



THE LANCET

Volume 356, Issue 9225, 15 July 2000, Pages 194-202

doi: [10.1016/S0140-6736\(00\)02480-8](https://doi.org/10.1016/S0140-6736(00)02480-8) [Cite or Link Using DOI](#)

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Articles

Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study

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Available online 24 July 2000.

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Sirolimus and ciclosporin for renal transplantation, *The Lancet*, Volume 356, Issue 9225, 15 July 2000, Pages 179-180

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Abstract

Background Acute rejection episodes after renal transplantation are an important clinical challenge, despite use of multidrug immunosuppressive regimens. We did a prospective, multicentre, randomised, double-blind trial to investigate the impact of the addition of sirolimus, compared with azathioprine, to a ciclosporin and prednisone regimen.

Methods 719 recipients of primary HLA-mismatched cadaveric or living-donor renal allografts who displayed initial graft function were randomly assigned, after transplantation, sirolimus 2 mg daily (n=284) or 5 mg daily (n=274), or azathioprine (n=161). We assessed the primary composite endpoint of efficacy failure, occurrence of biopsy-confirmed acute rejection episodes, graft loss, or death, and various secondary endpoints that characterise these episodes at 6 months and 12 months. Analyses were done by intention to treat.

Findings The rate of efficacy failure at 6 months was lower in the two sirolimus groups (2 mg 18.7%, p=0.002; 5 mg 16.8%, p<0.001) than in the azathioprine group (32.3%). The frequency of biopsy-confirmed acute rejection episodes was also lower (2 mg 16.9%, p=0.002; 5 mg 12.0%, p<0.001; azathioprine 29.8%). At 12 months, survival was similar in all groups for grafts (97.2%, 96.0%, and 98.1%) and patients (94.7%, 92.7%, and 93.8%). Patients on sirolimus showed a delay in the time to first acute rejection episode and decreased frequency of moderate and severe histological grades of rejection episodes and related antibody treatment, compared with the azathioprine group. Rates of infection and malignant disorders were similar in all groups.

Interpretation Use of sirolimus reduced occurrence and severity of biopsy-confirmed acute rejection episodes with no increase in complications. Further studies are needed to establish the optimum doses for the combined regimen.

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Introduction

Acute rejection episodes continue to present an important clinical challenge in renal transplantation. Despite the use of multidrug immunosuppressive regimens, 20–40% of recipients have these events, which increase health-care costs and probably represent an important risk factor for chronic allograft failure.[\[1, 2, 3 and 4\]](#)

In-vitro and in-vivo studies suggest that sirolimus with ciclosporin act in a complementary way.[\[5\]](#) Ciclosporin, a cyclic endecapeptide, inhibits the cytosolic enzyme calcineurin, [\[6\]](#) which dephosphorylates critical intermediates after antigen-driven cell activation (signal 1), including the nuclear factor of activated T lymphocytes, a regulatory protein that promotes transcription of proinflammatory cytokine genes encoding interleukins 2, 4, 7, 9, and 15, and interferon gamma. [\[7\]](#) The calcineurin inhibition is, however, only partial and is further mitigated by co-stimulation via the ciclosporin-resistant CD28 and CD154 signal 2 pathways. [\[1\]](#) By contrast, sirolimus blocks a regulatory kinase that participates in transduction of signals delivered by CD28 and T-cell growth-factor receptors (signal 3). [\[8\]](#) Although sirolimus monotherapy produces potent immunosuppression in animals, [\[9\]](#) and combination with azathioprine and prednisone gives moderate rejection prophylaxis in human beings, [\[10\]](#) more powerful, perhaps synergistic, effects are seen when the drug is combined with ciclosporin. [\[5 and 11\]](#) Therefore, we did a phase III multicentre, randomised, double-blind, pivotal trial of human renal transplantation to compare the potency of sirolimus with that of azathioprine in combination with a baseline ciclosporin microemulsion and prednisone regimen.

Methods

Patients

Eligible patients had end-stage renal disease, were aged 13 years or older, and weighed at least 40 kg. Women of childbearing age with a negative pregnancy test before study medication was started were eligible. We required that patients had white blood cell counts of $4 \times 10^9/L$ or more, platelet counts of $100 \times 10^9/L$ or more, triglyceride concentrations of 5.65 mmol/L or less, and cholesterol of 9.05 mmol/L or less. We excluded patients who had evidence of systemic infection, angina, myocardial infarction in the previous 6 months, or continuing maintenance therapy for life-threatening arrhythmia. Additional exclusion criteria included history of malignant disease, investigational drug use in the previous 4 weeks, use of immunosuppressive agents before transplantation, concomitant treatment with cytochrome P450 inducers or inhibitors,

Statistical analysis

Previous phase II multicentre studies showed an 18% rate of efficacy failure at 6 months for patients with sirolimus, ciclosporin, and prednisone[17] and 36% for a group who received azathioprine, ciclosporin, and prednisone. [12] We therefore calculated, by the method of Fleiss, [18] that we would need sample sizes of 234 patients in each sirolimus group and 117 patients in the azathioprine group to show a significant difference in the endpoint between the results of unequal-sized groups and to achieve a Bonferroni correction at a significance level of 0.025 and 90% power. To preserve an overall significance level of 0.05 for the entire trial, the Bonferroni correction was necessary because of the two pair-wise comparisons—sirolimus 2 mg daily with azathioprine and sirolimus 5 mg daily with azathioprine. We enrolled more patients than the required 600 to enable assessment of the safety of sirolimus. We did the study according to the principles established by the US Code of Federal Regulations, with the assistance of an independent drug safety monitoring board.

