Impact of Sirolimus Treatment in Kidney Allograft Recipients With Prolonged Cold Ischemia Times: 5-Year Outcomes

Maria Boratyńska,[1] Mirosław Banasik,[1] Dariusz Patrzałek,[2] Marian Klinger[1]

Abstract

Objectives: **Sirolimus, an effective and non-nephrotoxic immunosuppressant, may have an antiproliferative effect on renal tubular cells and increase their apoptosis, thus hindering the recovery of an injured kidney. The aim of this study was to evaluate the impact of combined sirolimus and cyclosporine therapy on the incidence and duration of delayed graft function and long-term graft function.**

Materials and Methods: **The study group consisted of 23 renal transplant recipients treated with a sirolimus-cyclosporine-prednisone regimen (sirolimus group). The reference group was composed of 23 patients treated with azathioprine-cyclosporine-prednisone. Because of a long cold ischemia time, all the patients were at high risk of developing delayed graft function.**

Results: **There was an equal frequency of delayed graft function in the sirolimus group compared with the reference group (39% vs 34.8%). The duration of delayed graft function was longer in sirolimus group compared with the reference group (21.2 ± 12.2 days vs 6.8 ± 2.5 days) (*P* < .004). The serum creatinine level at the 12th month was higher in patients with delayed graft function than it was in the remaining patients, independent of the immunosuppression protocol. One and 5-year graft survival rates were 100% and 87% in the sirolimus group, and 95% and 74% in the reference group. The 5-year patient survival rate was 100% in both groups.**

Conclusions: **Sirolimus significantly retards the recovery from posttransplant renal failure, but it does not increase the incidence of delayed graft function. Sirolimus therapy should be initiated after recovery from posttransplant renal failure. Sirolimus treatment is beneficial for long-term graft survival.**

Key words: *Kidney transplant, Cyclosporine, Delayed graft function, Creatinine, Renal allograft survival*

Delayed graft function is a prognostic factor for chronic graft nephropathy. Delayed graft function results from injuries associated, for example, with donor brain death and ischemia and reperfusion. The risk factors for delayed graft function include poor quality of the transplanted organ, long cold ischemia time, hemodynamic instability during transplant surgery, presensitization, rejection, and administration of calcineurin inhibitors before or immediately after transplant surgery (1). Another recently described risk factor for delayed graft function is early administration of sirolimus after surgery (2, 3).

Sirolimus so far has been considered non-nephrotoxic. In animal studies, sirolimus has been shown not to impair renal function, and its influence on kidney structure is dose-dependent: Sirolimus administered at 0.3 mg/kg did not cause impairments but increased the transforming growth factor beta-1 by approximately 45% (4). At the dose of 6.0 mg/kg, sirolimus caused lesions in rat kidneys and produced an acute model of nephrotoxicity consisting of tubular collapse, vacuolization, and nephrocalcinosis. These changes were similar to those usually caused by cyclosporine or tacrolimus (5). Recent clinical reports also revealed new, unknown adverse renal effects of sirolimus. Conversion from cyclosporine to sirolimus in patients with chronic graft dysfunction has been shown to result in an increase in the incidence of proteinuria and biopsy-proven glomerulonephritis (6).

From the [1]Department of Nephrology and Transplantation Medicine, and the [2]Department of General, Vascular and Transplantation Surgery, Wroclaw Medical University, Wroclaw, Poland
Address reprint requests to: *Maria Boratyńska, ul.Traugutta 57, Wrocław 50-417, Poland*
Phone: *+4871-7332511* ***Fax:*** *+4871-7332503* ***E-mail:*** *maria.boratynska@op.pl*

Experimental and Clinical Transplantation (2008) 1: 59-66

Introducing sirolimus into the treatment of progressive glomerulonephritis involving native kidneys has been shown to cause deterioration of renal function in half of those treated (6 of 12 patients) (7).

Concomitant administration of sirolimus with calcineurin inhibitors exacerbates their nephrotoxic effect. The toxicity is strongly related to the dosages of both drugs. In a chronic nephrotoxicity model, sirolimus, even at a subtherapeutic dose of 0.1 mg/kg, significantly potentiated nephrotoxicity induced by cyclosporine therapy, resulting in functional and structural impairment of the kidneys (5).

