6

Risk factors of of cyclosporine nephrotoxicity after conversion from sandimmune to neoral

Yvo Sijpkens[1], Marko Mallat[1], Carl Siegert[1], Aeilko Zwinderman[2], Rudi Westendorp[3], Hans de Fijter[1], Bob van Es[1], Leen Paul[1]

Departments of [1]Nephrology, [2]Medical Statistics and [3]Clinical Epidemiology, Leiden University Medical Center, The Netherlands

Clinical Nephrology 2001;55: 149-155

Abstract

Background In 1995-1996, we switched from a once-daily Sandimmune dose to a twice-daily dose regimen of Neoral. Concurrent with the switch we changed our target trough level from 100 µg/l at 24 hours to the generally accepted 12 hours level of 150 µg/l. We performed a retrospective cohort study to assess cyclosporine toxicity following this switch and to identify risk factors for nephrotoxicity.

Patients and methods Of 212 patients with a stable graft function pre-conversion clinical parameters at 1 and 12 months post-conversion were compared with those at time of conversion. Cyclosporine nephrotoxicity was defined as a significant decline of the reciprocal of the serum creatinine concentration over time post-conversion in the absence of other obvious causes for declining graft function. Risk factors of cyclosporine nephrotoxicity were assessed using logistic regression analysis.

Results The mean cyclosporine trough level rose from 87 µg/l at the time of conversion to 139 µg/l at 12 months post-conversion whereas the daily drug dose increased over the same period from 233 mg to 252 mg. Mean serum creatinine increased by 10% from 135 to 148 µmol/l ($P<0.001$). Cyclosporine nephrotoxicity was present in 42 patients (20%). Cyclosporine dose and trough level did not predict nephrotoxicity but beta blockers (OR 0.35, 95% CI 0.17 - 0.72) and calcium channel blockers (OR 0.35, 95% CI 0.19 - 0.82) reduced the risk of nephrotoxicity, independent from an effect on blood pressure.

Conclusions Twenty percent of stable renal transplant patients experienced chronic cyclosporine nephrotoxicity after conversion from a once-daily Sandimmune regimen to a twice-daily Neoral regimen with dose adjustments to a trough level of 150 µg/l. Beta blockers and calcium channel blockers reduced the risk of nephrotoxicity.

Introduction

Maintenance immunosuppression with cyclosporine after kidney transplantation has substantially improved the one-year graft survival rate compared with regimens not containing cyclosporine albeit that cyclosporine nephrotoxicity has remained a concern. It causes a reversible, dose-related decrease in glomerular filtration rate but its role in the pathogenesis of permanent structural lesions is less well understood. The assumption that it causes progressive nephropathy has been questioned because many patients receiving long-term therapy have stable graft function (1). In fact, it has been suggested that higher cyclosporine blood concentrations are associated with better long-term graft function (2). On the other hand, several studies have shown that discontinuation of cyclosporine does not adversely affect graft outcome (3,4).

Neoral, the micro-emulsion form of cyclosporine with a better and more consistent bioavailability has replaced Sandimmune in most centres. Neoral administration results in higher peak levels and a 30% increase in the dose-normalised area under the curve (5). In most conversion studies Neoral replaced Sandimmune in a one-to-one dosing ratio but the doses were subsequently reduced by 4 to 23% to maintain the same trough level range (6-10). Transient or persistent declines in renal function after conversion have also been reported (9,10).

Cyclosporine-based regimens remain largely empirical. Dosing regimens and target drug levels vary according to local practice. In our centre, Sandimmune used to be administered once-daily with dose adjustments to aim for a target 24 hours trough level of 100 µg/l (3). When we switched from Sandimmune to Neoral, we followed the generally used guideline to dose the drug twice-daily and to aim at a 12 hours trough level of 150 µg/l. The present paper describes a retrospective cohort study to assess cyclosporine toxicity following this switch and to identify risk factors for nephrotoxicity.