We included all randomised patients in the analysis by intention to treat, irrespective of whether study medication had been administered. The primary endpoint of the study was binary—patients either achieved the endpoint or they did not. Accordingly, we used the Cochran-Mantel-Haenszel method to compare each dose of sirolimus with azathioprine. The standard Cochran-Mantel-Haenszel method allows the comparison of the rates of endpoint for two groups while stratifying by the values of a third variable. Analysis of the primary endpoint was stratified by investigator. We used the Breslow-Day statistic to test the homogeneity of treatment effect across levels of the stratification factor used in the Cochran-Mantel-Haenszel test. A significant value of this statistic shows that there is at least one stratum treatment effect that is not consistent with the treatment effects seen in the other strata.

For the secondary analyses we used the Kaplan-Meier method to estimate the time to event; log-rank tests for survival of patients, graft failure, and first occurrence of an acute rejection episode; Fisher's exact test (with 95% CI) for binary events and frequency of events; and logistic-regression analyses to assess the impact of factors other than sirolimus on the occurrence of acute rejection episodes. Relative risk with 95% CI for the occurrence of an acute rejection episode was used to test the null hypothesis: a relative risk of 1 showed no difference, whereas a relative risk of less than 1 showed that the dose of sirolimus was more effective than azathioprine. The comparison of the histological severity of rejection in renal-allograft biopsy samples used a row means score statistic (generalised Cochran-Mantel-Haenszel method)[19] that compared the three rows of study treatments for distribution across the ordered response classifications. We used ANCOVA to compare patients' baseline measurements between treatment groups, and ANOVA for mean values of graft-function variables, since pretreatment values reflected the renal disease. In addition, planned subgroup analyses were done of outcomes in black recipients compared with those of other ethnic origins (a stratification factor), of living-donor compared with cadaveric-donor organs, and of kidneys mismatched by 0–3 compared with 4–6 HLA antigens. Scores for the randomly selected biopsy samples were analysed by a 2×2 table (local compared with central pathologist diagnosis of rejection vs no rejection). Cohen's κ summary statistic showed concurrence of local and central readings ($\kappa=0.721$).

Results

Demographic characteristics

719 patients were enrolled—284 were assigned sirolimus 2 mg daily, 274 sirolimus 5 mg daily, and 161 azathioprine (figure 1). In addition to the study-mandated stratification of black recipients, who comprised almost 25% of the whole study group, mean age, number of HLA mismatches, percentage panel-reactive antibody, height and weight, and primary causes of renal failure and donor source were similar in all three treatment groups (table 1). Most renal-allograft donors were white and were positive on serological analysis for exposure to cytomegalovirus. Significantly more women than men were assigned sirolimus 5 mg and azathioprine ($p<0.001$).

Table 1. Demographic and baseline characteristics of patients^a

Characteristic	Treatment group					
	Sirolimus 2 mg (n=284)		Sirolimus 5 mg (n=274)		Azathioprine (n=161)	
Ethnic origin						
White	160	(56%)	154	(56%)	92	(57%)
Black	63	(22%)	62	(23%)	41	(25%)
Hispanic	48	(17%)	42	(15%)	15	(9%)
Asian	7	(2%)	10	(4%)	10	(6%)
Other	6	(2%)	6	(2%)	3	(2%)
Demography						
Sex (F/M)	76	(27)*	104	(38)	70	(43)
Mean (SD) age (years)	44	·9 (13·6)	46	·8 (13·0)	45	·6 (13·0)
Mean (SE) HLA mismatch	3	·4 (0·2)	3	·5 (0·1)	3	·7 (0·3)
Mean (SD) percentage PRA	2	·4 (9·8)	3	·2 (11·9)	3	·7 (13·1)
Mean (SD) height (cm)	172	·6 (11·0)	170	·6 (10·3)	172	·1 (26·4)
Mean (SD) weight (kg)	77	·7 (17·4)	74	·7 (17·4)	76	·3 (17·6)
Donor source						
Cadaveric	180	(63%)	167	(61%)	119	(74%)
Living unrelated	18	(6%)	24	(9%)	9	(6%)
Living related	86	(30%)	83	(30%)	33	(20%)
Cause of end-stage renal disease						
Hypertension	72	(25%)	77	(28%)	47	(29%)
Diabetes	59	(21%)	53	(19%)	32	(20%)
Glomerulonephritis	64	(23%)	50	(18%)	18	(11%)
Other	89	(31%)	94	(35%)	64	(40%)

At least one dose of study medication was dispensed to 710 patients, 550 of whom were in the sirolimus groups. Nine patients were withdrawn after randomisation because of starting antibody induction therapy (four), protocol violation (three), the physician did not adhere to the study protocol (one), and early myocardial infarction (one).

Efficacy failure

Compared with the azathioprine group, there were lower rates of efficacy failure at 6 months in the sirolimus 2 mg group (relative risk 0·61 [95% CI 0·44–0·84]) and 5 mg group (0·58 [0·41–0·81]) than in the azathioprine group (table 2). The positive treatment effect of sirolimus was consistent across study centres. A benefit was seen with sirolimus 5 mg daily compared with azathioprine at 12 months (failure rate 19·7 vs 33·5%, $p=0·002$).

