Transpl Int (1996) 9: 115–125

ORIGINAL ARTICLE

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The beneficial effects of oral nifedipine on cyclosporin-treated renal transplant recipients – a randomised prospective study

Received: 19 May 1995
Received after revision: 11 September 1995
Accepted: 29 September 1995

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Abstract The aim of this study was to test the hypothesis that nifedipine will improve graft survival in cyclosporin A (CyA)-treated renal transplant recipients. One hundred and forty-seven patients were randomised to one of three regimens. Group A received CyA, 7 mg/kg per day, and prednisolone; group B followed the same regimen as group A plus oral nifedipine and group C received CyA, 4 mg/kg per day, prednisolone and azathioprine. Calcium channel blockers were avoided in groups A and C. The crude 2-year ($P = 0.0223$) and 4-year ($P = 0.0181$) graft survival was significantly better in group B (86 % and 81 %, respectively) than in group A (75 % and 63 %, respectively). Delayed initial function was seen least frequently in group B (10.2 %) compared to groups A (31 %) and C (28 %; $P < 0.01$). Group B also experienced fewer rejection episodes than groups A and C ($P < 0.05$). We conclude that the combination of oral nifedipine and CyA significantly improves initial graft function, rejection frequency and long term graft survival.

Key words Nifedipine, CyA, renal transplantation · CyA, nifedipine, renal transplantation · Renal transplantation, nifedipine, CyA

Introduction

Despite the beneficial impact of the widespread use of cyclosporin A (CyA) on solid organ graft survival rates [6, 12], CyA nephrotoxicity remains a significant clinical problem. It may be acute or chronic. Acute CyA nephrotoxicity has three forms: delayed initial graft function, thought to be due to the propensity of CyA to exacerbate renal ischaemic injury [30, 45]; acute reversible impaired graft function, which improves with CyA dose reduction [15, 22, 51] and less commonly an acute arteriolopathy, usually affecting the afferent arterioles, which may be associated with thrombotic microangiopathy [41, 50]. Chronic CyA nephrotoxicity is characterised by progressive irreversible impaired graft function, histologically associated with interstitial fibrosis [35, 39, 40].

Uncertainty about ideal regimens for CyA in kidney transplantation stems from two conflicting interests: the requirement for adequate immunosuppression and the long term risk of CyA nephrotoxicity. Although the mechanism of the nephrotoxicity is not fully defined, a major feature is the induction by CyA of intrarenal vasoconstriction, particularly of the afferent glomerular arteriole [34]. To combat this, therapeutic interventions using a variety of vasodilator agents have been investigated [7, 21, 36, 38, 42]; calcium channel blockade has

proved the most encouraging in experimental and clinical studies [4, 11, 13, 14, 18–20, 23, 24, 32, 33, 43, 46, 53]. Retrospective clinical data from this unit first suggested that renal allograft recipients receiving calcium channel blockers for hypertension had improved graft function as measured by serum creatinine levels [13]. This finding has since been confirmed by other retrospective studies and some preliminary prospective work [14, 18–20, 37, 43].

We present here graft survival, graft function and renal haemodynamic findings of a prospective study comparing our standard immunosuppressive regimen of CyA and prednisolone with two alternative protocols designed to minimise nephrotoxicity: (1) CyA and prednisolone combined with nifedipine and (2) low-dose CyA, prednisolone and azathioprine (triple therapy). Our previous practice had produced a 2-year graft survival of 76 %, which compared favourably with the UK national rate (1983–1989) of 72 % [data provided by the United Kingdom Transplant Support Services Authority (UKTSSA)].

Methods

Subjects

Between 1 February 1989 and 20 August 1992, renal transplant recipients at Leicester General Hospital (LGH) and Walsgrave General Hospital (WGH), Coventry were randomised to one of three regimens. Excluded from randomisation were patients receiving their fourth graft, those with high panel reactivity (> 50 %), known intolerance of one or other immunosuppressive agent, long-term treatment with hepatic enzyme inducers, and two haplotype-matched living related transplants. Approval was given by the Ethical Commitees of both centres.

Treatment groups

After obtaining informed consent, patients were randomised preoperatively on the day of transplantation to one of three regimens. In group A (double therapy), patients were administered CyA (initial dose 17 mg/kg per day, reducing stepwise by 2 mg/kg per day each week to 7 mg/kg per day at 6 weeks) and prednisolone (initial dose 100 mg/day, reducing by 10 mg/day to 40 mg/day at day 7 and reducing to 10 mg on alternate days by 6 months). Patients in group B received CyA and prednisolone as in group A plus oral nifedipine. Those in group C (triple therapy) were given low-dose CyA (initial dose 10 mg/kg per day, reducing stepwise by 1 mg/kg per day each week to 4 mg/kg per day at 6 weeks), prednisolone as in group A and azathioprine (2 mg/kg per day).

Diabetic patients received a modified steroid regime (initial dose 60 mg/day, reducing by 5 mg/day to 30 mg/day at day 7, tailing to a maintenance dose of 5 mg/day at 6 months).

Calcium channel blockers were avoided in groups A and C, other agents being used for blood pressure control. These included atenolol, frusemide, doxazosin and minoxidil. Angiotensin-converting enzyme inhibitors were avoided in all groups.