Patients and methods

Patients and immunosuppressive treatment

The renal transplant patients studied received Sandimmune and prednisone since transplantation. In our centre, Sandimmune was administered once-daily and we aimed at 24 hours trough levels of 100 µg/l (range 50-150), as determined by the Incstar RIA kit using a specific monoclonal antibody. A total of 302 patients who were more than six months after transplantation were switched from Sandimmune to Neoral between April 1995 and November 1996 using an initial one-to-one dosing conversion ratio. Neoral was administered

twice-daily and dose adjustments were made to aim at a 12 hours trough level of 150 µg/l. To monitor the conversion clinical and biochemical evaluations were done before conversion, at one and at 12 months post-conversion. To identify patients with a stable graft function before conversion, regression lines were retrospectively constructed of the reciprocal of the serum creatinine levels from 6 months after transplantation onwards to the date of conversion. In 288 patients sufficient data points were available. Seventy-six patients had a negative slope of 1/Cr, which was significantly different from zero, and were considered to have a declining renal function pre-conversion and were therefore excluded from further evaluation. Two hundred and twelve patients with a stable graft function before conversion and a follow-up after conversion of at least 12 months were included in the study.

Cyclosporine toxicity

Cyclosporine toxicity in patients with a stable graft function pre-conversion was assessed by comparing clinical and biochemical data obtained 1 and 12 months post-conversion with those at the time of conversion. The following parameters were evaluated: cyclosporine dose and trough level, serum creatinine concentration, endogenous creatinine clearance, proteinuria, serum cholesterol and uric acid concentration, the use of HMG CoA-reductase inhibitors, the blood pressure and the number and the kind of antihypertensive drugs.

Cyclosporine nephrotoxicity

Cyclosporine nephrotoxicity was defined as a statistically significant ($P<0.05$) decline of the reciprocal of the serum creatinine concentration over time post-conversion in the absence of other obvious causes for declining graft function. Regression lines of 1/Cr were constructed from the date of conversion to the end of follow-up, or until January 1, 1998. Figure 1 illustrates the pre- and post-conversion regression lines of an individual patient. Chart and graft histology data of patients with a decline in renal function post-conversion were reviewed to exclude other causes of graft dysfunction. In the patients with cyclosporine nephrotoxicity we extended the follow-up of graft function and immunosuppressive treatment until January 1, 1999.

We studied the following risk factors for cyclosporine nephrotoxicity: donor source, donor and recipient age, delayed graft function, presence of previous acute rejection episodes, Sandimmune dose (> 300 mg/day) and trough level (< 100 µg/l), serum creatinine, mean arterial pressure and the number and the kind of antihypertensive drugs. Patients with a stable graft function post-conversion were used as control group.

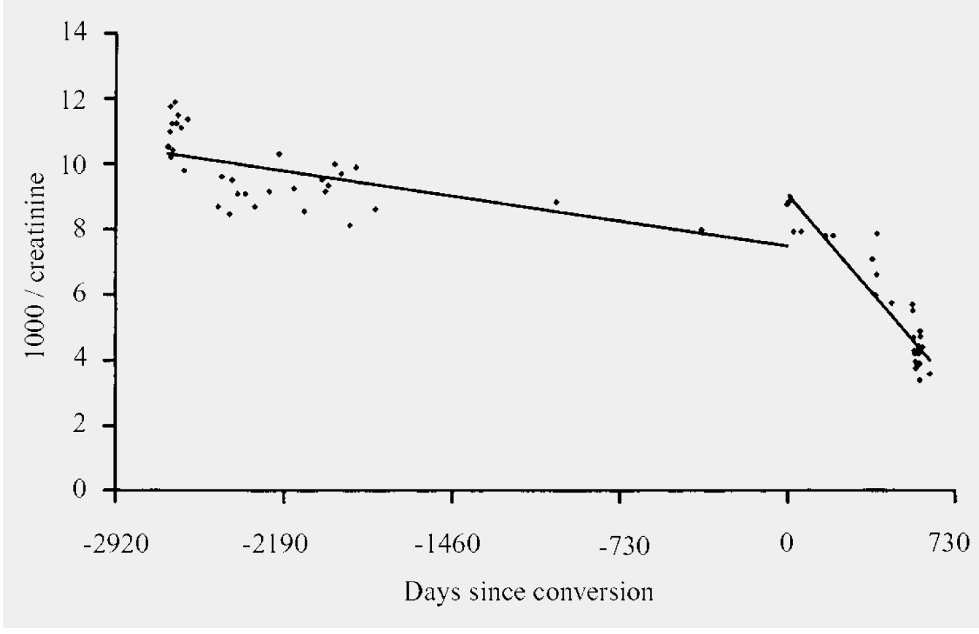

Figure 1 Regression lines of the reciprocal creatinines in a patient with a stable renal function before conversion and a significant decline in renal function after the switch from Sandimmune to Neoral

Statistical analysis

Clinical and biochemical parameters at 1 and 12 months post-conversion were compared with the parameters at time of conversion using a paired-samples *t* test. This test compares the mean of the differences with zero. We used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for risk factors of cyclosporine nephrotoxicity. Data are expressed as mean ± SD or number (%). A P value < 0.05 was considered significant.