Table 2. Composite efficacy failure rates^a

Efficacy failure rate	Sirolimus				Azathioprine
	2 mg	p	5 mg	p	
Overall					
6 months	53/284 (18.7)	0.002	46/274 (16.8)	< 0.001	52/161 (32.3)
12 months	75/284 (26.4)	0.175	54/274 (19.7)	0.002	54/161 (33.5)
Ethnic origin					
6 months					
Other ethnic groups	31/221 (14.0)	< 0.001	35/213 (16.4)	0.001	38/119 (31.9)
Black	22/63 (34.9)	1.00	11/61 (18.0)	0.102	14/42 (33.3)
12 months					
Other ethnic groups	48/221 (21.7)	0.049	41/213 (19.3)	0.011	38/119 (31.9)
Black	27/63 (42.9)	0.688	13/61 (21.3)	0.077	16/42 (38.1)
Donor source					
6 months					
Living	14/104 (13.5)	< 0.001	18/107 (16.8)	0.001	18/42 (42.9)
Cadaveric	39/180 (21.7)	0.216	28/167 (16.8)	0.020	34/119 (28.6)
12 months					
Living	19/104 (18.3)	0.003	20/107 (18.7)	0.003	18/42 (42.9)
Cadaveric	56/180 (31.1)	0.899	34/167 (20.4)	0.069	36/119 (30.3)

The rates of efficacy failure among non-black recipients were lower in the two sirolimus groups than in the azathioprine group (table 2). By contrast, efficacy failure rates did not differ significantly among black recipients treated with sirolimus and azathioprine, although there was a slight benefit among those receiving 5 mg sirolimus at 6 months and 12 months (table 2). Similarly, a greater treatment effect was seen with sirolimus than with azathioprine among recipients of allografts from living compared with cadaveric donors. Patients in the 5 mg sirolimus group had a significant benefit at 6 months ($p=0.02$) and a slight, but non-significant, benefit at 12 months ($p=0.069$).

Acute rejection episodes

The main component of the composite primary endpoint in the first 6 months was the occurrence of acute rejection episodes. The frequency of biopsy-confirmed acute rejection episodes was significantly lower in patients in the sirolimus groups than in those in the azathioprine group (table 3). At 6 months, the relative risks for decrease in frequency of acute rejection episodes for sirolimus compared with azathioprine were 0.58 (0.41–0.81) and 0.49 (0.34–0.71) for the 2 mg and 5 mg groups, respectively. The positive treatment effect was consistent across transplant centres (sirolimus 2 mg $p=0.471$, 5 mg $p=0.431$). Among recipients of kidneys mismatched by 0–3 antigens, the rate of acute rejection was lower in the two the sirolimus groups (2 mg $p=0.008$, 5 mg $p<0.001$) than in the azathioprine group, but for 4–6 HLA mismatches, a significant effect was seen only for the 5 mg sirolimus group ($p=0.027$).

Table 3. Rates of biopsy-confirmed acute rejection episodes^a

Acute rejection rate	Sirolimus				p	Azathioprine
	2 mg	p	5 mg			
Overall						
6 months	48/284 (16.9)	0.002	33	/274 (12.0)	< 0.001	48/161 (29.8)
12 months	62/284 (21.8)	0.046	40	/274 (14.6)	< 0.001	50/161 (31.1)
Ethnic origin						
6 months						
Other ethnic groups	29/221 (13.1)	< 0.001	24	/213 (11.3)	< 0.001	36/119 (30.3)
Black	19/63 (30.2)	1.00	9	/61 (14.8)	0.134	12/42 (28.6)
12 months						
Other ethnic groups	40/221 (18.1)	0.014	29	/213 (13.6)	< 0.001	36/119 (30.3)
Black	22/63 (34.9)	1.00	11	/61 (18.0)	0.102	14/42 (33.3)
Donor source						
6 months						
Living	13/104 (12.5)	< 0.001	13	/107 (12.2)	< 0.001	18/42 (42.9)
Cadaveric	35/180 (19.4)	0.254	20	/167 (12.0)	0.004	30/119 (25.2)
12 months						
Living	17/104 (16.4)	0.001	15	/107 (14.0)	< 0.001	18/42 (42.9)
Cadaveric	45/180 (25.0)	0.787	25	/167 (15.0)	0.016	32/119 (26.9)
Antibody treatment at 6 months	16/284 (5.6)	0.017	8	/274 (2.9)	< 0.001	20/161 (12.4)
HLA mismatches at 6 months						
0–3	21/155 (13.6)	0.008	10	/140 (7.1)	< 0.001	23/82 (28.1)
4–6	27/126 (21.4)	0.137	23	/132 (17.4)	0.027	25/79 (31.7)

Similar proportions of recipients in each treatment group had acute rejection episodes, irrespective of the observed average ciclosporin whole blood trough concentrations in the first month after transplantation (odds ratio 1.0) and of whether the values were higher or lower than the median concentration (334 ng/mL). Only three (3%) of 95 recipients in the 2 mg sirolimus group and six (6%) of 108 in the 5 mg group, compared with 15 (20%) of 77 recipients in the azathioprine group, had an acute rejection episode, despite a mean trough ciclosporin concentration lower than the median. Similar frequencies of acute rejection episodes were seen among patients who had trough concentrations higher than the median—nine (8%) of 109 in the 2 mg sirolimus group, six (6%) of 107 in the 5 mg group, and 15 (24%) of 63 in the azathioprine group—but the association between the occurrence of episodes and ciclosporin trough concentrations was not significant ($p=0.632$).