In clinical studies, biopsy-proven nephrotoxicity was found in 36% to 50% of patients treated with a combination of sirolimus and calcineurin inhibitors (8). The interaction between sirolimus and cyclosporine, which is a consequence of similar transport and metabolism pathways, may exert a synergistic nephrotoxic effect (9). Administering both drugs soon after transplant surgery may cause deterioration of pre-existing injuries and delayed graft function.

The aim of this study was to evaluate the impact of combined sirolimus and cyclosporine therapy on the incidence and duration of delayed graft function, and the impact of delayed graft function on graft functioning 1 and 5 years after transplant in patients with a high risk of delayed graft function because of a long cold ischemia time.

Materials and Methods

This study comprised 46 white patients who received a primary renal transplant at the Department of Nephrology and Transplant Medicine at Wroclaw Medical University in Wroclaw, Poland, in 2002. Because of a long cold ischemia time (> 24 hours), all patients were at a high risk of developing delayed graft function. All patients provided informed consent to participate in the study. The study protocol was approved by the local bioethical committee of Wroclaw Medical University and conforms with the ethical guidelines of the 1975 Helsinki Declaration. The recipients were divided into 2 groups, depending on immunosuppression therapy. A total of 23 patients (15 men, 8 women; mean age, 44.3 ± 13 years) were treated with sirolimus, cyclosporine, and prednisone (sirolimus group), and 23 patients (17 men, 6 women; mean age, 44.4 ± 9 years) were treated with conventional triple immunosuppressive therapy composed of azathioprine, cyclosporine, and prednisone (reference group). The patients were similar with respect to demographic data (Table 1). The patients received kidneys from deceased donors with 2 to 5 HLA antigen mismatches.

Immunosuppression

Patients in the sirolimus group received a sirolimus loading dose of 6 mg within 24 hours of the transplant, followed by 2 mg per day. From the seventh day, the dosage was adjusted to maintain whole-blood trough levels of 4 to 12 ng/mL. Cyclosporine was begun the day after the transplant at 8 mg/kg/day adjusted to maintain a whole-blood trough level between 200 and 350 ng/mL for 3 months. Then, the dosage was reduced to maintain a blood trough level of 150 to 200 ng/mL. Methylprednisolone 500 mg was given intraoperatively, then at 125 mg on day 1. From the second day after the transplant, prednisone was given at 20 mg/day. After 1 month, the prednisone dosage was tapered to 10 mg/day for 2 months.

In the reference group, cyclosporine (5 mg/kg) was introduced before graft implantation in 18 patients; 5 patients received cyclosporine within 24 hours after the transplant. Cyclosporine trough blood levels were targeted at 250 to 300 ng/mL for 6 months and then at 150 to 200 ng/mL until the end of the first year. Azathioprine (3 mg/kg/day) was introduced before transplant and reduced to 2 mg/kg on the first day after surgery and tapered to 1 mg/kg/day 6 weeks after the transplant. Methylprednisolone 500 mg was given intraoperatively, then at 250 mg at day 1, and 125 mg at days 2 and 3. Prednisone was given on day 4 at 0.5 mg/kg and reduced to 20 mg on the 14th day, then tapered to 10 mg per day for 6 months.

Donors

The mean donor age was 42.5 ± 13.6 years (16 men, 7 women) in the sirolimus group and 48.6 ± 12.8 years (11 men, 12 women) in the reference group. Donor serum creatinine levels were between 80 and 153 μmol/L. Five recipients in the sirolimus group and 8 in the reference group received kidneys from donors who had died of a cerebrovascular stroke. All kidneys were preserved by cold storage in University of Wisconsin solution.

Diagnosis of delayed graft function

Delayed graft function was defined by 3 different methods: (1) the requirement for dialysis during the first week after transplant; (2) rising serum creatinine

level or a level unchanged during the 3 days after surgery; or (3) a serum creatinine level greater than 250 μmol/L on the fifth day after surgery. Delayed graft function was assumed to last until the patient no longer required dialysis. All patients with delayed graft function underwent routine graft biopsy on the seventh day after surgery. A biopsy was repeated at the third or fourth week in patients with prolonged delayed graft function and additionally in patients with signs of acute rejection.