Group B patients received nifedipine (Adalat Retard) in an initial dose of 10 mg three times per day, increasing to 40 mg twice daily for hypertension as required. In experimental models it has been shown that the ameliorative effect of calcium channel blockade occurs only when present before CyA exposure [32]. The first dose of nifedipine was therefore given pre-operatively approximately 2–3 h before reperfusion, which is within the time frame of maximal serum nifedipine levels from a single oral dose [48].

Graft function parameters

In conjunction with regular haematological and biochemical tests performed as part of the normal patient care, additional studies were conducted. In patients with functioning grafts, measurements of glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and creatinine clearance were made at 1,6,12 and 24 months. GFR and ERPF were measured following a single-shot isotope technique using ^{51}Cr-EDTA and ^{131}I-hippuran and expressed as ml/min per 1.73 m^2. The haemodynamic parameters of renal blood flow (RBF), filtration fraction (FF) and renal vascular resistance (RVR) were then calculated from the GFR and ERPF results as follows: FF = GFR/ERPF; RBF = ERPF/1-packed cell volume; RVR = mean arterial blood pressure/RBF (kPa l^{-1}s). CyA dose, CyA whole blood level and blood pressure were documented at the above time points and a transplant biopsy was performed.

Initial non-function was defined as dialysis dependence at day 4. A rejection episode was defined as impaired graft function in association with histological evidence of rejection requiring additional immunosuppressive treatment. For two such episodes to be classed as separate events, an intervening period of graft function stability (post-treatment return to baseline creatinine level) of 2 months was required.

CyA levels

CyA was measured by high-performance liquid chromatography (HPLC) on a Therapeutic Drug X-Systems Analyser (TDX) using a CyA-specific monoclonal antibody in whole blood in pre-dose trough samples. All patients received CyA at 12-h intervals.

Statistics

The randomisation did not impinge on management freedom to alter antihypertensive medication and CyA dose as indicated by clinical events. All data were therefore analysed on an intention to treat basis.

Patient and graft survival data were analysed. Crude graft survival was calculated in which death with a functioning graft was considered a graft failure. In addition since a substantial number of deaths occurred with a functioning graft, "censored" graft survival was also calculated in which death with a functioning graft was considered as censored data and not an event.

Serial measurements of graft function parameters for surviving grafts were studied by the analysis of summary measures [2, 28], addressing differences between the three groups both in terms of the rate of change of each parameter and of its overall value. The summary measures therefore chosen for an individual patient were (1) the rate of change of the variable (regression coefficient) with time and (2) the mean of all the measurements [2, 28]. Additional parameters monitored by serial measurements (e.g. blood pressure) were also studied by summary measures as above.

Differences in categorical data between the three groups were analysed using chi-squared tests, together with 95 % confidence intervals [2, 47]. Whilst differences in continuous data between the groups were analysed using Student's *t*-tests, the Mann-Whitney U-test and analysis of variance where appropriate [2, 47]. Differ-

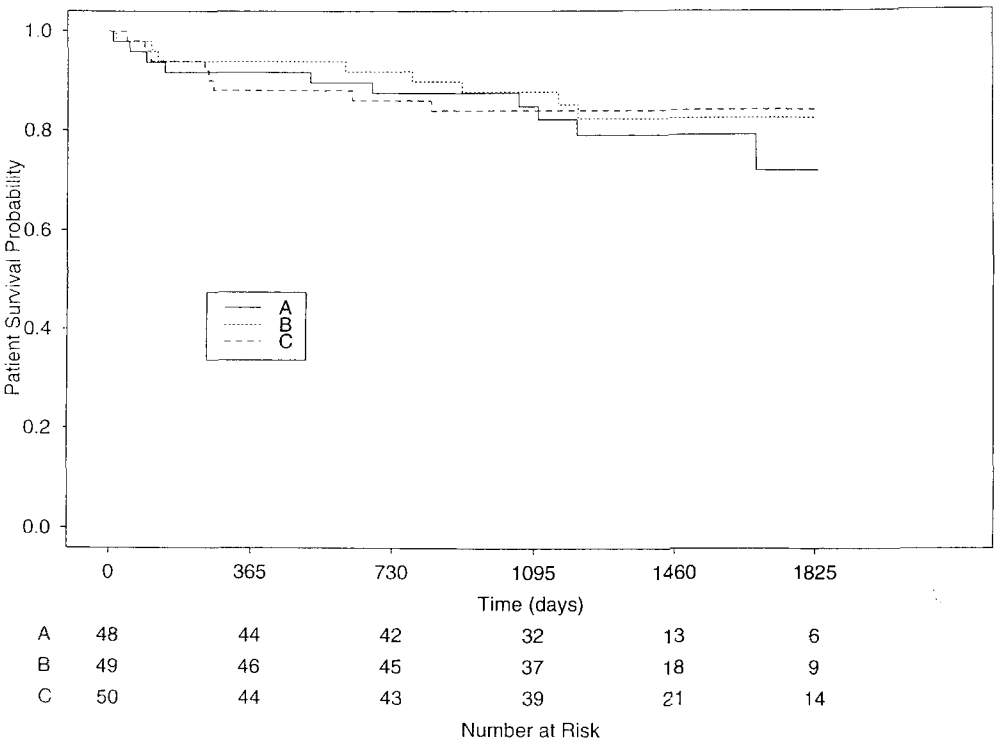

Fig. 1 Kaplan-Meier patient survival curve (—— group A, high-dose CyA and prednisolone; . . . . group B, high-dose CyA, prednisolone and nifedipine; - - - - group C, triple therapy: low-dose CyA, prednisolone, azathioprine)

ences in survival data were displayed using Kaplan-Meier survival curves and analysed using the log-rank test, performed using the SAS statistics package. Values are quoted as mean ± standard error of the mean unless otherwise stated.