Results

Patients

Two hundred and twelve patients with a stable graft function pre-conversion had a mean serum creatinine concentration of 135 ± 46 µmol/l at time of conversion; these patients were 4.6 ± 2.8 years after surgery; their mean age was 50 ± 13 years, 80 (38%) were women and 22 (10%) patients received their graft from a living donor.

Table 1. Clinical and biochemical parameters before and after conversion from Sandimmune to Neoral in 212 kidney transplant patients with a stable graft function pre-conversion

	Conversion	1 month	12 months
Cyclosporine dose (mg)	233 ± 75	251 ± 69[c]	252 ± 69[c]
Cyclosporine dose/kg (mg/kg)	3.2 ± 1.1	3.5 ± 1.1[c]	3.5 ± 1.1[c]
Cyclosporine trough level (µg/l)	87 ± 27	124 ± 35[c]	139 ± 36[c]
Serum creatinine (µmol/l)	135 ± 46	138 ± 49[b]	148 ± 60[c]
Creatinine clearance (ml/min)	70 ± 27	69 ± 25	62 ± 25[c]
Proteinuria (g/24h)	0.3 ± 0.7	0.4 ± 0.8[a]	0.6 ± 1.2[b]
Cholesterol (mmol/l)	6.1 ± 1.0	6.0 ± 1.0	6.2 ± 1.2
HMG-CoAreductase inhibitors – nr. (%)	87 (41)	98 (41)	111 (52)
Uric acid (mmol/l)	0.44 ± 0.11	0.46 ± 0.12[c]	0.48 ± 0.12[c]
Systolic blood pressure (mmHg)	139 ± 17	140 ± 19	143 ± 18[b]
Diastolic blood pressure (mmHg)	82 ± 10	83 ± 9	83 ± 9
Mean Arterial Pressure (mmHg)	101 ± 11	102 ± 11	103 ± 10[a]
Antihypertensive medication – nr	1.6 ± 1.0	1.7 ± 1.0[a]	1.9 ± 1.1[c]

Results are reported as mean ± SD unless otherwise stated. [a]P<0.05, [b]P<0.01, [c]P<0.001: 1 and 12 months post-conversion versus time of conversion tested by a paired-samples *t* test.

Cyclosporine toxicity

Table 1 shows the clinical parameters of the 212 patients with a stable graft function pre-conversion. To reach the target cyclosporine trough level of 150 µg/l after conversion the mean cyclosporine dose had been increased from 233 to 252 mg at 12 months (P<0.001). Mean serum creatinine concentration increased by 10% from 135 to 148 µmol/l (P<0.001) and the mean endogenous 24 hours creatinine clearance decreased from 70 to 62 ml/min (P<0.001). Proteinuria, serum uric acid concentration, systolic blood pressure and the need of antihypertensive drugs increased significantly at 12 months post-conversion. We did not observe any acute rejection episodes after the conversion.

Cyclosporine nephrotoxicity

Of the 212 patients with a stable graft function pre-conversion 70 (33%) had a significant decline of 1/Cr post-conversion. In 28 patients obvious causes for the decline in function were evident and included chronic rejection (9), recurrent original disease (6), infection (6) and other causes (7). By exclusion, cyclosporine nephrotoxicity was the most likely diagnosis in 42 patients (20%). Tabel 2 compares the baseline characteristics of these 42 patients with 142 patients without cyclosporine toxicity. Donor source, recipient or donor age, delayed graft function and presence of previous acute rejection episodes were not associated with nephrotoxicity. In the patients with nephrotoxicity the mean cyclosporine dose and trough level rose from 231 to 256 mg and from 85 (24 hours target) to 141 µg/l (12 hours target) respectively at 12 months post-conversion. The mean slope of 1/Cr pre- and post-conversion of the 42 patients with nephrotoxicity