In limited subgroup analyses, rates of acute rejection episodes were lower among recipients of living-donor allografts at 6 months and 12 months in the two sirolimus groups (each $p<0.001$) than among those in the azathioprine group. The rates of acute rejection episodes for cadaveric allografts were, however, significantly reduced only in patients treated with 5 mg sirolimus (6 months, $p=0.004$, 12 months, $p=0.016$; [table 3](#)). Among non-black recipients, acute-rejection rates were uniformly lower at 6 months and 12 months among patients treated with sirolimus 2 mg and 5 mg than among those treated with azathioprine (each $p<0.001$ at 6 months and $p=0.014$ and $p<0.001$, respectively, at 12 months). By contrast, the lower rates of acute rejection episodes seen at 6 months and 12 months among black patients in the 5 mg sirolimus group did not differ significantly from those in the azathioprine group ($p=0.134$ and $p=0.102$), but the numbers of black recipients were limited. We found a difference in outcomes between black patients and those in other ethnic groups at various transplant centres, especially among patients in the 5 mg sirolimus group ($p=0.004$), but not in the 2 mg sirolimus group ($p=0.504$), which suggests that non-stratified features of care at some sites contributed positively to the benefit seen with sirolimus 5 mg.

Secondary endpoints

There was a delay to first biopsy-confirmed acute rejection episodes in the two sirolimus groups compared with the azathioprine group ($p=0.042$ and $p<0.001$, respectively, [figure 2](#)) and fewer moderate and severe histological grades of rejection (2 mg $p=0.006$, 5 mg $p=0.025$, [table 4](#)). The tendency towards milder acute rejection episodes was supported by the lower proportion of patients who required antibody treatment for rejection episodes in the 2 mg ($p=0.017$) and 5 mg ($p<0.001$) sirolimus groups than in the azathioprine group ([table 3](#)).

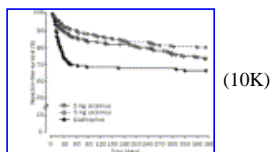


Figure 2. Time to occurrence of acute rejection episodes Log rank analysis p=0.001.

Table 4. Histological grades of biopsy-confirmed first acute rejection episodes

Treatment	n	Number of patients (%) [*]					
		No episodes [†]	Other [‡]	I (mild)	II (moderate)	III (severe)	II and III
Sirolimus 2 mg	284	231 (81.3)	6 (2.1)	21 (7.4)	19 (6.7)	7 (2.5)	26 (9.2)
Sirolimus 5 mg	274	228 (83.2)	15 (5.5)	19 (6.9)	8 (2.9)	4 (1.5)	12 (4.4)
Azathioprine	161	109 (67.7)	5 (3.1)	19 (11.8)	23 (14.3)	5 (3.1)	28 (17.4)

Renal-allograft function

At 6 months and 12 months, the mean serum creatinine concentrations were significantly higher in patients in the two sirolimus groups than in those in the azathioprine group (p<0.001, [table 5](#)) and mean creatinine clearance was lower (2 mg p<0.01, 5 mg p<0.001). Higher serum creatinine concentrations were associated with being male (p<0.001), increasing age of donor (p<0.001), and cadaveric donor organs (p=0.03), but not with ciclosporin whole blood trough concentrations.

Table 5. Mean (SE) laboratory values at 6 months and 12 months^{*}

	<u>Sirolimus 2 mg</u>		<u>Sirolimus 5 mg</u>		<u>Azathioprine</u>	
Creatinine						
6 months						
Serum ($\mu\text{mol/L}$)	154	$\cdot 2 (3\cdot 7)\dagger$	157	$\cdot 6 (4\cdot 6)\dagger$	129	$\cdot 4 (5\cdot 5)$
Calculated clearance (mL/min)	62	$\cdot 29 (1\cdot 22)\ddagger$	59	$\cdot 15 (1\cdot 51)\dagger$	68	$\cdot 78 (2\cdot 13)$
12 months						
Serum ($\mu\text{mol/L}$)	160	$\cdot 0 (4\cdot 9)\ddagger$	171	$\cdot 1 (6\cdot 0)\dagger$	133	$\cdot 1 (5\cdot 1)$
Calculated clearance (mL/min)	61	$\cdot 95 (1\cdot 36)??$	55	$\cdot 48 (1\cdot 62)\dagger$	67	$\cdot 51 (1\cdot 83)$
Serum cholesterol (mmol/L)						
6 months						
	6	$\cdot 66 (0\cdot 16)\ddagger$	7	$\cdot 20 (0\cdot 126)\dagger$	5	$\cdot 80 (0\cdot 24)$
12 months						
	6	$\cdot 39 (0\cdot 17)$	6	$\cdot 53 (0\cdot 17)$	5	$\cdot 86 (0\cdot 23)$
Serum triglycerides (mmol/L)						
6 months						
	3	$\cdot 20 (0\cdot 30)??$	4	$\cdot 12 (0\cdot 30)\dagger$	2	$\cdot 10 (0\cdot 44)$
12 months						
	3	$\cdot 28 (0\cdot 28)$	3	$\cdot 53 (0\cdot 29)$	2	$\cdot 61 (0\cdot 39)$
Haemoglobin (g/L)						
6 months						
	131	$\cdot 48 (1\cdot 4)$	123	$\cdot 38 (1\cdot 5)\ddagger$	130	$\cdot 52 (2\cdot 1)$
12 months						
	137	$\cdot 41 (1\cdot 8)$	127	$\cdot 25 (1\cdot 8)??$	134	$\cdot 64 (2\cdot 3)$
Platelet count ($\times 10^9/\text{L}$)						
6 months						
	221	$\cdot 1 (4\cdot 3)??$	218	$\cdot 3 (4\cdot 5)\ddagger$	240	$\cdot 6 (6\cdot 4)$
12 months						
	215	$\cdot 7 (5\cdot 1)??$	220	$\cdot 4 (5\cdot 2)$	237	$\cdot 0 (6\cdot 9)$
White blood cell count ($\times 10^9/\text{L}$)						
6 months						
	7	$\cdot 90 (0\cdot 18)??$	7	$\cdot 58 (0\cdot 19)$	7	$\cdot 12 (0\cdot 27)$
12 months						
	7	$\cdot 69 (0\cdot 20)\ddagger$	7	$\cdot 28 (0\cdot 20)$	6	$\cdot 64 (0\cdot 26)$