Results

One hundred and forty-seven patients were randomised, 108 from Leicester General Hospital (LGH) and 39 from Walsgrave General Hospital (WGH). A similar number were randomised to each group: 48 to group A, 49 to group B, and 50 to group C. Thirteen patients received their second graft (LGH 9, WGH 4) and three patients their third graft (LGH 2, WGH 1). There were six living related transplants, all at LGH (three in group A, one in group B and two in group C). There were a similar number of diabetics randomised to each group (seven in groups A and B and five in group C). Mean follow-up was 4 years (range 2.5–6 years). One patient in group B was intolerant of nifedipine, three patients in groups A and C were given nifedipine for hypertension resistant to all other medication. These alterations from intended protocol all occurred at least 6 weeks after transplantation.

Recipient and donor age, tissue type mismatches, ischaemic times and frequency of vascular and ureteric complications were similar in all three groups (Table 1).

Patient, crude and "censored" graft survival (Table 2, Figs. 1–3)

Patient survival

Two-year and 4-year patient survival did not differ in the three groups (Table 2, Fig. 1). In total there were seven deaths attributable to immunosuppression: pneumonia ($n = 3$), overwhelming systemic infection ($n = 2$), pancreatitis ($n = 1$) and malignancy ($n = 1$).

Table 1 Demographic and other data. Figures in parentheses denote deaths attributable to immunosuppression

Groups	A	B	C	*P* value
Randomised	48	49	50	
Recipient age (years)	45.6 ± 2.3	45.6 ± 2	46.8 ± 2.3	NS
Donor age (years)	40 ± 2.4	39.1 ± 2.2	36.5 ± 2.7	NS
Deaths	10(2)	8(2)	8(3)	NS
Tissue mismatches				
A	0.91 ± 0.1	0.96 ± 0.1	0.96 ± 0.1	NS
B	1.02 ± 0.1	1.08 ± 0.1	1.13 ± 0.1	NS
DR	0.52 ± 0.1	0.71 ± 0.1	0.65 ± 0.1	NS
Ischaemic times				
Total (h)	19.8 ± 1.2	20.6 ± 1.2	20.4 ± 1.1	NS
Anastomosis (min)	33.9 ± 1.2	33.1 ± 1.4	31.5 ± 1.3	NS
Vascular complications	1	2	3	NS
Ureteric complications	6	5	3	NS

Table 2 Survival data. Figures in parentheses indicate 95 % confidence intervals

Groups	UK	A	B	C	*P* value
Patient survival					
2-year	90 % (89 %–91 %)	88 % (79 %–97 %)	92 % (85 %–100 %)	86 % (77 %–96 %)	NS
4-year	82 % (81 %–83 %)	79 % (68 %–93 %)	82 % (72 %–94 %)	84 % (74 %–95 %)	NS
Crude graft survival					
2-year	72 % (71 %–73 %)	75 % (64 %–88 %)	86 %[a] (77 %–96 %)	76 % (65 %–89 %)	= 0.0223[a]
4-year	64 % (59 %–61 %)	63 % (50 %–80 %)	81 %[b] (70 %–93 %)	70 % (58 %–85 %)	= 0.0181[b]
"Censored" graft survival					
2-year	76 % (75 %–77 %)	79 % (69 %–92 %)	92 %[c, d] (85 %–100 %)	78 % (67 %–90 %)	= 0.044[c] = 0.0439[d]
4-year	70 % (71 %–72 %)	74 % (62 %–88 %)	90 %[e, f] (82 %–99 %)	72 % (60 %–87 %)	= 0.0306[e] = 0.0416[f]