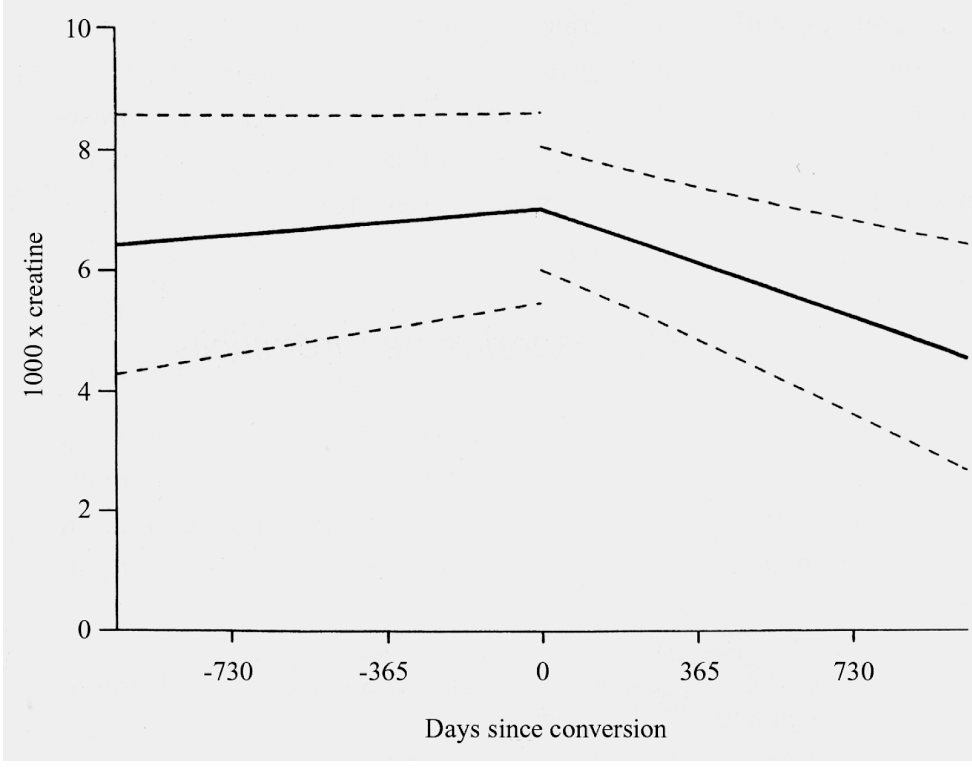

Figure 2 Mean regression line (95% confidence interval) of the reciprocal creatinines pre- and post-conversion in 42 patients with cyclosporine nephrotoxicity after the switch from Sandimmune to Neoral

is shown in Figure 2. In patients without nephrotoxicity the mean serum creatinine increased from 135 to 139 µmol/l at 12 months post-conversion whereas in patients with nephrotoxicity it rose from 131 to 161 µmol/l. In 10/42 patients, a graft biopsy was done on clinical indication post-conversion and the presence of significant arteriolar hyalinosis confirmed the diagnosis of cyclosporine nephrotoxicity in all cases. Patients who were biopsied had a higher mean serum creatinine level at time of conversion (145 µmol/l) and at 12 months post-conversion (195 µmol/l) compared with the 32/42 patients who were not biopsied (125 and 151 µmol/l, respectively). At the end of the extended follow-up, 33 ± 4 months post-conversion, dose reduction or conversion to mycophenolate was done in 23/ 42 and 6/42 patients, respectively. The decline in renal function was not progressive in the remainder 13/42 patients and no dose-reduction was instituted; in this group the mean serum creatinine stabilised at 163 µmol/l.

Table 3 shows the risk factors of cyclosporine nephrotoxicity. A high Sandimune dose (>300 mg) or a low trough level (<100 µg/l) before conversion was not associated with toxicity. Neither renal dysfunction (creatinine > 150 µmol/l)

Table 2. Baseline characteristics of kidney transplant patients with or without cyclosporine nephrotoxicity after switch from Sandimmune to Neoral