Causes of death and graft loss

Survival of patients and causes of death did not differ significantly between groups in the first 12 months after transplantation. Overall survival of patients was 96.9% (figure 3). 22 (3.1%) died from infections, cardiac events, malignant disorders, or miscellaneous causes (table 6). Survival of grafts was higher at 6 months among patients in the 2 mg sirolimus group than in the 5 mg sirolimus or azathioprine groups, but the difference decreased between 6 months and 12 months because of deaths with functioning transplants (three), non-adherence to treatment (two), chronic rejection (one), and abandoned immunosuppression because of massive gastrointestinal bleeding (one). At 12 months, graft survival was similar in the three groups: 94.3%, 92.7%, and 94.4% for sirolimus 2 mg, sirolimus 5 mg, and azathioprine, respectively (figure 3). Among the 45 graft losses (6.3%), the most frequent cause was death with a functioning graft (17), followed by refractory acute rejection, persistent non-function, renal vascular thrombosis, and miscellaneous causes (table 6), including non-compliance, chronic rejection, gastrointestinal bleeding, respiratory distress, haematoma, or thrombotic thrombocytopenic purpura.

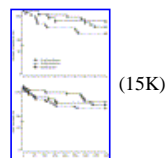


Figure 3. **Survival of patients and grafts in first 12 months after transplantation** Survival of patients $p=0\cdot 625$; allograft survival $p=0\cdot 593$.

Table 6. Deaths and graft losses during first 12 months after transplantation

	Sirolimus 2 mg (n = 284)	Sirolimus 5 mg (n = 274)	Azathioprine (n = 161)	Total (n = 719)
Deaths				
Infection	5 (1.8%)	2 (0.7%)*	1 (0.6%)*	8 (1.1%)
Cardiac event	0	7 (2.6%)†	0	7 (1.0%)
Malignant disease	1 (0.4%)	0	1 (0.6%)	2 (0.3%)
Miscellaneous	2 (0.7%)	2 (0.7%)	1 (0.6%)	5 (0.7%)
Graft loss				
Death from functioning graft	7 (2.5%)	8 (2.9%)	2 (1.2%)	17 (2.4%)
Refractory acute rejection	1 (0.4%)	6 (2.2%)	3 (1.9%)	10 (1.4%)
Persistent non-function‡	1 (0.4%)	2 (0.7%)	3 (1.9%)	6 (0.8%)
Renal vascular thrombosis	2 (0.7%)	1 (0.4%)	1 (0.6%)	4 (0.6%)
Miscellaneous	5 (1.8%)	3 (1.1%)	0	8 (1.1%)

Discontinuation and safety

More patients stopped study medication in the first 6 months in the azathioprine group than in the 2 mg sirolimus group ($p=0.011$, [table 7](#)). The main cause for discontinuation in the azathioprine group was efficacy failure, and in the sirolimus groups patients were withdrawn because of putative acute tubular necrosis, toxic effects from ciclosporin, raised serum creatinine concentrations, arthralgia, nausea, thrombocytopenia, haemolytic uremic syndrome, abnormal liver-function tests, hyperlipidaemia, and hypercholesteraemia. Study-drug doses were reduced by similar amounts in each group: 7% in the 2 mg sirolimus group, 11% in the 5 mg sirolimus group, and 12% in the azathioprine group.

Table 7. Reasons for treatment discontinuations in first 6 months

	Sirolimus 2 mg (n = 284)		Sirolimus 5 mg (n = 274)		Azathioprine (n = 161)	
Reasons for discontinuation						
Unsatisfactory response	34	(12.0%)	24	(8.8%)	34	(21.1%)
Adverse event	19	(6.7%)	29	(10.6%)	15	(9.3%)
Other medical event	16	(5.6%)	21	(7.7%)	10	(6.2%)
Patient's request	10	(3.5%)	12	(4.4%)	6	(3.7%)
Protocol violation	11	(3.9%)	14	(5.1%)	4	(2.5%)
Other non-medical event	1	(0.4%)	1	(0.4%)	2	(1.2%)
Lost to follow-up	1	(0.4%)	1	(0.4%)	1	(0.6%)
Discontinuations for abnormal laboratory values						
Anaemia*	1	(0.4%)	4	(1.5%)	0	
Raised blood urea nitrogen	1	(0.4%)	0		0	
Raised creatinine	3	(1.1%)	3	(1.1%)	4	(2.5%)
Raised liver-function tests†	0		3	(1.1%)	2	(1.2%)
Hypercholesterolaemia	0		3	(1.1%)	0	
Hyperglycaemia	1	(0.4%)	1	(0.4%)	0	
Hypertriglyceridaemia‡	1	(0.4%)	2	(0.7%)	0	
Hypoglycaemia	0		1	(0.4%)	0	
Leucopenia	0		1	(0.4%)	4	(2.5%)
Thrombocytopenia	1	(0.4%)	3	(1.1%)	1	(1.2%)