[a, b, c, e] Comparisons with group A
[d, f] Comparisons with group C

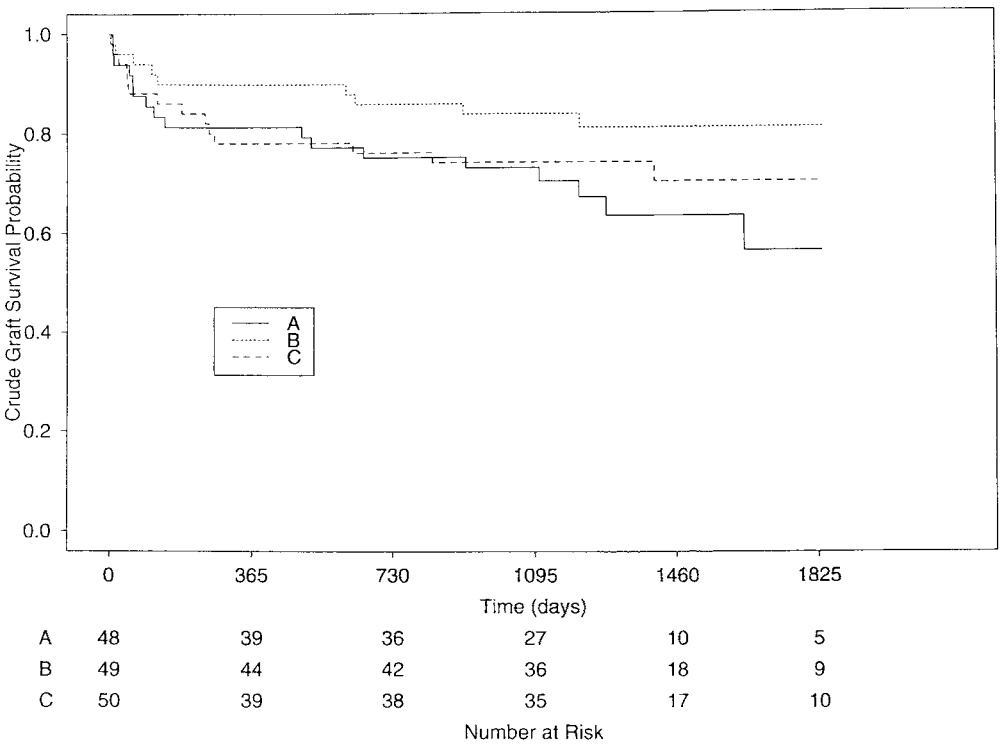

Fig. 2 Kaplan-Meier crude graft survival curve (—— group A, high-dose CyA and prednisolone; . . . . group B, high-dose CyA, prednisolone and nifedipine; - - - - group C, triple therapy: low-dose CyA, prednisolone, azathioprine)

Crude graft survival

In group A, 2-year (75 %) and 4-year (63 %) crude graft survival rates were comparable with national figures: 72 % and 64 %, respectively (UKTSSA). There was no significant difference between 2-year and 4-year crude graft survival rates in groups A and C (Table 2, Fig. 2). However, group B experienced better graft survival at 2 years (86 %, $P = 0.0223$) and 4 years (81 %, $P = 0.0181$) than group A.

"Censored" graft survival

Two-year and 4-year "censored" graft survival in groups A and C were similar. In contrast, group B had significantly better "censored" graft survival than both groups A and C at 2 years ($P = 0.044$ and $P = 0.0439$, respectively) and 4 years ($P = 0.0306$ and $P = 0.0416$, respectively; Table 2, Fig. 3).

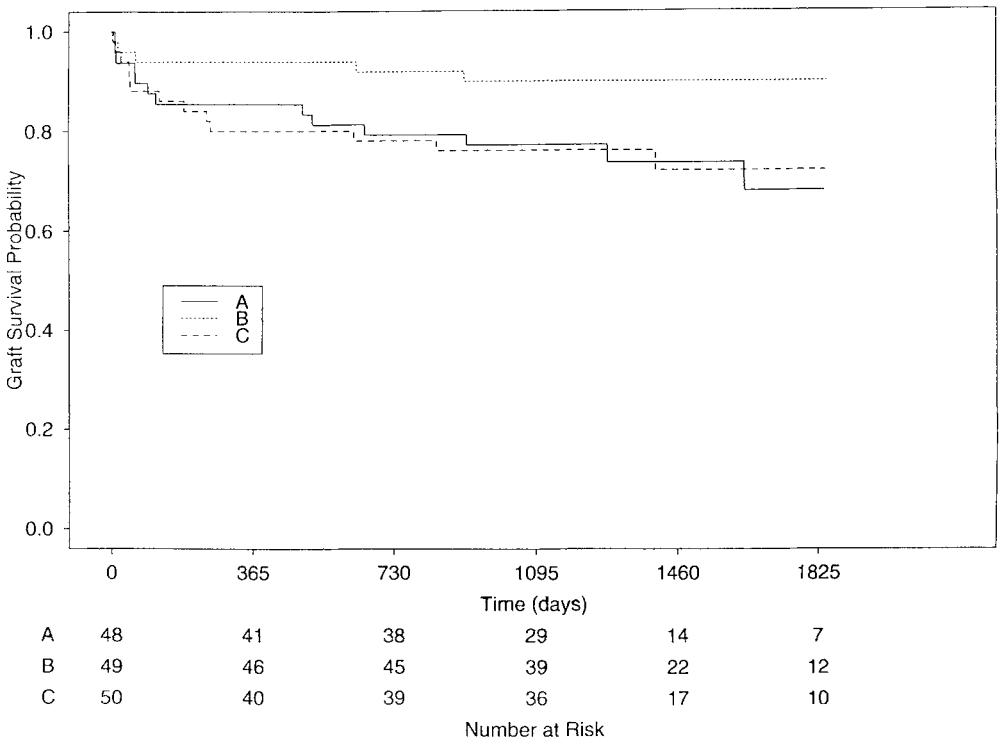

Fig. 3 Kaplan-Meier "censored" graft survival curve (—— group A, high-dose CyA and prednisolone; . . . . group B, high-dose CyA, prednisolone and nifedipine; - - - - group C, triple therapy: low-dose CyA, prednisolone, azathioprine)

Table 3 Initial graft function, rejection and graft failure

Groups	A	B	C	*P* value
Initial non-function	15	5	14	< 0.01
Rejection episodes per patient	0.6	0.33	0.58	< 0.05
OKT3	7	2	7	NS
Technical graft failures	2	2	1	NS
Non-technical immune failures	7	0	7	< 0.01

Graft failures

The number of technical graft failures did not differ in the three groups (Table 3). There were five in total: transplant artery occlusion ($n = 2$), transplant vein thrombosis ($n = 2$) and unresolved obstruction ($n = 1$).