	Stable function (142)	Cyclosporine toxicity (42)
Transplantation to switch (years)	4.8 ± 3.0	4.2 ± 2.5
Recipient age (years)	46 ± 13	45 ± 13
Donor age (years)	37 ± 14	40 ± 13
Delayed graft function - no (%)	35 (25)	9 (20)
Acute rejection - no (%)	82 (58)	22 (48)
Cyclosporine dose (mg)	234 ± 74	231 ± 75
Cyclosporine level (µg/l)	88 ± 26	85 ± 30
Serum creatinine (µmol/l)	135 ± 47	131 ± 45
Creatinine clearance (ml/min)	71 ± 28	69 ± 23
Proteinuria (g/24hr)	0.2 ± 0.4	0.3 ± 0.5
Mean arterial pressure (mmHg)	100 ± 10	100 ± 12
# antihypertensive drugs	1.7 ± 1.0	1.3 ± 1.0 [a]
Diuretics - no (%)	28 (20)	4 (9)
Beta blockers - no (%)	87 (62)	17 (38) [a]
Calcium channel blockers - no (%)	78 (55)	16 (36) [a]
Converting enzyme inhibitors - no (%)	42 (30)	17 (38)

Results are reported as mean (SD) unless otherwise stated. [a]$P < 0.05$

nor hypertension (mean arterial pressure > 100 mmHg) at time of conversion predicted nephrotoxicity. However, patients treated with antihypertensive drugs (OR per drug 0.59, 95% CI 0.41 – 0.86), especially beta blockers (OR 0.35, 95% CI 0.17 – 0.72) or calcium channel blockers (OR 0.35, 95% CI 0.19 – 0.82), had a lower risk of nephrotoxicity.

Discussion

We observed cyclosporine nephrotoxicity after conversion from Sandimmune to Neoral in 20% of stable renal transplant patients. Our original cyclosporine protocol differed from that in most other centres in that we used to administer Sandimmune once-daily, aiming at a 24 hours trough levels of 100 µg/l (range 50-150 µg/l) (3). After conversion to twice-daily Neoral a target 12 hours trough level of 150 µg/l was adopted as per a nationwide guideline. To reach this level the mean cyclosporine dose was increased from 3.2 to 3.5 mg/kg. Nephrotoxicity was not observed in the first month post-conversion. Deteriorating graft function, proteinuria, hyperuricemia and hypertension, all known manifestations of cyclosporine toxicity (11) became evident only late after conversion.

Other groups studying toxicity after the conversion from Sandimmune to Neoral in stable renal transplant patients reported variable results. A single centre study from Berlin reported that a one-to-one conversion was efficacious and safe (6) but at 12 months the trough levels were lower (102 µg/l) compared with baseline (114 µg/l). The International Sandimmune Neoral study group

has confirmed safety and tolerability of Neoral and found no significant difference in renal function when switched from Sandimmune to Neoral (7). In another conversion study, nephrotoxicity was prevented using an individualised approach of rapid dose reduction in response to increased cyclosporine levels (8). The randomised, multicentre study of the Canadian Neoral Renal Study Group reported a transient increase in serum creatinine concentration after the switch to Neoral whereas the mean cyclosporine trough levels were similar in both groups (9). In another study, serum creatinine concentration remained elevated more than 30% above baseline in 16% of patients converted from Sandimmune to Neoral and followed for up to 11 months despite substantial dose reductions and a decrease in mean cyclosporine level from 156 to 130 µg/l (10). A recent study of cardiac transplant patients who were switched from Sandimmune to Neoral reported that an increase in cyclosporine trough level from 119 to 175 µg/l in parallel with a rise in serum creatinine concentration from 136 to 162 µmol/l 12 months post-conversion despite of a decrease in dose (12).

In our cohort of patients, it is likely that the changes in cyclosporine administration resulted in increased drug exposure and concomitant nephrotoxicity post-conversion. The 12 hours target trough level of 150 µg/l for Neoral appeared to be too high. We had favourable results with our once-daily Sandimmune regimen aiming at 24 hours trough levels of 50-150 µg/l as the 8-year graft survival censored for death with functioning graft was 80% (3). Trough levels, however, are poor indicators for total drug exposure. Sparse-sampling algorhytms are currently being developed to estimate area under the curve (AUC) values (13). Correlations between predicted and actual AUC are stronger for Neoral compared to the convential formulation (14). Long-term prospective studies are needed to define the optimal AUC target range for maintenance therapy. Awaiting these data, we reduced the target level to 100 - 125 µg/l for all patients.