Diagnosis and treatment of acute rejection

Diagnosis of acute rejection was confirmed by a percutaneous kidney graft biopsy. All rejection episodes were treated with intravenous methylprednisolone 500 mg for 3 days. Two patients from the sirolimus group received antilymphocyte antibodies (ATG-Fresenius) because of acute rejection that was resistant to steroids.

Statistical analyses

The impact of the dose and level of sirolimus as well as the dose and trough level of cyclosporine, donor age, and cold ischemia time on developing delayed graft function was examined. The influence of delayed graft function on the incidence of acute rejection, graft function, and graft and patient survival rates also was evaluated.

We compared the data from the 2 cohorts: the sirolimus group and the reference group. The Mann-Whitney *U* test was used to test the differences between quantitative and qualitative variables. Curves of the recovery of renal function were generated using the log-rank test and the Kaplan-Meier method. A value for *P* less than .05 was considered statistically significant.

Results

The age and sex of donor and the recipient, cold and warm ischemia times (vessel anastomosis time), presensitization, number of HLA mismatches, and method of pretransplant dialysis were similar in the 2 cohorts (Table 1). However, the donors were older for the patients with delayed graft function in the both groups, but this result was not statistically significant (Table 2).

Delayed graft function

At our transplant center, the overall rate of delayed graft function is about 34%, and its duration is about 7 days. In the examined group of recipients, the frequency of delayed graft function, defined as the need for dialysis within 1 week of the transplant, was similar: 9 of 23 patients (39%) in the sirolimus group

Table 1. Patient demographics and characteristics according treatment .

	Sirolimus group	Reference group
Total number	23	23
White race	23	23
Sex, M/F	15/8	17/6
Recipient age (y)	44.3 ± 12.9	44.4 ± 8.8
HLA mismatches	3.39 ± 0.8	3.1 ± 0.9
PRA (%)	5 ± 10.3	1.8 ± 4.4
Donor age (y)	42.5 ± 13.6	48.6 ± 12.8
Months of dialysis before transplantation	33.4 ± 26.9	37.5 ± 45.5
Cold ischemia time (h)	25.9 ± 6.5	26.7 ± 7.3
Warm ischemia time (min)	23.8 ± 5.5	25.7 ± 5.3
Cause of ESRD		
Glomerulonephritis	9	12
Hypertension	3	2
Diabetes mellitus	2	1
PKD	3	3
Others	6	5
Serum creatinine (μmol/L)		
12 months after transplant	136 ± 34	146 ± 43

Abbreviations: ESRD, end-stage renal disease; HLA, human leukocyte antigen; PKD, polycystic renal disease; PRA, panel reactive antibodies
P = NS between the sirolimus and reference groups

Table 2. Results of patients in the examined groups with and without delayed graft function.

	Sirolimus group		Reference group	
	DGF (n=9)	no DGF (n=14)	DGF (n=8)	no DGF (n=15)
Age (y)	44 ± 12	45 ± 14	43 ± 10	45 ± 9
Male sex, n (%)	6 (67)	9 (64)	6 (75)	11 (73)
Cold ischemia time (h)	26.1 ± 7	24.9 ± 4	28 ± 8	26.1 ± 7
Warm ischemia time (min)	24.7 ± 5	23.4 ± 6	26.5 ± 6	24.6 ± 5
Donor age (y)	45.8 ± 16	40.6 ± 12	51.6 ± 11	47.1 ± 13
Male donor	7 (78%)	9 (64%)	3 (37%)	8 (53%)
Acute rejection	7 (78%)[d]	3 (21%)[d]	6 (75%)	7 (47%)
Serum creatinine (μmol/L)				
month 1	399 ± 280[a]	136 ± 25[a]	229 ± 102	153 ± 42
month 3	187 ± 42	144 ± 25	238 ± 187	144 ± 34
month 12	170 ± 42	127 ± 34	168 ± 50	136 ± 25
day when serum creatinine < 250 μmol/L	33.9 ± 20.5[b,c]	4.3 ±1.4[b]	16.8 ± 6.0[c]	5.3 ± 2.2
dose of SRL during 1st month (mg)	3.17 ± 2.29	2.63 ± 0.61		
serum level of SRL during 1st month (ng/mL)	6.7 ± 3.6	6.9 ± 3.2		
dose of CsA during 1st month (mg)	393 ± 118	433 ± 121	440 ± 163	398 ± 82
serum level of CsA during 1st month (ng/mL)	234 ± 75	292 ± 87	254 ± 62	294 ± 58