In contrast, there were no immune related failures in group B throughout the period of follow-up ($P < 0.01$ compared to groups A and C; Table 3).

Graft function (Tables 3–5, Figs. 4–6)

Initial graft function (Table 3)

Initial non-function was seen least frequently in group B ($P < 0.01$; Table 3). Only 17 of 34 (50 %) of those individuals who experienced initial non-function still have a functioning graft at the time of writing compared to 93 of 113 (82 %) patients who experienced good initial function ($P < 0.001$).

Serum creatinine (Table 5, Fig. 4)

Serum creatinine concentration in surviving patients was lower in group B than in group A ($P < 0.02$) or group C ($P < 0.04$).

GFR (Tables 4, 5; Fig. 5)

In surviving grafts the overall GFR in group C was significantly greater than in group A ($P < 0.05$), although group C did not differ from group B.

ERPF, creatinine clearance and filtration fraction (Tables 4, 5)

No difference was shown in either the overall value of these parameters or in their rate of decline with time between the three groups.

Table 4 Rate of change of graft function variable with time (*GFR* glomerular filtration rate, *ERPF* effective renal plasma flow, *RVR* renal vascular resistance)

Groups	A	B	C	*P* value
GFR (ml/min per 1.73 m^2/month)	−0.21 ± 0.11	−0.11 ± 0.08	−0.21 ± 0.08	NS
ERPF (ml/min per 1.73 m^2/month)	−0.22 ± 0.4	−0.23 ± 0.4	−0.06 ± 0.3	NS
Creatinine clearance (ml/min per month)	−0.13 ± 0.16	−0.01 ± 0.1	−0.19 ± 0.13	NS
Filtration fraction (per month)	−(14.5 ± 5.1) x 10^{-4}	−(7.1 ± 3.4) x 10^{-4}	−(4.1 ± 4.1) x 10^{-4}	NS
RVR (kPa l^{-1} · S per month)	(6.4 ± 12.2) x 10^{-3}	−(5.7 ± 6.5) x 10^{-3}	(9.6 ± 88) x 10^{-3}	NS

Table 5 Overall value of graft function variable (*GFR* glomerular filtration rate, *ERPF* effective renal plasma flow, *RVR* renal vascular resistance)

Groups	A	B	C	*P* value
Serum creatinine (μmol/l)	267 ± 25.4	191 ± 16[a, b]	274 ± 35	< 0.02[a] < 0.04[b]
GFR (ml/min per 1.73 m^2)	39.4 ± 2.1	43.9 ± 1.9	46.8 ± 2.3[c]	< 0.05[c]
ERPF (ml/min per 1.73 m^2)	211 ± 19.7	234 ± 8.9	241 ± 15.2	NS
Creatinine clearance (ml/min)	43.2 ± 3.8	50.5 ± 2.9	53.5 ± 4.2	NS
Filtration fraction	0.199 ± 0.014	0.191 ± 0.007	0.211 ± 0.009	NS
RVR (kPa l^{-1} · s)	0.404 ± 0.023	0.292 ± 0.012[d]	0.32 ± 0.012[e]	= 0.009[d] = 0.011[e]
Mean blood pressure (mm Hg)	102.4 ± 2.3	103.9 ± 1.8	102.3 ± 1.9	NS
Maintenance CyA dose (mg/kg per day)	5.4 ± 0.3	6.5 ± 0.2[f]	4.4 ± 0.2	= 0.003[f]
CyA levels (ng/ml)	249.8 ± 18	300 ± 22[g]	190.1 ± 14.8	= 0.085[g]

[a, c, d, e, f, g] Comparisons with group A
[b] Comparison with group C

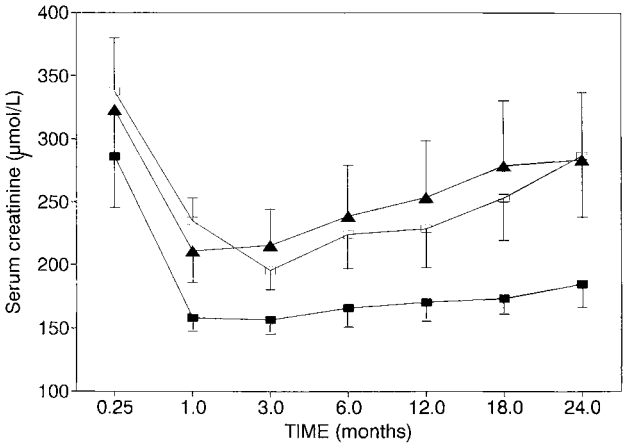

Fig. 4 Serum creatinine concentration in surviving patients. Mean and error bars. (□ group A, high-dose CyA and prednisolone; ■ group B, high-dose CyA, prednisolone and nifedipine; ▲ group C, triple therapy: low-dose CyA, prednisolone, azathioprine)

RVR (Tables 4, 5; Fig. 6)

Although no difference was apparent in the change in RVR with time between the three groups, the overall value of RVR was significantly lower in group B ($P = 0.009$) and in group C ($P = 0.011$) than in group A.