As anticipated, most patients (>97%) had at least one adverse event during the trial. Treatment-related adverse events leading to study-drug discontinuation were equally distributed across the three groups

($p=0.247$). Of the 550 patients who received at least one dose of sirolimus, 380 (69%) remained on treatment at 6 months (figure 1). Some adverse events reported during this period (table 8) seemed to represent an exacerbation of ciclosporin-related toxic effects: hypercholesterolaemia, hypertension, headache, hirsutism, hyperkalaemia, and acne. Other adverse effects—hypertriglyceridaemia, diarrhoea, thrombocytopenia, and lymphocele formation—seemed more likely to be related to sirolimus. The groups did not differ significantly in the frequency of abnormal blood glucose, calcium, or magnesium concentrations (data not shown).

Table 8. Frequency of clinically important adverse events at 6 months and 12 months^a

Adverse events	Sirolimus 2 mg (n = 281)		12 months		Sirolimus 5 mg (n = 269)		12 months		Azathioprine (n = 159)		12 months	
	6 months	%*	6 months	%*	6 months	%	6 months	%	6 months	%	6 months	%
Acne	24	%*	25	%*	18	%	19	%	11	%	11	%
Diarrhoea	18	%†	20	%	8	%	32	%†	5	%	14	%
Epistaxis	3	%	4	%	5	%‡	6	%‡	<1	%	<1	%
Headache	16	%‡	18	%	19	%*	23	%*	8	%	10	%
Hirsutism	5	%	5	%	12	%†	12	%†	2	%	3	%
Hypercholesterolaemia	30	%	33	%	35	%‡	37	%‡	21	%	24	%
Hyperkalaemia	12	%	13	%	8%	*	10	%‡	19	%	19	%
Hypertension	34	%‡	38	%*	33	%	34	%	22	%	23	%
Hyperlipidaemia	30	%	34	%	38	%†	42	%†	18	%	24	%
Insomnia	10	%	10	%	2	%*	20	%*	12	%	13	%
Leucopenia	5	%‡	6	%‡	10	%	12	%	11	%	12	%
Lymphocele	12	%	12	%	13	%†	15	%†	3	%	3	%
Thrombocytopenia	9	%	10	%	17	%†	18	%*	6	%	7	%

Mean fasting serum cholesterol and triglyceride concentrations increased from baseline in all groups, but to a greater extent among patients who received sirolimus than among those who received azathioprine. At 6 months, but not at 12 months, the mean cholesterol and triglyceride concentrations were significantly higher among patients in the sirolimus groups than in the azathioprine group (table 5). Although in the first 6 months more recipients had serum cholesterol concentrations higher than 6.19 mmol/L in the 2 mg (62%) and 5 mg (67%) sirolimus groups than in the azathioprine group (38%), only three patients (in the 5 mg sirolimus group) stopped treatment because of hypercholesterolaemia (table 7). Similarly, in the first 6 months, more patients in the 2 mg (19%) or 5 mg (20%) sirolimus groups had moderate hypertriglyceridaemia (4.51–11.29 mmol/L) than those in the azathioprine group (2%). One patient in the 2 mg sirolimus and three in the 5 mg sirolimus group showed triglyceride concentrations raised to more than 11.3 mmol/L, concentrations that have been associated with an increased risk of pancreatitis, although this complication was seen in similar frequencies among the treatment groups (three patients in the 2 mg sirolimus group, two in 5 mg sirolimus group, and two in the azathioprine group), and no affected patient had raised triglyceride concentrations. Only one patient in the 2 mg sirolimus group and two in the 5 mg sirolimus group discontinued study medication because of hypertriglyceridaemia (table 7).

Mean haemoglobin values were significantly lower in the 5 mg sirolimus group than in the 2 mg sirolimus or azathioprine groups at 6 months and 12 months. Although the 1 month peak values for mean platelet counts were lower among sirolimus-treated patients than among azathioprine-treated patients (2 mg group $p=0.004$, 5 mg group $p<0.001$, data not shown), the differences were less pronounced at 6 months and 12 months (table 5). No difference seemed clinically relevant, since only 2.9% of patients in the 2 mg group, 1.9% in the 5 mg group, and 1.3% in the azathioprine group had grade 2 toxic effects ($50\text{--}100\times 10^9/L$), and only one in the azathioprine group and four of the sirolimus-treated patients discontinued treatment for thrombocytopenia (table 7). No patient had platelet counts lower than $50\times 10^9/L$. Lower leucocyte counts were seen at 6 months and 12 months among patients in the azathioprine group ($p=0.017$ and $p=0.001$, respectively) compared with the 2 mg sirolimus groups.

Infections and malignant disorders

Groups did not differ significantly in the first 12 months after transplantation in the overall frequency of infections (table 9). Infections included those due to sepsis, cytomegalovirus, Epstein-Barr virus, and Herpes zoster, as well as infections in various sites, including lungs. Only mucosal lesions were more frequent in the 5 mg sirolimus group than in the other two groups ($p<0.001$), presumably due to Herpes simplex virus.