Abbreviations: CsA, cyclosporine; DGF, delayed graft function; SRL, sirolimus
[a]*P* < .02 sirolimus group with vs without delayed graft function
[b]*P* < .003 sirolimus group with vs without delayed graft function
[c]*P* < .04 sirolimus group with delayed graft function vs reference group with delayed graft function
[d]*P* < .008 sirolimus group with delayed graft function vs sirolimus group without delayed graft function

compared with 8 of 23 patients (35%) in the reference group. Delayed graft function, defined as failure of the creatinine level to decrease for 3 consecutive days or a failure of the creatinine level to reach < 250 μmol/L [3 mg/dL] on the fifth day), occurred less frequently in the sirolimus group: 48% versus 52% and 48% versus 65%, respectively.

The duration of delayed graft function (need for dialysis) was significantly longer for patients in the sirolimus group (21.2 ± 12.2 days) than it was for patients in the reference group (6.8 ± 2.5 days) ($P = .004$) (Figure 1). Mean serum creatinine levels decreased below 250 μmol/L after 36 ± 22 days in the sirolimus group compared with 16.8 ± 6 days in the reference group ($P < .04$). In 2 patients with long-lasting anuria, sirolimus was discontinued, and mycophenolate mofetil 2 g/day was given. Two weeks later, their kidney function returned. The prevalence of delayed graft function as a function of time after transplant depending on the immunosuppression regimen used is shown in Figure 2. In the sirolimus group, on the 17th and 30th days after transplant, the delayed graft function rates were 21.7% and 13%, respectively. Delayed graft function resolved in all the patients in the reference group within 12 days after surgery. In the sirolimus group, delayed graft function resolved in all patients within 6 weeks.

The sirolimus dose up to the seventh day was identical in all patients. Afterwards, the dosage was higher in patients in the delayed graft function group (3.5 ± 2.3 mg/day) compared with patients without delayed graft function (2.6 ± 0.6 mg/day), whereas similar blood levels were achieved (6.9 ± 3.2 vs 6.7 ± 3.6 ng/mL). During the first month, cyclosporine trough levels were about 30% lower (230 ng/mL) in patients in the delayed graft function group than they were in patients in the nondelayed graft function group (310 ng/mL) (Table 2).

Histopathological findings during delayed graft function

Fourteen biopsies were done in the sirolimus group and 7 were done in the reference group during the time patients had delayed graft function. Tubular epithelial cell loss of the brush border was found in all the biopsy specimens. In 2 patients from the sirolimus group and 1 from the reference group, there was evidence of diffused tubular epithelial cell necrosis. Accumulated debris in the tubular lamina was found in 3 patients from the sirolimus group and 2 patients from the reference group. Eosinophilic silhouettes of tubular epithelium were found in 3 patients from the sirolimus group and 1 patient from the reference group. In 2 patients from the sirolimus group, cytorrhexis, fissuring, dehiscence, and crack formation were observed. The severity of the injuries in the tubules was similar in the both groups. Repeat biopsies, taken an average of 27 days after the transplant, in the sirolimus group revealed partially necrotized and partially regenerating tubular cells in 2 patients and flat tubular epithelium in 1 patient.

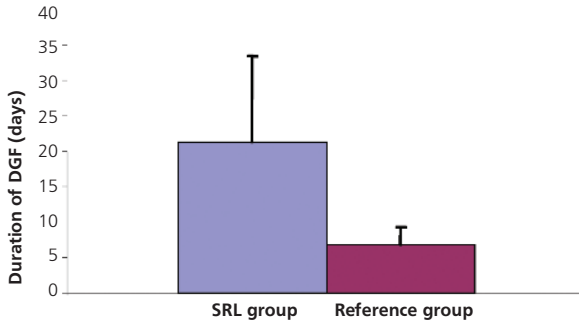

Figure 1. Duration of DGF in SRL group and reference group ($P = .004$)
Abbreviations: DGF, delayed graft function; SRL, sirolimus