Blood pressure control (Table 5, Fig. 7)

There was no significant difference in mean blood pressure [(2 × diastolic pressure + systolic pressure)/3] between the three groups at any time point.

CyA dosage (Table 5, Fig. 8)

The mean CyA dose received by groups B and C was very close to that intended in the initial protocol. However, the group A CyA dose was slowly reduced for clinical reasons (mainly nephrotoxicity); by 24 months group A received very similar CyA doses to group C. Overall, group B received significantly more maintenance CyA (after 6 weeks post-transplant) than group A ($P = 0.003$).

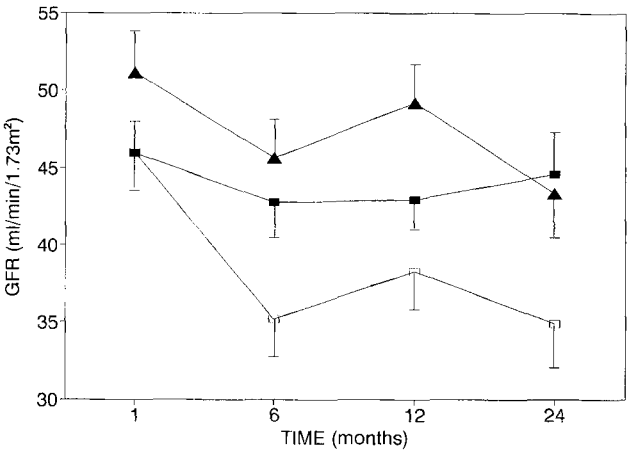

Fig. 5 Glomerular filtration rate in surviving grafts. Mean and error bars. (□ group A, high-dose CyA and prednisolone; ■ group B, high-dose CyA, prednisolone and nifedipine; ▲ group C, triple therapy: low-dose CyA, prednisolone, azathioprine)

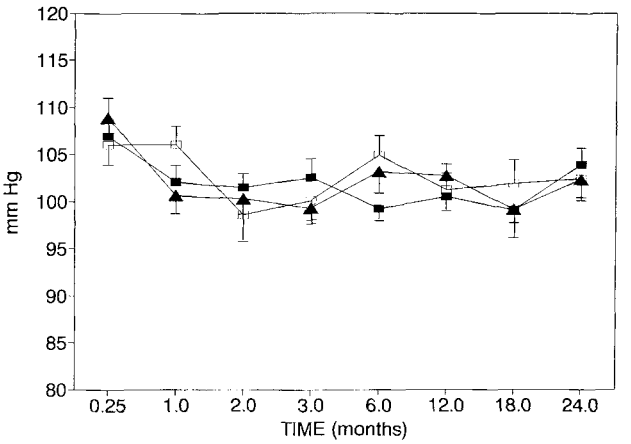

Fig. 7 Mean blood pressure in patients with surviving grafts. Mean and error bars. (□ group A, high-dose CyA and prednisolone; ■ group B, high-dose CyA, prednisolone and nifedipine; ▲ group C, triple therapy: low-dose CyA, prednisolone, azathioprine)

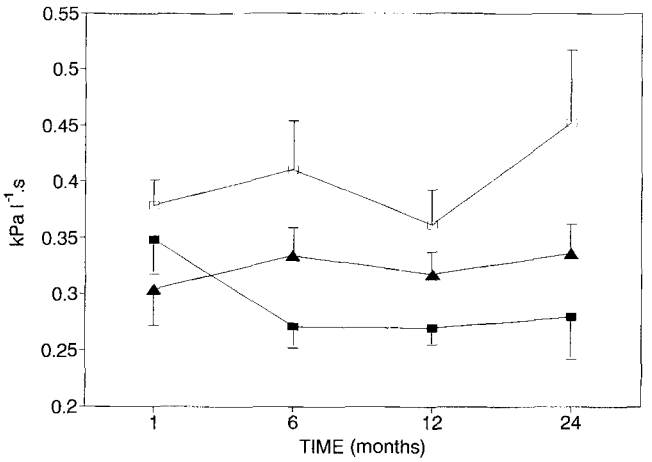

Fig. 6 Renal vascular resistence in surviving grafts. Mean and error bars. (□ group A, high-dose CyA and prednisolone; ■ group B, high-dose CyA, prednisolone and nifedipine; ▲ group C, triple therapy: low-dose CyA, prednisolone, azathioprine)

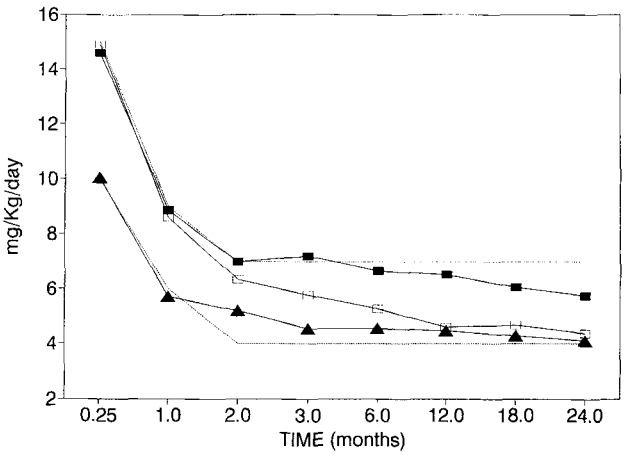

Fig. 8 Cyclosporin dose received. Mean and error bars. (□ group A, high-dose CyA and prednisolone; ■ group B, high-dose CyA, prednisolone and nifedipine; ▲ group C, triple therapy: low-dose CyA, prednisolone, azathioprine; .... intended regimen for groups A and B; —— intended regimen for group C)

CyA levels (Table 5, Fig. 9)

Whole blood CyA levels were higher in group B than in group A in the maintenance period (after 6 weeks). However, this difference did not reach conventional significance levels ($P = 0.085$).