Table 3. Risk factors for cyclosporine nephrotoxicity

	OR	95% CI
Serum creatinine (> 150 µmol/l)	0.96	0.42 – 2.14
Cyclosporine dose (> 300 mg)	0.94	0.41 – 2.16
Cyclosporine trough level (< 100 µg/l)	1.75	0.77 – 3.98
Mean arterial pressure (>100 mmHg)	1.66	0.33 – 1.32
Number of antihypertensive drugs	0.59	0.41 – 0.86[a]
Diuretics	0.43	0.19 – 1.30
Beta blockers	0.35	0.17 – 0.72[a]
Calcium channel blockers	0.35	0.19 – 0.82[a]
Converting enzyme inhibitors	1.22	0.62 – 2.64

OR: Odds Ratio, CI: Confidence interval. [a] P<0.05

We attempted to identify risk factors for cyclosporine nephrotoxicity by stringently defining patients with nephrotoxicity and to compare them with patients with a stable graft function post-conversion. The diagnosis of cyclosporine nephrotoxicity was based on a statistically significant deterioration of graft function in temporal relation to the switch of cyclosporine administration after exclusion of other obvious causes of graft dysfunction. Patients with nephrotoxicity had a stable graft function for a mean period of 4.2 years pre-conversion. Graft histology in ten patients, showing severe arteriolar hyalinosis (15) confirmed cyclosporine nephrotoxicity. Furthermore, cyclosporine dose reduction (16) or conversion from cyclosporine to mycophenolate mofetil (17) resulted in stabilisation of renal function, another feature consistent with cyclosporine nephrotoxicity.

Reports assessing risk factors of cyclosporine nephrotoxicity are scarce. We found that factors associated with pre-existent graft damage such as older donor age, delayed graft function or previous acute rejection episodes did not account for the nephrotoxicity. A Sandimmune dose of at least 300 mg/d, suggestive of poor absorption and a pre-conversion trough level lower than 100 µg/l were also not predictive for nephrotoxicity. Drug exposure, defined by AUC, could have been different between patients with and without nephrotoxicity, but this was not measured. In the Sandimmune era, cyclosporine induced episodes of acute deterioration in renal function and trough levels correlated best with the development chronic cyclosporine nephrotoxicity (18). In patients with autoimmune diseases who develop cyclosporine induced nephropathy initial higher doses of cyclosporine were given and patients with toxicity were older compared with patients in whom nephropathy did not develop (19).

We found that patients treated with calcium channel blockers or beta blockers were less likely to develop nephrotoxicity. This effect seems independent from their effect on the blood pressure. The renoprotective effect of calcium channel blockers in cyclosporine treated transplant patients has recently been reported by other investigators (20,21). Our observation that beta blockers have a similar effect has not been reported before. If there is reinnervation of the graft following transplantation (22), such a beneficial effect could be explained on the basis of cyclosporine's ability to increase sympathetic nerve activation (23), which in turn could result in renal vasoconstriction and increased renin production. Angiotensin-converting enzyme inhibitors did not affect the risk of nephrotoxicity. In a retrospective analysis, these agents were safe and well tolerated in a cohort of renal transplant recipients using cyclosporine in 86% (24).

In summary, we report considerable nephrotoxicity of cyclosporine late after conversion from Sandimmune to Neoral and twice-daily dosing aiming at a 12 hours target trough level of 150 µg/l, the standard practise in many centres. Beta blockers

and calcium channel blockers reduced the risk of cyclosporine nephrotoxicity, independent from their effect on blood pressure.