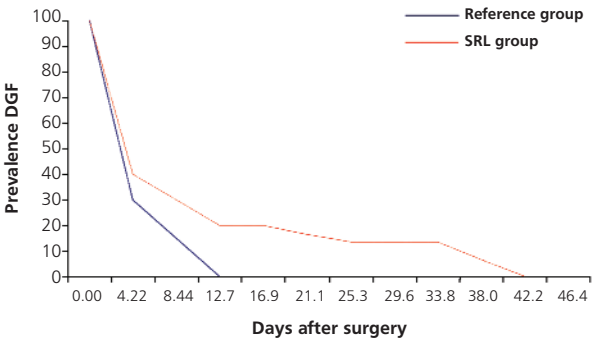

Figure 2. Duration of DGF by treatment protocol
Abbreviations: DGF, delayed graft function; SRL, sirolimus

Acute rejection

Biopsy-proven acute rejection occurred in 10 patients in the sirolimus group and in 13 patients in the reference group; most of these episodes occurred during periods of delayed graft function. In the sirolimus group, acute rejection occurred in 78% of the delayed graft function patients during delayed graft function and in 21% of the remaining patients without delayed graft function ($P < .008$). In 2 patients with delayed graft function, a steroid-resistant rejection developed, which resolved with ATG treatment. During ATG treatment, cyclosporine was withdrawn and sirolimus was reduced to 1 mg/day.

In the reference group, acute rejection developed in 75% of the patients with delayed graft function and in 47% of the patients without delayed graft function; this percentage is significantly higher than that of the sirolimus group. Acute rejection was treated with a 3-day course of methylprednisolone. None of the patients was treated with ATG.

Renal function and graft survival

Serum creatinine levels at the third and 12th months after transplant were higher in patients with delayed graft function than in patients without delayed graft function, both in the sirolimus and the reference group; however, this difference was not statistically significant. Nevertheless, serum creatinine levels in the sirolimus and reference groups were essentially identical (153 ± 26 vs 150 ± 42 μmol/L at the third month and 136 ± 34 vs 146 ± 43 μmol/L at 1 year). Glomerular filtration rate, calculated by the Cockroft-Gault formula, at 1 and 5 years after transplant in the sirolimus group, was 65 mL/minute and 56 mL/minute; the rate was higher in the sirolimus group than in the reference group (62 mL/min vs 49 mL/min).

One graft in the reference group was lost because of urologic complications 3 months after transplant. In the sirolimus group, during 5-year follow-up in 4 patients, sirolimus was withdrawn in 1 patient because of thrombotic microangiopathy; in 1 patient because of severe, long-lasting pneumonia; in 1 patient because of poor control of hypercholesterolemia and hypertriglyceridemia; and in 1 woman because of pregnancy. In the reference group, only 1 patient changed immunosuppression therapy and this was because of Kaposi's sarcoma. Cyclosporine and azathioprine were withdrawn, and sirolimus was administered in this patient, and complete regression of Kaposi's sarcoma with good renal function was observed 4 years later.

One and 5-year patient survival rates in both groups were 100%. One and 5-year graft survival rates were 100% and 87% in the sirolimus group, and 95% and 74% in the reference group.

Discussion

Our single-center transplant study showed that sirolimus combined with cyclosporine, administered early after transplant surgery, significantly retarded the recovery from posttransplant renal failure in patients with long-lasting cold ischemia time. The duration of recovery from delayed graft function was 3 times longer in patients treated with sirolimus and cyclosporine than it was in patients treated with conventional triple therapy. In 2 patients with long-lasting anuria, kidney function recovered only after sirolimus was discontinued. The probability that a sirolimus-treated patient would have delayed graft function longer than 1 month was 13%. A similar value was reported by Knight and associates in patients treated with thymoglobulin or basiliximab combined with sirolimus and delayed introduction of reduced doses of cyclosporine. In their study, however, the donor age was lower and the length of the cold ischemia was shorter (10). Sixteen percent of the patients reached a creatinine level below 212 μmol/L (2.5 mg/dL) within 30 to 60 days after transplant, and 3% reached that level 60 days or more after transplant. Their more-recent report of 894 patients revealed that 5% experienced prolonged recovery from delayed graft function lasting longer than 6 weeks (11). The mean time to produce a urine volume greater than 500 mL was short (1.6 ± 2.9 days); however, the median time required for the creatinine level to drop to 2.5 mg/dL in all patients was 12 days. These results indicate rather slow recovery of renal allograft function. Slow recovery of graft function is believed to be as equally important a prognostic factor as is delayed graft function.