Rejection episodes (Table 3)

Rejection episodes were least frequent in group B ($P < 0.05$). This was reflected in the smaller number of patients requiring OKT3 treatment in group B, although this difference was not significant.

Only 37 of 58 (64 %) patients who had at least one rejection episode have a functioning graft at the time of writing compared to 75 of 89 (84 %) patients who did not experience rejection ($P < 0.01$).

Transplant histology

In addition to routine histological assessment, all biopsies underwent morphometric analysis to define interstitial volume. A significantly lower interstitial volume (indicative of less interstitial fibrosis) was seen in biopsies of patients in group B than in groups A and C.

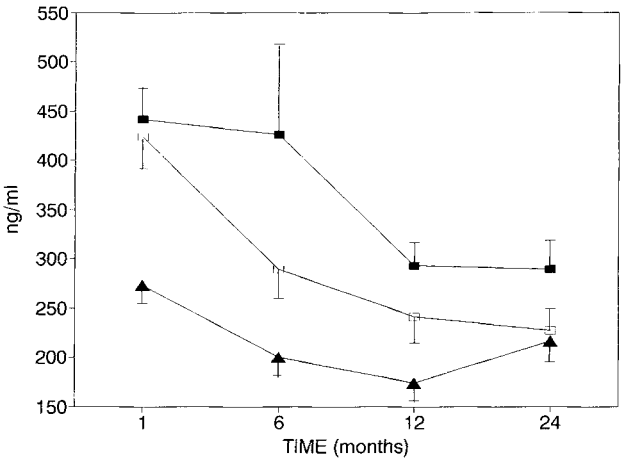

Fig. 9 Cyclsporin whole blood levels. Mean and error bars. (□ group A, high-dose CyA and prednisolone; ■ group B, high-dose CyA, prednisolone and nifedipine; ▲ group C, triple therapy: low-dose CyA, prednisolone, azathioprine)

These findings have been reported in detail elsewhere [29].

Comparison of the results in the two study centres

There were no significant differences in patient or graft survival or in any other parameter between the two centres (data not shown). There is therefore no evidence of a "centre effect" that might influence interpretation of the results of this study.

Discussion

Continuing clinical experience with CyA in renal transplantation has highlighted the tension between the need for adequate immunosuppression and the prevention of CyA nephrotoxicity. One approach has been to minimise the dose of CyA with additional azathioprine, but there is no compelling evidence that such triple therapy is superior to CyA and steroids in long-term graft outcome (5, 8, 25, 44).

This study assessed an alternative approach – the use of the calcium channel blocker nifedipine to minimise nephrotoxicity without the need to reduce CyA dosage. This strategy is based on the evidence that CyA nephrotoxicity is due, at least in part, to intrarenal vasoconstriction particularly affecting the afferent glomerular arteriole which, in the short term, produces reversible functional change but, in the long term, produces irreversible change associated with interstitial fibrosis [15, 35, 39, 40, 51]. Calcium channel blockers are a logical choice of vasodilator to minimise these effects since their dilator influence is chiefly at the afferent arteriole [27]. Moreover, their effect is more marked when the afferent arteriole is pre-constricted (as will occur with CyA) than when tone is normal [27]. Calcium channel blockers have additional effects that may be of benefit in renal transplantation: they are modestly immunosuppressive [16] and also may favourably influence the ischaemia reperfusion injury [9] that is unavoidable in cadaveric renal transplantation.

Nifedipine was chosen for this study since it is known not to influence CyA metabolism, in contrast to most other calcium channel blockers of the dihydropyridine and other classes [31]. The study design was simple: nifedipine was given orally in addition to an immunosuppressive regimen (CyA and prednisolone double therapy) that represented standard practice in the Leicester unit at the time this study was initiated (1989). Nifedipine was started pre-operatively and continued long term even if the patient was normotensive. Calcium channel blockers were avoided completely in the other study groups. The study compared two strategies for minimising nephrotoxicity: the addition of nifedipine to double therapy and a reduced dose of CyA (without nifedipine) in triple therapy.

While the dose of CyA used in our double therapy regimen would now be thought unusually high by many investigators (initially 17 mg/kg, falling to a maintenance dose of 7 mg/kg), it represented the standard first choice regimen in the Leicester unit at the time this study was initiated, it had produced satisfactory results in our hands in the period 1983–1988 (crude 2-year graft survival 76 %) and it continued to do so during the study (2- and 4-year crude graft survival 75 % and 63 %, respectively, in group A).

Recruitment to the study was restricted as little as possible in order to assess the wide applicability of the study regimens in clinical practice and included those receiving first, second and third cadaver grafts, diabetics and living related transplants with a one haplotype match. Exclusions were chiefly those recipients in whom we wished to individualise the immunosuppressive regimen.