Table 9. Infections and malignant disorders

Cause	Sirolimus 2 mg (n = 281)		Sirolimus 5 mg (n = 269)		Azathioprine (n = 159)	
Bacterial infections						
Sepsis	24	(8.5%)	22	(8.0%)	6	(3.7%)
Urinary tract	54	(19.1%)	60	(22.1%)	45	(28.5%)
Pneumonia	8	(2.8%)	16	(5.8%)	3	(1.9%)
Wound	17	(6.0%)	24	(8.8%)	8	(5.0%)
<i>Pneumocystis carinii</i> pneumonia*	2	(0.7%)	1	(0.4%)	0	
Viral infections						
Systemic cytomegalovirus	9	(3.2%)	8	(2.9%)	9	(5.6%)
Tissue-invasive cytomegalovirus	3	(0.7%)	3	(1.1%)	2	(1.2%)
Herpes zoster	9	(3.2%)	12	(4.4%)	8	(5.0%)
Herpes simplex	13	(4.6%)	28	(10.2%) [†]	7	(4.4%)
Epstein-Barr virus	0		1	(0.4%)	0	
Malignant disorders						
Lymphoma	1	(0.4%)	2	(0.7%)	1	(0.6%)
Other malignant disorders	1	(0.4%)	8	(2.9%)	4	(2.5%)

The frequency of lymphoma in the 12 months after transplantation were similar in all treatment groups. One patient in the 2 mg sirolimus group died because of a central-nervous-system lymphoma, and two patients in the 5 mg sirolimus group discontinued study medication 9 days before or 9 days after the the diagnosis of lymphoproliferative disorders. One patient in the azathioprine group was receiving an alternate immunosuppressive regimen with muromonab-CD3, mycophenolate mofetil, and tacrolimus before and at the time of diagnosis of lymphoproliferative disorder. The overall incidences of malignant disease, other than lymphoma and lymphoproliferative disorders, were similar in all three treatment groups.

Discussion

Sirolimus improved the immunosuppressive activity of a ciclosporin and prednisone regimen. Acute rejection episodes were significantly fewer, delayed in onset, and had less histopathological change and requirement for treatment with antilymphocyte antibodies. Rates of acute rejection episodes were similar to those seen in an earlier, single-blind, multicentre, international, phase II trial of sirolimus,^[17] despite multiple adverse demographic factors—23% of patients were black, average age was younger than 55 years, the mean number of HLA mismatches was high (3.4), and donor grafts were cadaveric (65%).^[4] Despite being a large trial, this study was not adequately powered to detect a benefit in these subgroups of patients. However, benefit was seen with sirolimus despite a relatively low frequency of acute rejection episodes in the azathioprine cohort; namely, 29.8% compared with 40.8% in the US multicentre trial of mycophenolate mofetil, which also used induction therapy with antilymphocyte antibodies.^[2] The 29.8% rate in the azathioprine group in our study is similar to the 24% or 26% frequency reported after administration of tacrolimus and prednisone in two similarly sized, phase III randomised trials,^[20 and 21] and the 27% frequency reported for a regimen of mycophenolate mofetil, tacrolimus, and prednisone.^[22]

The favourable results in the azathioprine group in our study might be at least partially attributable to four factors. First, the rigorous baseline ciclosporin and prednisone trough-concentration-controlled regimen stipulated by the protocol provided substantial degrees of drug exposure, although previous studies have not shown a benefit of higher ciclosporin concentrations to reduce rejection rates to lower than 30%.^[23] Second, the addition of azathioprine to the ciclosporin and prednisone regimen might have had a significant impact, although previous studies have shown no effect.^[24] Third, the administration of the microemulsion rather than the oil-based formulation of ciclosporin might have improved the outcome, although the benefit seen in a previous study was slight.^[25] Fourth, and probably the most significant factor, was the selection of recipients after transplantation at reduced risk of delayed graft function, since the primary penalty of this disorder seems to be an increased rate of acute rejection episodes.^[26]

Despite the improved rejection prophylaxis provided by sirolimus, survival of patients and grafts was not altered. All three study groups showed rates at or above those reported to The United Network for Organ Sharing,^[27] and those described by Halloran and colleagues^[2] in the pooled analysis of the mycophenolate mofetil trials. Although the use of immunosuppressant drugs is associated with an increased frequency and severity of infectious diseases and neoplasms,^[28] we showed that the addition of sirolimus to a ciclosporin and prednisone regimen did not increase the rate of either type of event (except for mucosal putative herpes simplex virus lesions). Therefore, the contribution of sirolimus might be more selective for alloimmune than for non-specific host responses. Whether the low rejection rates we observed reflected a synergistic effect of sirolimus to make the immunosuppressive effects of ciclosporin more potent in clinical renal transplantation, in the way previously described for experimental models,^[5] will need to be studied in trials seeking to assess the possibility of lowering exposure to individual drugs, a characteristic of synergistic interactions.