In our study, patients with delayed graft function were treated with higher sirolimus dosages because of a reduction in cyclosporine that could lengthen the recovery of graft function. In contrast, Knight and associates found that recipients with a high sirolimus trough level 1 week after transplant exhibited lower mean serum creatinine levels at 1 week compared with recipients with lower sirolimus levels (10). Based on these data, Knight and associates suggest that increased exposure to sirolimus does not impair recovery from delayed graft function. However, a study by Smith and associates showed that a 1-mg increment in the sirolimus dosage increased the risk of developing delayed graft function by 10% to 13% (2).

Retardation of recovery from ischemic renal failure results mainly from the antiproliferative and apoptosis-induction effects of sirolimus on epithelial tubular cells. Recovery from acute renal failure depends greatly on the balance between proliferation of cells that survive the injury and apoptosis. Renal tubular cells that survive an acute injury enter the cell

cycle and begin to proliferate to repair the injured tubules and to replace of lost cells. Sirolimus inhibits protein kinase activity, termed mammalian target of rapamycin (mTOR), which is necessary to continue the cell cycle. mTOR and the sirolimus-binding protein (FKBP12) are expressed not only in lymphocytes but also in tubular epithelial cells, mesangial, endothelial, smooth muscle cells, fibroblasts, and other cells. Inhibition of mTOR affects the activity of the 40S ribosomal protein S6 kinase (p70S6k), which plays a key role in the pathways governing cell proliferation and apoptosis (12). Experimental research by Lieberthal and associates showed an elevation of the active form of p70S6k in kidney tissue after ischemia-reperfusion injury, and suggests that this kinase is necessary for recovery from acute renal failure (12). Treatment with sirolimus markedly diminished the amount of activated p70S6k in the renal tissues of rats subjected to ischemic renal failure. In morphologic examinations of kidney specimens, Lieberthal and associates showed that the degree of tubular necrosis, apoptosis, and obstruction of the tubular lumen by casts was unchanged in sirolimus-treated animals, whereas it diminished in vehicle-treated rats 4 days after surgery. The number of apoptotic cells in sirolimus-treated animals was twice the number of apoptotic cells in vehicle-treated rats.

In clinical studies by Stallone and associates, renal graft biopsies taken at weekly intervals during delayed graft function revealed markedly delayed proliferative activity of tubular cells in patients treated with low doses of cyclosporine, sirolimus, and prednisone in comparison with patients from a control group treated with cyclosporine, mycophenolate mofetil, and prednisone (13). In our study, the severity of injuries in the tubules was similar in the sirolimus group and the reference group in the first series of biopsies. However, repeat biopsies taken 4 weeks after transplant in the sirolimus group revealed still partially necrotized and partially regenerating tubular cells.

The vasoconstrictive and nephrotoxic effect of calcineurin inhibitors may exacerbate tubular damage. Smith and associates reported numerous atypical eosinophilic casts filling tubular lumina apart from typical changes for acute tubular necrosis in delayed graft function patients treated with sirolimus and tacrolimus (2). These casts were, in part, composed of degenerating epithelial cells. The authors defined the histologic findings as cast nephropathy, because of their similarity to myeloma cast nephropathy. Biopsy-proven nephrotoxicity was a reason to withdraw the tacrolimus-sirolimus combination in half of the patients. Blood trough levels were maintained at 10 to 15 ng/mL and 5 to 10 ng/mL, respectively. In our study, no patient treated with sirolimus and cyclosporine had cast nephropathy.

The duration of delayed graft function depends on the severity of its causes. Long-lasting delayed graft function may deteriorate graft survival. Giral-Classe and associates analyzed approximately 800 recipients and found that delayed graft function longer than 6 days strongly decreased 10-year graft survival rates (67% vs 78% for patients with delayed graft function < 6 days) ($P < .0001$) (14). In that study, delayed graft function was defined as the time required for the kidney to reach a Cockroft calculated creatinine clearance level of 10 mL/minute or more. The authors also suggested that patients with poor renal function (creatinine clearance < 10 mL/minute), but who were not dialyzed were at the same risk of graft loss as dialyzed patients.