1. Lipkowitz GS, Madden RL, Mulhern J, et al. Long-term maintenance of therapeutic cyclosporine levels leads to optimal graft survival without evidence of chronic nephrotoxicity. Transpl Int 1999;12: 202-207
2. Burke JF, Pirsch JD, Ramos EL, et al. Long-term efficacy and safety of cyclosporine in renal- transplant recipients. N Engl J Med 1994;331: 358-363
3. Hollander AA, Van Saase JL, Kootte AM, et al. Beneficial effects of conversion from cyclosporin to azathioprine after kidney transplantation. Lancet 1995;345: 610-614
4. Heim-Duthoy KL, Chitwood KK, Tortorice KL, Massy ZA, Kasiske BL. Elective cyclosporine withdrawal 1 year after renal transplantation. Am J Kidney Dis 1994;24: 846-853
5. Kovarik JM, Mueller EA, Van Bree JB, et al. Cyclosporine pharmacokinetics and variability from a microemulsion formulation; a multicenter investigation in kidney transplant patients. Transplantation 1994;58: 658-663
6. Neumayer HH, Farber L, Haller P, et al. Substitution of conventional cyclosporin with a new microemulsion formulation in renal transplant patients: results after 1 year. Nephrol Dial Transplant 1996;11: 165-172
7. Frei UA, Neumayer HH, Buchholz B, Niese D, Mueller EA. Randomized, double-blind, one-year study of the safety and tolerability of cyclosporine microemulsion compared with conventional cyclosporine in renal transplant patients. International Sandimmun Neoral Study Group. Transplantation 1998;65: 1455-1600
8. Curtis JJ, Lynn M, Jones PA. Neoral conversion from Sandimmune in maintenance renal transplant patients: an individualized approach. J Am Soc Nephrol 1998;7: 1293-1300
9. Cole E, Keown P, Landsberg D, et al. Safety and tolerability of cyclosporine and cyclosporine microemulsion during 18 months of follow-up in stable renal transplant recipients: a report of the Canadian Neoral Renal Study Group. Transplantation 1998;65: 505-510
10. Bartucci M, Koshla B, Fleming-Brooks S, et al. Renal function following conversion from Sandimmune to Neoral in stable renal transplant recipients. J Transpl Coord 1997;7: 78-81
11. Shihab FS. Cyclosporine nephropathy: pathophysiology and clinical impact. Semin Nephrol 1996: 536-547
12. Khajehdehi P, Yip D, Bastani B. The impact of (1:1) cyclosporine A conversion to its microemulsion formulation on the kidney function of patients with cardiac allografts. Clin Transplant 1999;13: 176-180
13. Mahalati K, Belitsky P, Sketris I, West K, Panek R. Neoral monitoring by simplified sparse sampling area under the concentration-time curve: its relationship to acute rejection and cyclosporine nephrotoxicity early after kidney transplantation. Transplantation 1999;68: 55-62

14. Primmett DR, Levine M, Kovarik JM, Mueller EA, Keown PA. Cyclosporine monitoring in patients with renal transplants: two- or three-point methods that estimate area under the curve are superior to trough levels in predicting drug exposure. Ther Drug Monit 1998;20: 276-283
15. Mihatsch MJ, Kyo M, Morozumi K, Yamaguchi Y, Nickeleit V, Ryffel B. The side-effects of ciclosporine-A and tacrolimus. Clin Nephrol 1998;49: 356-363
16. Mourad G, Vela C, Ribstein J, Mimran A. Long-term improvement in renal function after cyclosporine reduction in renal transplant recipients with histologically proven chronic cyclosporine nephropathy. Transplantation 1998;65: 661-667
17. Ducloux D, Fournier V, Bresson-Vautrin C, et al. Mycophenolate mofetil in renal transplant recipients with cyclosporine associated nephrotoxicity: a preliminary report. Transplantation 1998;65: 1504-1506
18. Mihatsch MJ, Steiner K, Abeywickrama KH, Landmann J, Thiel G. Risk factors for the development of chronic cyclosporine-nephrotoxicity. Clin Nephrol 1988;29: 165-175
19. Feutren G, Mihatsch MJ. Risk factors for cyclosporine-induced nephropathy in patients with autoimmune diseases. International Kidney Biopsy Registry of Cyclosporine in Autoimmune Diseases. N Engl J Med 1992;326: 1654-1660
20. Kirk AJ, Omar I, Dark JH. Long-term improvement in renal function using nifedipine in cyclosporine-associated hypertension. Transplantation 1990;50: 1061
21. Rahn KH, Barenbrock M, Fritschka E, et al. Effect of nitrendipine on renal function in renal-transplant patients treated with cyclosporin: a randomised trial. Lancet 1999;354: 1415-1420
22. Shannon JL, Headland R, MacIver AG, Ferryman SR, Barber PC, Howie AJ. Studies on the innervation of human renal allografts. J Pathol 1998;186: 109-115
23. Scherrer U, Vissing SF, Morgan BJ, et al. Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. N Engl J Med 1990;323: 693-699
24. Stigant, CE, Cohen, J, Vivera, M, Zaltzman, JS. ACE inhibitors and angiotensin II antagonists in renal transplantation: an analysis of safety and efficacy. Am J Kidney Dis