This double-blind trial confirmed the side-effect profile for the ciclosporin, prednisone, and sirolimus regimen: thrombocytopenia, hypercholesterolaemia, and hypertriglyceridaemia. However, hypertriglyceridaemia was rarely the cause for stopping treatment in the two sirolimus groups. Even the administration of fibrates as counter-measure treatment for hypertriglyceridaemia was infrequent, which

suggests that dietary intervention, protocol-mandated tapering of the prednisone dose, and rigorous control of the blood glucose concentrations were sufficient, in most cases, to mitigate raised triglyceride concentrations over time. Because the changes in triglycerides were more consistent than the increases in serum cholesterol values, the prognostic implications of the lipid alterations for cardiovascular disease are unclear. Although fatal cardiac events occurred in seven patients in the 5 mg sirolimus group, this finding was not significant or associated with severe lipid abnormalities. Future trials of duration and size sufficient to estimate the cardiac risk must be done. In addition, the mechanism or mechanisms leading to an increased frequency of lymphocele is unclear, but may relate to disruption of proliferative signals necessary to seal perivascular lymphatics and to promote wound healing.

Treatment with sirolimus, especially at 5 mg daily, seemed to exacerbate ciclosporin-induced toxic effects of renal dysfunction, hypercholesterolaemia, hypertension, hirsutism, and acne.[29] Although increased serum creatinine values were reported as treatment-emergent adverse events with a similar frequency in all groups, the mean serum creatinine concentrations were slightly but significantly higher among patients treated with sirolimus than among those treated with azathioprine. Since there is substantial evidence that sirolimus has no [30] or, at most, a slight renal tubular [31] effect in rats, and since patients treated with sirolimus, azathioprine, and prednisone display better renal function at 6 months and 12 months than those treated with ciclosporin, azathioprine, and prednisone, [10] the increased creatinine concentrations might have been brought about by the concomitant administration of ciclosporin. The exposure to ciclosporin was likely to be increased by a pharmacokinetic interaction with sirolimus. This hypothesis is supported by the observation that significantly lower ciclosporin doses were required to achieve whole blood target concentrations among sirolimus-treated patients than among azathioprine-treated patients (data not shown). A kinetic interaction might have occurred despite similar ciclosporin whole blood trough concentrations in all the groups, since these values correlate poorly with overall drug exposure, as estimated by measurements of the area under the concentration-time curve. [23] This hypothesis seems to be supported by preliminary pharmacokinetic data in a few patients: higher ciclosporin area-under-curve values were seen in patients in the two sirolimus groups than in the azathioprine group (data not shown). Therefore, despite the use of a 4 h separation to reduce pharmacokinetic interactions between ciclosporin and sirolimus, [14] there may have been significant effects on activities of p-glycoprotein, cytochrome P450 3A4, or both in the absorptive intestinal luminal cell, or on the distribution, metabolism, or clearance phases of drug disposition.

A second possible pharmacokinetic interaction that impacts on renal dysfunction is suggested by the results of treatment with sirolimus and ciclosporin in rats. Napoli and colleagues[32] observed that sirolimus increases ciclosporin partitioning into renal tissue to a greater extent than it increases whole-blood concentrations. Although these interactions might explain the renal dysfunction, they are unlikely to account for the improvement in rejection prophylaxis, based on previous studies of the ciclosporin dose-effect response. [23] Although we mandated treatment with doses of ciclosporin to achieve therapeutic concentrations necessary to fulfill the immunosuppressive needs of the azathioprine group, future clinical use of sirolimus to adjust ciclosporin doses to produce trough concentrations at values lower than the putative therapeutic range for a purely ciclosporin-based regimen might be prudent. Furthermore, larger doses of sirolimus might permit even greater ciclosporin sparing or early ciclosporin elimination, which would facilitate renal recovery and keep nephrotoxic injuries to a minimum after transplantation.

Despite the size of our study, it was not sufficiently powered to detect a difference in survival of patients and grafts between treatment groups because of the high rates of success. We did, however, see benefits with sirolimus in the decrease of acute rejection episodes in the overall cohort. The ability of sirolimus to uniquely inhibit cytokine-driven pathways that lead to fibroblast and myocyte proliferation processes mediating vasculopathic and interstitial cicatricial changes[33] poses the possibility that the drug may interrupt antigen-dependent immunological and antigen-independent procurement or preservation and chronic nephropathic injuries. Continuing phase IV clinical studies are addressing this question, and dose-finding studies are being done in groups of patients at high risk, such as black recipients, to investigate the impact on clinical outcomes of variations between individuals of sirolimus concentrations, and seeking to elucidate predictive factors for the occurrence and therapeutic strategies to lessen the severity of drug-induced adverse reactions. One publication has documented correlations between drug concentrations and clinical outcomes. [34] We believe, however, that 2 mg sirolimus daily would be appropriate for non-black recipients of living-donor kidneys, and that the 5 mg sirolimus daily might be more useful for recipients at high risk of rejection, which may include black recipients or highly mismatched cadaveric-organ recipients.

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Acknowledgements

We thank the members of the drug safety monitoring board (J Wesley Alexander, University of Cincinnati, Dan Anbar, Millenium Biostatistics, and Bruce Julian, University of Alabama); Maureen Caulfield, Robert Goldberg-Alberts, Jonathan Jaffe, Bernadette Maida, Joseph Scarola, and Keqin Qi from Wyeth-Ayerst Research, for their assistance with the trial and the preparation of the paper; Natasha Teixeira, James Gurr, and Kate Ó Súilleabháin for editorial assistance with the paper. BDk was supported by a grant from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK 38016-11) and by clinical funds from Wyeth-Ayerst Research, Philadelphia, PA, USA.

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The Lancet

[Volume 356, Issue 9225](#) , 15 July 2000, Pages 194-202

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