Duration of delayed graft function in patients treated with sirolimus may be a consequence of the extent of the lesions caused by multiple insults to the graft and the slow recovery resulting from the effects of sirolimus. Higher serum creatinine concentrations at 1 year after transplant in delayed graft function patients (independent of immunosuppressive regimen) can to some extent be a result of acute rejection, which affects most delayed graft function patients. A large survey by Hariharan and associates pointed out that serum creatinine level at 1 year after transplant has a dramatic effect on long-term survival (15). In our study, 1- and 5-year graft survival was higher in patients treated with sirolimus than it was in patients in the reference group. Delayed graft function did not affect long-term allograft function in sirolimus-treated patients.

In the available multicenter randomized studies, frequency and duration of delayed graft function was not analyzed with regard to sirolimus treatment. In the study by Gonwa and associates, patients with delayed graft function were excluded, unless renal function improved sufficiently to allow them to receive cyclosporine by the seventh day (16). In the recent report by Simon and associates, 361 sirolimus-treated patients were retrospectively analyzed: 27.1% had delayed graft function, whereas 22.5% patients treated with other immunosuppressive regimens experienced delayed graft function (3). Smith and associates found more-frequent delayed graft function in patients

treated with sirolimus than in patients treated without sirolimus (25% vs 9%) (2).

Our study showed no evidence of an increased incidence of delayed graft function, defined by the need for dialysis the first week after transplant or by a lack of a decreased creatinine level during the first 3 days in patients treated with sirolimus. When delayed graft function was defined as a failure of the creatinine level to fall below 250 μmol/L on the fifth day after surgery, patients treated with sirolimus had a lower incidence of delayed graft function than did patients not treated with sirolimus. In the studies by Knight and associates, only 14% of 145 sirolimus-treated patients required hemodialysis within the first week after transplant with a low risk of acute rejection (10).

Experimental studies point out that sirolimus does not induce acute tubular necrosis, and that its harmful effect is apparent in previously impaired kidneys during the recovery phase (17). In a rat syngenic kidney transplant model of ischemia-reperfusion injury, the extended cold ischemia time (and thus, the severity of tubular cells damage) was a decisive factor of acute tubular necrosis in sirolimus-treated animals.

Sirolimus is usually implemented in a calcineurin inhibitor-free regimen with mono or polyclonal antibodies for recipients of marginal donor kidneys or those with delayed graft function. Such treatment resulted in low rates of acute rejection and excellent early patient and graft survival rates (18, 19). However, duration of delayed graft function was not assessed. In a pilot protocol introduced by Shaffer and associates, in 1 patient with severe acute tubular necrosis, the kidney failed and a transplant nephrectomy was done 3 months after the transplant (18). In a work by Chang and associates, the mean time to initiation of calcineurin inhibitors was 21 ± 13 days (20). It can be inferred that in their study, the delayed graft function period lasted for 21 ± 13 days. In a study by McTaggart and associates, de novo use of sirolimus prolonged recovery from delayed graft function (21).

In summary, sirolimus significantly retards recovery from posttransplant renal failure; however, it does not increase the incidence of delayed graft function. Patients, with posttransplant acute renal failure had worse renal function at 1 year after transplant, independent of the treatment protocol used. Combined therapy of sirolimus and cyclosporine should be under careful control during the period of delayed graft function, or sirolimus therapy should be initiated after recovery from posttransplant renal failure. Long-term follow-up showed improved renal graft survival in patients treated with sirolimus.

