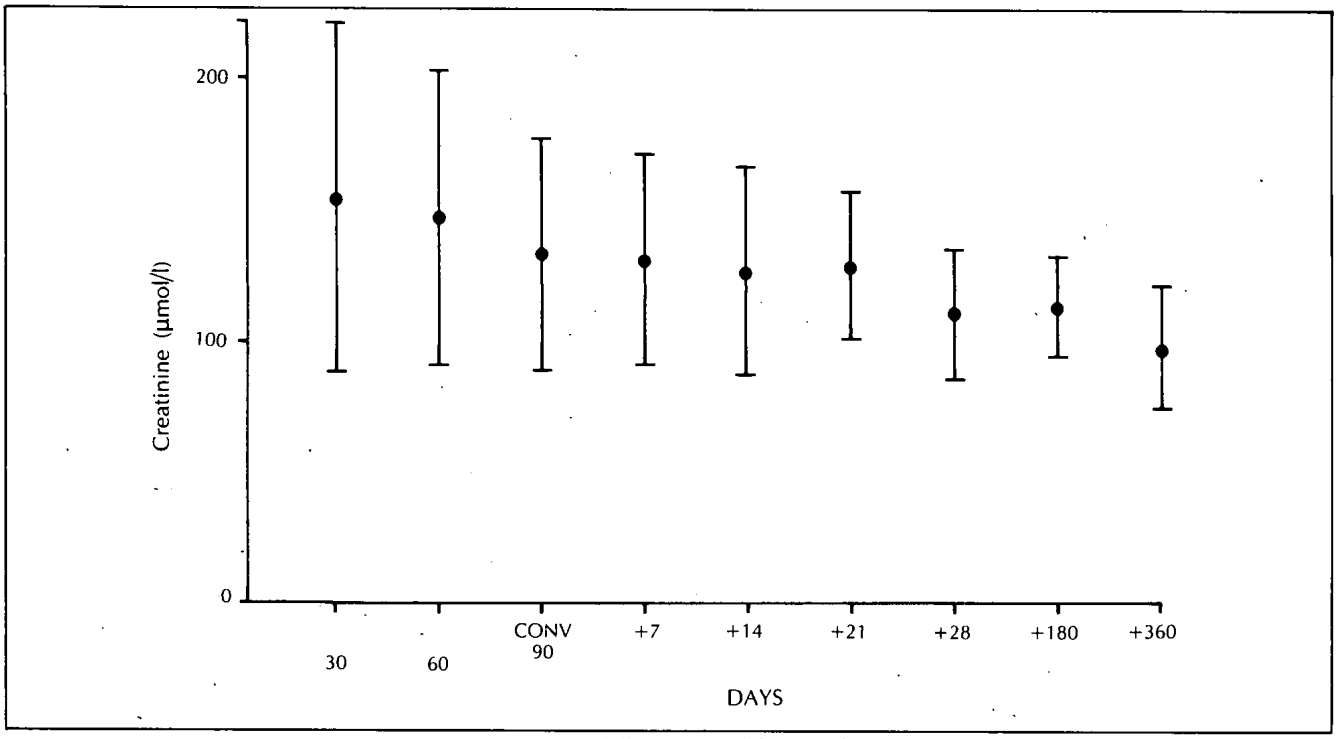

Fig. 2.—Serial serum creatinine (µmol/l) in patients successfully converted from triple therapy to azathioprine and prednisolone at 90 days (n = 8). Mean values (± one standard deviation) are shown at 30 and 60 days after transplantation and immediately before conversion at 90 days, subsequent values are shown as the number of days after conversion.

conversion and rejection, but also by its indolent character. Classical clinical signs of rejection were not apparent in many patients, with slowly rising serum creatinine value and cellular infiltration on graft biopsy as the predominant features. The number of patients is too small and the lack of a control group prevents a firm conclusion, but our pilot study suggests that initial triple therapy could modify the character of rejection seen after conversion. It was interesting that rejection after conversion was restricted to HLA-DR mismatched kidneys, though the small numbers (despite formal statistical significance) suggest that the results of a larger study will be needed to confirm this finding.

The second penalty of conversion to standard doses of azathioprine was myelosuppression which proved to be a significant problem in nearly one quarter of the patients (4 of 17) with two stopping maintenance azathioprine entirely. These infections occurring three months after transplantation may or may not relate to the transient increase in overall immunosuppression caused by our protocol, but virus infection at this time is a common feature in all transplanted patients [15].

Renal function improves after conversion when the cyclosporine dose immediately before conversion is of the order of 10 mg/kg [13, 16] and this is largely explicable on the basis of improved renal blood flow [17]. Our study has shown that marginal improvement in serum creatinine can also be seen after successful conversion from low dose cyclosporine.

In conclusion our pilot study has shown that conversion from triple therapy to azathioprine and prednisolone maintenance is successful and uncomplicated in a proportion of patients. Conversion of HLA-DR matched first graft recipients may confer long term advantages while the short term penalties could outweigh those advantages in recipients of poorly matched first grafts.

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