The use of oral nifedipine in this study had a number of beneficial effects. Although there was no difference in patient survival between the three study groups, graft survival was improved. Crude graft survival in the nifedipine group at 2 years (86 %) and 4 years (81 %) was significantly better than in group A. This improved graft survival was not achieved with triple therapy. A key factor appears to be that none of the 49 patients in the nifedipine group had a graft loss attributable to immune failure during the period of follow-up of 2.5–6 years (mean 4 years). Nor was graft survival in the double and triple therapy groups unusually low, producing misleading comparisons: 2-year graft survival in these groups of 75 % and 76 % compares favourably with the outcome in our own unit in

the 5 years before this study (76%) and with UK national figures for the same period of 72%. Two-year "censored" graft survival compared favourably in all three groups with UK national data (76%) and was significantly better in group B than in the double or triple therapy groups.

The improved long-term graft survival is consistent with morphology of the routine transplant biopsies performed in this study. Interstitial volume was measured morphometrically as an indicator of interstitial fibrosis and was significantly less at 6 months in the nifedipine group than in either the double or triple therapy group [37].

Renal function was measured with several parameters. Serum creatinine was consistent with graft outcome since it was significantly lower at 2 years in the nifedipine group. In apparent contradiction, GFR was higher in the triple therapy group than in the double therapy group, with GFR in the nifedipine group intermediate and not significantly different from either the double or triple therapy group. It should be noted however that serum creatinine was measured in all surviving patients, including those whose grafts had failed and had returned to dialysis; it therefore reflected the renal function of the whole group. By contrast, isotopic measurements of renal function were only made in patients with functioning grafts, excluding those whose grafts had already failed, and therefore do not reflect the renal function of the whole group.

Nevertheless, although GFR and ERPF in survivng grafts were not improved at 2 years in the nifedipine group, calculated RVR was significantly lower, consistent with the presumption that one aspect of the benefit of nifedipine is lessening of the afferent glomerular arteriolar vasoconstriction induced by CyA.

Two of the most important arbiters of good graft outcome are initial graft function [8, 49] and prevention of early acute rejection [1, 3, 17, 26]. In this study initial non-function was associated with a 2.7-fold risk of graft failure or death, at least one rejection episode was associated with a twofold risk. The beneficial effect of nifedipine appears to extend beyond the amelioration of vasoconstrictive nephrotoxicity, since nifedipine influenced the frequency of both these adverse factors. Initial non-function occurred in only 10.2% of the nifedipine group, significantly lower than in the two groups not receiving a calcium channel blocker. This confirms the preliminary data from this study published elsewhere [18] and the findings of another retrospective study [14]. In the present study, nifedipine was first given to the recipient pre-operatively; there was no specific management of the retrieved cadaver kidneys. Although the addition of other calcium channel blocking drugs (diltiazem, verapamil) to the perfusion fluid used at retrieval has been shown to improve primary function rates [10, 52], this approach has the disadvantage that it would require standardisation of retrieval procedures to ensure widespread benefit, compared to the simplicity of oral treatment for the recipient.

The number of rejection episodes was also significantly reduced in the group receiving nifedipine compared to double or triple therapy, and this was reflected in the absence of any immune graft failures during follow up in the nifedipine group. Nifedipine is itself modestly immunosuppressive [16], but the use of nifedipine also allowed a larger maintenance dose of CyA to be sustained throughout the study. Although it was intended that the double therapy group should receive the same maintenance dose of CyA (7 mg/kg) as the nifedipine group, it proved necessary to make dose reductions due to CyA nephrotoxicity in the double therapy group so that achieved maintenance dosage (mean 5.4 mg/kg) on double therapy was not significantly different from that intended and achieved on triple therapy (mean achieved dose 4.4 mg/kg). Rejection episodes did not differ between double and triple therapy despite additional azathioprine and equivalent CyA dosage.

This study shows worthwhile clinical benefits when oral nifedipine is given to renal transplant recipients treated with CyA. This prospective randomised study has confirmed the evidence from published retrospective and short-term prospective reports [13, 14, 18–20, 37, 43]. Benefits have been demonstrated in immediate and long term graft function, graft morphology and graft outcome. It is likely that the main positive influence of nifedipine is to minimise vasoconstrictive CyA nephrotoxicity, thus allowing a higher maintenance dose of CyA to be used and reducing the incidence of rejection. There is also important benefit in improved initial graft function.

The use of nifedipine is simple, safe and cheap, and the majority of CyA-treated renal transplant patients will, in any case, require hypotensive therapy. We recommend that oral nifedipine be part of the routine medication of renal transplant recipients who receive CyA.

Acknowledgements SJH is a Wellcome Trust Advanced Training Fellow (grant 034937/91) and was in receipt of additional financial support for this study from the BMA Elizabeth Wherry Award and Bayer UK Ltd. JM is supported by Bayer UK Ltd. UK national statistics were prepared by the UK Transplant Support Service Authority from the National Transplant Database maintained on behalf of the UK transplant community. The authors are grateful to Dr. Nick Taub, Department of Epidemiology and Public Health, University of Leicester, for additional statistical advice, and to Natu Mistry and Steve Watson for measuring CyA levels.

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