References

1. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL. Delayed graft function: risk factors and implications for renal allograft survival. Transplantation. 1997;63(7):968-974.
2. Smith KD, Wrenshall LE, Nicosia RF, et al. Delayed graft function and cast nephropathy associated with tacrolimus plus rapamycin use. J Am Soc Nephrol. 2003;14(4):1037-1045.
3. Simon JF, Swanson SJ, Agodoa LY, Cruess DF, Bohen EM, Abbott KC. Induction sirolimus and delayed graft function after deceased donor kidney transplantation in the United States. Am J Nephrol. 2004;24(4):393-401.
4. Shihab FS, Bennett WM, Yi H, Choi SO, Andoh TF. Sirolimus increases transforming growth factor-beta1 expression and potentiates chronic cyclosporine nephrotoxicity. Kidney Int. 2004;65(4):1262-1271.
5. Andoh TF, Burdmann EA, Fransechini N, Houghton DC, Bennett WM. Comparison of acute rapamycin nephrotoxicity with cyclosporine and FK506. Kidney Int. 1996;50(4):1110-1117.
6. Dittrich E, Schmaldienst S, Soleiman A, Hörl WH, Pohanka E. Rapamycin-associated post-transplantation glomerulonephritis and its remission after reintroduction of calcineurin-inhibitor therapy. Transpl Int. 2004;17(4):215-20.
7. Fervenza FC, Fitzpatrick PM, Mertz J, et al. Acute rapamycin nephrotoxicity in native kidneys of patients with chronic glomerulopathies. Nephrol Dial Transplant. 2004;19(5):1288-1292.
8. Masterson R, Leikis M, Perkovic V, Nicholls K, Walker R. Sirolimus: a single center experience in combination with calcineurin inhibitors. Transplant Proc. 2003;35(Suppl 3):99S-104S.
9. Bai S, Stepkowski SM, Kahan BD, Brunner LJ. Metabolic interaction between cyclosporine and sirolimus. Transplantation. 2004;77 (10):1507-1512.
10. Knight RJ, Kerman RH, Schoenberg L, et al. The selective use of basiliximab versus thymoglobulin in combination with sirolimus for cadaveric renal transplant recipients at low risk versus high risk for delayed graft function. Transplantation. 2004;78(6):904-910.
11. Knight RJ, Kahan BD. Impact of sirolimus on early graft function after deceased donor kidney transplantation. Transplantation. 2005;79(8):991-992.
12. Lieberthal W, Fuhro R, Andry CC, et al. Rapamycin impairs recovery from acute renal failure: role of cell-cycle arrest and apoptosis of tubular cells. Am J Physiol Renal Physiol. 2001;281(4):F693-F706.
13. Stallone G, Di Paolo S, Schena A, et al. Addition of sirolimus to cyclosporine delays the recovery from delayed graft function but does not affect 1-year graft function. J Am Soc Nephrol. 2004;15(1):228-333.
14. Giral-Classe M, Hourmant M, Cantarovich D, et al. Delayed graft function of more than six days strongly decreases long-term survival of transplanted kidneys. Kidney Int. 1998;54(3):972-978.
15. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int. 2002;62(1):311-318.
16. Gonwa TA, Hricik DE, Brinker K, Grinyo JM, Schena FP; Sirolimus Renal Function Study Group. Improved renal function in sirolimus-treated renal transplant patients after early cyclosporine elimination. Transplantation. 2002;74(11):1560-1567.
17. Fuller TF, Freise CE, Serkova N, Niemann CU, Olson JL, Feng S. Sirolimus delays recovery of rat kidney transplants after ischemia-reperfusion injury. Transplantation. 2003;76(11):1594-1599.
18. Shaffer D, Langone A, Nylander WA, Goral S, Kizilisik AT, Helderman JH. A pilot protocol of a calcineurin-inhibitor free regimen for kidney transplant recipients of marginal donor kidneys or with delayed graft function. Clin Transplant. 2003;17(suppl 9):31-34.
19. Hong JC, Kahan BD. A calcineurin antagonist-free induction strategy for immunosuppression in cadaveric kidney transplant recipients at risk for delayed graft function. Transplantation. 2001;71(9):1320-1328.

20. Chang GJ, Mahanty HD, Vincenti F, et al. A calcineurin inhibitor-sparing regimen with sirolimus, mycophenolate mofetil, and anti-CD25 mAb provides effective immunosuppression in kidney transplant recipients with delayed or impaired graft function. Clin Transplant. 2000;14(6):550-554.

21. McTaggart RA, Gottlieb D, Brooks J, et al. Sirolimus prolongs recovery from delayed graft function after cadaveric renal transplantation. Am J Transplant. 2003;3(4):416-423.